IN THE SUPREME COURT OF THE STATE OF NEVADA

THOMAS A. PICKENS, INDIVIDUALLY AND AS TRUSTEE OF THE LV BLUE TRUST,

Appellant,

vs.

DR. DANKA K. MICHAELS, INDIVIDUALLY AND AS TRUSTEE OF THE MICH-MICH TRUST,

Respondent;

Electronically Filed
Feb 23 2022 11:59 a.m.
Elizabeth A. Brown
Clerk of Supreme Court

S.C. DOCKET NO.: 83491
D.C. Case No. D-17-560737-D

APPENDIX

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ATTORNEYS FOR APPELLANT

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Plaintiff's Trial Exhibit 52 - 2008 1120 Income Tax Return for Blue Point Development LLC	02/14/2020	XXVIII/AA06692-XXIX/AA06759
Plaintiff's Trial Exhibit 53 - 2009 1120 Income Tax Return for Blue Point Development LLC	02/14/2020	XXIX/AA06760-06832
Plaintiff's Trial Exhibit 54 - 2010 1120 Income Tax Return for Blue Point Development LLC	02/14/2020	XXIX/AA06833-06862
Plaintiff's Trial Exhibit 55 - 2011 1120 Income Tax Return for Blue Point Development LLC	02/14/2020	XXIX/AA06863-06912
Plaintiff's Trial Exhibit 56 - 2012 1120 Income Tax Return for Blue Point Development LLC	02/14/2020	XXIX/AA06913-06930
Plaintiff's Trial Exhibit 57 - 2013 1120 Income Tax Return for Blue Point Development LLC	02/14/2020	XXIX/AA06931-06962
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Plaintiff's Trial Exhibit 63 - Wells Fargo Business Checking #9112 titled in the name of Blue Point Development 05/29/2014 through 12/31/2014	02/14/2020	XXX/AA07001-07002
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Plaintiff's Trial Exhibit 71 - Wells Fargo Business Checking #9112 titled in the name of Blue Point Development 01/01/2019 through 04/30/19	02/14/2020	XXX/AA07012-07013
Plaintiff's Trial Exhibit 74 - Wells Fargo Checking ending 3436 titled in the names of Thomas A. Pickens and Danka K. Michaels 07/01/2014 through 12/31/14	02/14/2020	XXX/AA07014

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Plaintiff's Trial Exhibit 79 - Wells Fargo Checking ending 3436 titled in the names of Thomas A. Pickens and Danka K. Michaels 01/01/2017 through 12/31/17	02/14/2020	XXX/AA07051
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Plaintiff's Trial Exhibit 93 - Lowes house summary with supporting Wells Fargo Home Mortgage #9607 (PMA #3436) titled in the names of Danka Katarina Michaels and Thomas A. Pickens 07/02/14 through 07/01/2016	02/14/2020	XXX/AA07229-07230
Plaintiff's Trial Exhibit 97 - American Express Statements #63006 titled in the name of Thomas Pickens 12/08/10 through 12/08/11	02/14/2020	XXX/AA07231
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Plaintiff's Trial Exhibit 129 - Pinnacle Health Systems – Danka K. Michaels. Statements 9/30/13 and 12/31/13	02/14/2020	XXXIII/AA 07773-07778
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Defendant's Trial Exhibit C – Documentation of $450,000 loan taken by Danka K. Michaels, M.D., PC for tenant improvements	02/14/2020	XXXIV/AA 08250-XXXV/AA 08257
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Appendix of Exhibits in Support of Defendant's Motion to Compel Discovery Responses	04/22/2019	II/AA00398-00440
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SOUTHWEST PENSION SERVICES, INC.
SOUTHWEST PENSION SERVICES, INC.
2320 POTOSI STREET
SUITE 150
LAS VEGAS , NV 89146-0312

Nationwide
On Your Side*

DANKA MICHAELS
9517 QUEEN CHARLOTTE
LAS VEGAS NV 89145-8673

SSN:	XXX-XX-9079
Date of Birth:	11/26/1985
Date of Hire:	07/01/2003
Date of Entry:	11/14/2012

DANKA K. MICHAELS, M.D. P.C.

503 – 00006

YOUR TOTAL ACCOUNT VALUE IS:
$285,563.79 AS OF 09/30/2013

YOUR RETIREMENT PORTFOLIO FROM 07/01/2013 TO 09/30/2013

Your Account At A Glance

Opening Value on 07/01/2013	$254,771.98
Contributions	$6,270.81
Additional Credits/Debits *	$3,176.62
Investment Gain/(Loss)	$21,344.38
Total Account Value on 09/30/2013	**$285,563.79**

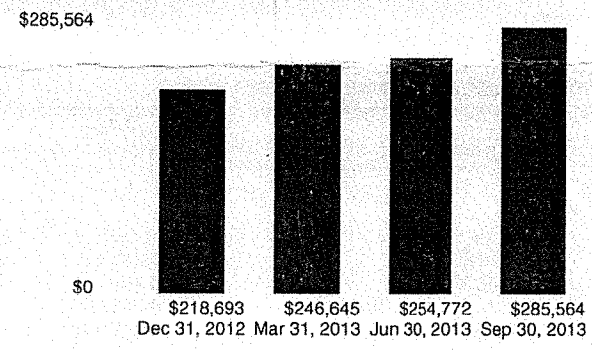
* Additional Credits/Debits displays deposits made to your account other than your normal payroll deferral and employer deposits, if applicable. This could include any loan repayments or rollover deposits.

Investment Volatility

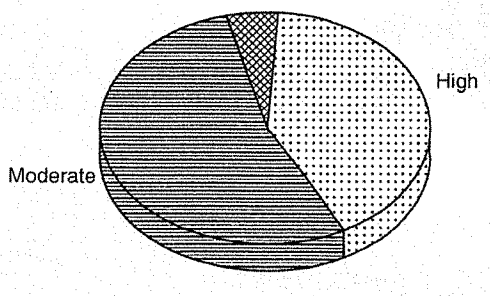
	% of Total	Total Fund Balance	Unit Value
High	**41.53 %**		
Fidadv Gr Oppr A		$31,766.56	1.138304
Harbor Intl Inv		$25,699.19	1.502915
Jpm Mdcap Gr A		$30,996.20	1.450299
Opp Mn St Smmdcap A		$30,145.74	1.988214
Moderate	**54.17 %**		
Amfds Cap Wld Gr Inc R3		$26,435.62	1.440301
Amfds Gr Fd Am R3		$55,810.56	1.441875
Gdmnscs Mdcap Val A		$14,882.36	1.592391
Invsco Comstk A		$29,354.98	2.228984
Mfs Intl New Disc A		$28,208.93	2.238629
Low	**4.29 %**		
Pimco Ttl Rtn A		$12,263.65	1.811853
Total Account Value	100%	$285,563.79	

Due to rounding, Total Account Value percentage may not equal 100%. Your actual balance may be different if you are not yet fully vested with your employer. Please contact your employer for details.

Your Recent Retirement Account History*



*Corrections made after the close of past periods are not reflected in this representation.



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SOUTHWEST PENSION SERVICES, INC.
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2320 POTOSI STREET
SUITE 150
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Nationwide
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9517 QUEEN CHARLOTTE
LAS VEGAS NV 89145-8673

SSN: XXX-XX-9079
Date of Birth: 11/26/1985
Date of Hire: 07/01/2003
Date of Entry: 11/14/2012

DANKA K. MICHAELS, M.D. P.C.

503 - 00006

YOUR TOTAL ACCOUNT VALUE IS:
$315,808.05 AS OF 12/31/2013

YOUR RETIREMENT PORTFOLIO FROM 10/01/2013 TO 12/31/2013

Your Account At A Glance

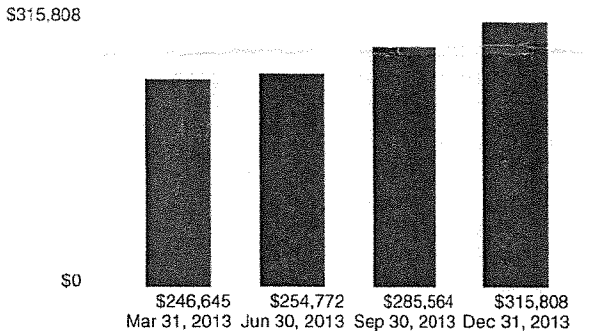
Opening Value on 10/01/2013	**$285,563.79**
Contributions	$6,718.81
Additional Credits/Debits *	$3,040.50
Investment Gain/(Loss)	$20,484.95
Total Account Value on 12/31/2013	**$315,808.05**

* Additional Credits/Debits displays deposits made to your account other than your normal payroll deferral and employer deposits, if applicable. This could include any loan repayments or rollover deposits.

Investment Volatility	% of Total	Total Fund Balance	Unit Value
High	30.43 %		
Harbor Intl Inv		$27,781.37	1.566570
Jpm Mdcap Gr A		$35,022.08	1.589792
Opp Mn St Smmdcap A		$33,312.05	2.129670
Moderate	65.55 %		
Amfds Cap Wld Gr Inc R3		$29,339.54	1.543132
Amfds Gr Fd Am R3		$62,771.58	1.569468
Fidadv Gr Oppr A		$34,718.40	1.207502
Gdmnscs Mdcap Val A		$16,481.93	1.708730
Invsco Comstk A		$33,344.06	2.452526
Mfs Intl New Disc A		$30,358.52	2.329999
Low	4.01 %		
Pimco Ttl Rtn A		$12,678.52	1.801800
Total Account Value	100%	$315,808.05	

Due to rounding, Total Account Value percentage may not equal 100%. Your actual balance may be different if you are not yet fully vested with your employer. Please contact your employer for details.

Your Recent Retirement Account History*



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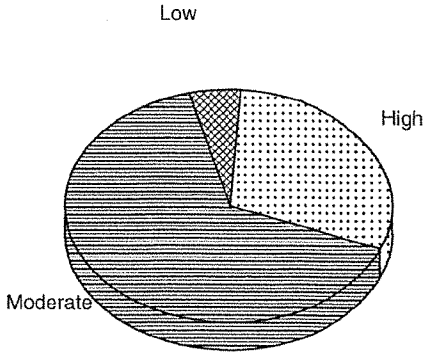

04010

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AA07002
TP04444

Account Statement

For the Period: 07/01/2013 - 09/30/2013

VALIC®

THOMAS E GOUGH
(800) 892-5558 x87907
Your financial advisor

(800) 448-2542 *Speak with a Client Service Professional*
VALIC by Phone, automated account access
7:00 a.m. to 8:00 p.m. (CST), Monday through Friday
www.VALIC.com *VALIC Online, internet account access*

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9517 QUEEN CHARLOTTE DR
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You have enormous financial power at the tap of one finger. The new VALIC iPad app will be launching in Q4 2013. Access your account 24/7 using the new application to conveniently manage your accounts; get the latest industry news; Twitter feeds; and market quotes. Plus, watch VALIC educational videos, and more. Learn more at www.valic.com/mobile.

iPad is a registered trademark of Apple Inc.

▶ Portfolio Snapshot

Ending value 09/30/13: **$27,934.98**

Activity at a Glance

Beginning value 07/01/13	**$27,184.34**
Net change in value	$750.64
Ending value 09/30/13	**$27,934.98**

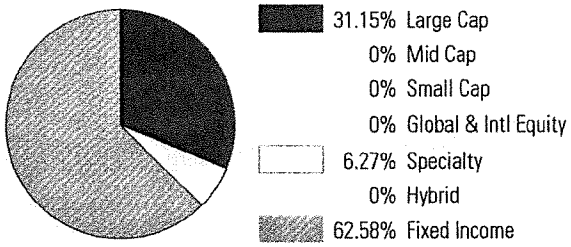
Personal Performance

Portfolio Value

For the period 07/01/13-09/30/13	Year to date 01/01/13-09/30/13	For 12 months 09/30/12-09/30/13
2.76%	5.66%	5.62%

*VALIC is pleased to provide you with your investment's personal performance. All active accounts at end of the quarter were included in the calculation, using the actual number of days your funds were invested.
*Past Performance is not a guarantee of future performance.
*Individual fund performance is available online at VALIC.com.

Asset Allocation



Contributions and Balances

Plan type	Contributions for the period 07/01/13 - 09/30/13	Ending value 09/30/13
PERSONAL		
Individual Retirement Account-Rollover	$0.00	$27,934.98

At Your Service

Approximately 46% of Americans have less than $10,000 saved for retirement. At the rule-of-thumb 4% withdrawal rate that would mean only $400 a month to live on during retirement. Make sure you're on target with your personal retirement goals by visiting the VALIC Retirement Planner tool online at www.valic.com/retirementplanner, or talk to your VALIC financial advisor.

Source: Employment Benefit Research Institute and Mathew Greenwald & Associates, Inc., 2003-2013 Retirement Confidence Surveys.

Remember as a kid smashing your piggy bank to get the money? During National Save for Retirement Week, October 20 - 26, the nation will be focused on saving. Will you? Find out what happens if you let the piggy grow - focus on saving for your future; increase savings when you can; simple ways to cut spending and increase savings, and much more. The piggy will thank you.

Account Statement

For the Period: 10/01/2013 - 12/31/2013

VALIC

THOMAS E GOUGH
(800) 892-5558 x87907
Your financial advisor

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VALIC by Phone, automated account access
7:00 a.m. to 8:00 p.m. (CST), Monday through Friday
www.VALIC.com *VALIC Online, internet account access*

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9517 QUEEN CHARLOTTE DR
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Tired of waiting? With Personal Deliver-e VALIC will electronically alert you when account statements, transaction confirmations and certain regulatory documents are available. Faster and more secure than paper mail, always at your fingertips...and customized to your needs. Watch for exciting news on VALIC.com

► Portfolio Snapshot

Ending value 12/31/13: **$29,018.06**

Activity at a Glance

Beginning value 10/01/13	**$27,934.98**
Net change in value	$1,083.08
Ending value 12/31/13	**$29,018.06**

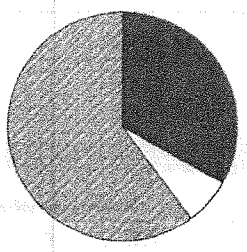
Personal Performance

Portfolio Value

For the period 10/01/13-12/31/13	Year to date 01/01/13-12/31/13	For 12 months 12/31/12-12/31/13
3.87%	9.76%	9.76%

*VALIC is pleased to provide you with your investment's personal performance. All active accounts at end of the quarter were included in the calculation, using the actual number of days your funds were invested.
*Past Performance is not a guarantee of future performance.
*Individual fund performance is available online at VALIC.com.

Asset Allocation



- 33.10% Large Cap
- 0% Mid Cap
- 0% Small Cap
- 0% Global & Intl Equity
- 6.66% Specialty
- 0% Hybrid
- 60.24% Fixed Income

Contributions and Balances

Plan type	Contributions for the period 10/01/13 - 12/31/13	Ending value 12/31/13
PERSONAL		
Individual Retirement Account-Rollover	$0.00	$29,018.06

At Your Service

Have better control of your assets whether rolling from a previous plan or retiring. Consolidating with an IRA from VALIC can help simplify your finances, continue your account's tax-deferred status, and give access to expanded options for investment and distribution. VALIC can help you pre- and post-retirement...that's our expertise.

As life changes, your retirement and financial planning may also need to change to keep you on track toward financial stability. See your VALIC financial advisor annually to review and update your financial plan. Let us put our experience to work for you.

Account Statement
July 01, 2015 - September 30, 2015

VALIC®

Account Number: 4099975

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9517 QUEEN CHARLOTTE DR
LAS VEGAS NV 89145-8673

YOUR CURRENT VALUE
$30,200.93

Important Information

When it comes to your financial future, more is better. During National Save for Retirement Week, October 18-24, take time to ensure your current saving strategy is keeping up with your goals. If it's not, just a few small changes in spending could give you the extra boost you need. Find out more at www.valic.com/nationalsaveforretirementweek.

Looking for help? Help yourself to the latest retirement information, facts, stats, brain teasers...and entertaining reading. Log in to your account at VALIC.com and click on Retirement Essentials.

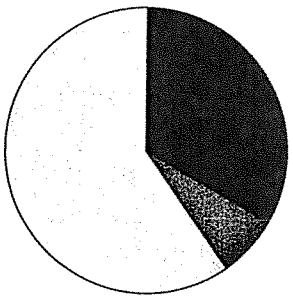
Value Summary

	For the period	Since inception
Beginning Value	$31,040.30	
Your contributions	$0.00	$2,000.00
Internal exchanges/transfers	$0.00	$15,436.00
Net change in value	−$839.37	
Ending Value	**$30,200.93**	

Surrender value	
As of 09/30/15	$30,200.93
As of 06/30/15	$31,040.30

Asset Allocation Summary

Asset class	Ending value	% of total
Large Cap	$10,036.79	33.23%
Specialty	$2,115.28	7.00%
Fixed Income	$18,048.86	59.77%
Total	**$30,200.93**	**100%**



Account Statement
July 01, 2015 - September 30, 2015
MICHALECKO, DANKA

VALIC®

Investment Summary

Funds by Asset Class	Beginning value	Additions	Reductions	Net change in value	Ending value	Future contrib
Large Cap						
Core Equity Fund	$2,010.47	$0.00	$0.00	-$172.10	$1,838.37	50%
Stock Index Fund	$8,790.12	$0.00	$0.00	-$591.70	$8,198.42	
Total Large Cap	**$10,800.59**	**$0.00**	**$0.00**	**-$763.80**	**$10,036.79**	**50%**
Specialty						
Science & Technology Fund	$2,293.16	$0.00	$0.00	-$177.88	$2,115.28	50%
Total Specialty	**$2,293.16**	**$0.00**	**$0.00**	**-$177.88**	**$2,115.28**	**50%**
Fixed Income						
Fixed Account Plus	$9,482.29	$0.00	$0.00	$70.91	$9,553.20	
Government Securities Fund	$4,279.54	$0.00	$0.00	$56.92	$4,336.46	
International Government Bond	$4,184.72	$0.00	$0.00	-$25.52	$4,159.20	
Total Fixed Income	**$17,946.55**	**$0.00**	**$0.00**	**$102.31**	**$18,048.86**	
Total	**$31,040.30**	**$0.00**	**$0.00**	**-$839.37**	**$30,200.93**	**100%**

Performance Summary

	For the period 07/01/15 - 09/30/15	Year to date 01/01/15 - 09/30/15	For 12 months 09/30/14 - 09/30/15
PERSONAL			
INDIVIDUAL RETIREMENT ACCOUNT-ROLLOVE	-2.70%	-2.20%	-0.32%

Personalized rate of return is a measure of the performance of the investments that you hold in your retirement plan account. It indicates the return on investments over a period of time and factors in the activities that affect your account including 1) performance of investments, 2) contributions and 3) withdrawals and loans.
Remember past performance does not guarantee future results.
Performance information for each fund is available online at VALIC.com.

You can choose to receive e-mail notifications when your account statements, certain regulatory documents and transaction confirmations become available online with Personal Deliver-e. Save paper, time and energy. It's easy to sign-up. Just visit VALIC.com today to get started.

PERSONAL ACCOUNT

INDIVIDUAL RETIREMENT ACCOUNT-ROLLOVE
ROLLOVER WITHIN VALIC IRA
Contract Date: 06/24/1996

Transactions by Account

UIT-194 HED02 02643 9079
PORTFOLIO DIRECTOR (A324) UIT-194-WSC

Effective date	Description	Amount	Investment	Number of Units/Shares	Unit/Share Price
	Beginning value 07/01/15	**$31,040.30**			
		$9,482.29	Fixed Account Plus		
		$2,010.47	Core Equity Fund	592.183106	$3.395014
		$4,279.54	Government Securities Fund	1,208.895362	$3.540039
		$4,184.72	International Government Bond	1,422.421252	$2.941973
		$2,293.16	Science & Technology Fund	465.324720	$4.928088

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ColumbiaManagement

DANKA K MICHAELS
9517 QUEEN CHARLOTTE DR
LAS VEGAS NV 89145-8673

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PINNACLE HEALTH SYSTEMS
DANKA K MICHAELS

Reporting Period
07/01/2013 - 09/30/2013

Your Portfolio Overview

Change in Value Summary

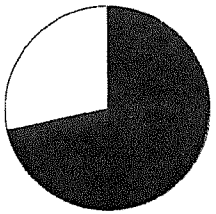
Portfolio Value on 07/01/2013	**$100,134.44**
+ Contributions / Other Credits	$0.00
+ Earnings & Gain / (Loss)	$6,098.74
- Distributions / Debits / Fees	($49.20)
Portfolio Value on 09/30/2013	**$106,183.98**

Participant Profile

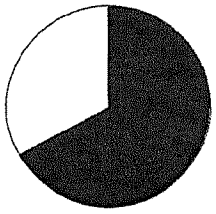
Plan Number R0003700

Your Portfolio Allocation

Current Investment Mix



Current Contribution Allocation



Current Invest. Mix	Current Contrib. Allocation	Investment Type Fund Name	Number of Shares	Share Price	Actual Value on 09/30/2013
71.10%	**67.00%**	GROWTH			
46.20%	33.00%	COLUMBIA ACORN FUND-C	1557.088	$31.4700	$49,001.55
24.90%	34.00%	COLUMBIA EQUITY VALUE FUND- C	2036.063	$13.0000	$26,468.82
28.90%	**33.00%**	VALUE			
28.90%	33.00%	COLUMBIA DIVIDEND INCOME FUND-C	1841.344	$16.6800	$30,713.61
100%	**100%**	**Total**			**$106,183.98**

Questions?

Automated 24-hour Helpline
(800) 799-7526
Retirement Plan Services Representatives are available Monday - Friday 8:00 a.m. to 5:00 p.m. ET

Website
columbiamanagement.com
Visit our website for access to your account information 24 hours a day

Dealer's Name

AGUILAR/DELGADO-SCHUETZE/GARO
TRICOR FINANCIAL, LLC
10501 W GOWAN RD STE 260
LAS VEGAS NV 89129-6603

AA07007
TP04449

51-57-0051-NSB 04-2010 (53126)

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ColumbiaManagement

DANKA K MICHAELS
9517 QUEEN CHARLOTTE DR
LAS VEGAS NV 89145-8673

PINNACLE HEALTH SYSTEMS
DANKA K MICHAELS

Reporting Period
01/01/2013 - 12/31/2013

Your Portfolio Overview

Change in Value Summary

Portfolio Value on 01/01/2013	**$89,046.15**
+ Contributions / Other Credits	$0.00
+ Earnings & Gain / (Loss)	$25,692.50
- Distributions / Debits / Fees	($194.69)
Portfolio Value on 12/31/2013	**$114,543.96**

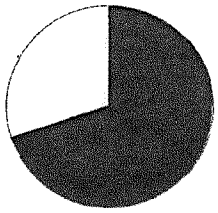
Participant Profile

Plan Number R0003700

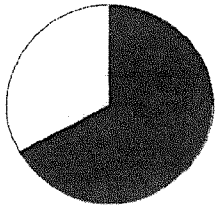
001445

Your Portfolio Allocation

Current Investment Mix



Current Contribution Allocation



Current Invest. Mix	Current Contrib. Allocation	Investment Type Fund Name	Number of Shares	Share Price	Actual Value on 12/31/2013
70.80%	**67.00%**	GROWTH			
45.70%	33.00%	COLUMBIA ACORN FUND-C	1656.300	$31.6400	$52,405.33
25.10%	34.00%	COLUMBIA EQUITY VALUE FUND- C	2112.948	$13.5800	$28,693.83
29.20%	**33.00%**	VALUE			
29.20%	33.00%	COLUMBIA DIVIDEND INCOME FUND-C	1871.561	$17.8700	$33,444.80
100%	**100%**	**Total**			**$114,543.96**

Questions?

Automated 24-hour Helpline
(800) 799-7526

Retirement Plan Services Representatives are available Monday - Friday 8:00 a.m. to 5:00 p.m. ET

Website
columbiamanagement.com

Visit our website for access to your account information 24 hours a day

Dealer's Name

E DELGADO-SCHUETZE/GAROFALO
TRICOR FINANCIAL, LLC
10501 W GOWAN RD STE 260
LAS VEGAS NV 89129-6603

AA07008
TP04450

51-55-0051NSB 04-2010 (53126)

UBS

UBS Financial Services Inc.
10801 W Charleston Boulevard
4th Floor
Las Vegas NV 89135-1200

CPZ3002103477 1215 X12 KV 0

Summary of your UBS Portfolio

December 2015

DANKA MICHAELS
ROLLOVER IRA
9517 QUEEN CHARLOTTE DRIVE
LAS VEGAS NV 89145-8673

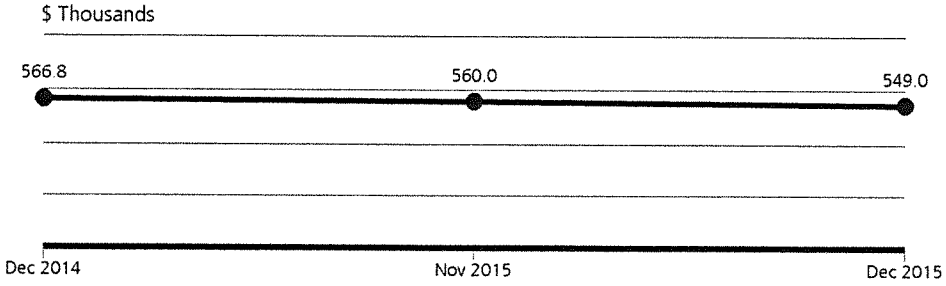
Your Financial Advisor:
SHELLEY M DUBIN
Phone: 702-731-1121/800-428-7573

Visit our website:
www.ubs.com/financialservices

Value of your portfolio

	on November 30 ($)	on December 31 ($)
Your assets	560,010.20	549,045.65
Your liabilities	0.00	0.00
Value of your portfolio	**$560,010.20**	**$549,045.65**

Tracking the value of your portfolio



Sources of your portfolio growth during 2015

Value of your portfolio at year end 2014	$566,808.73
Net deposits and withdrawals	-$10,171.59
Your investment return:	
Dividend and interest income	$13,600.88
Change in market value	-$21,192.37
Value of your portfolio on Dec 31, 2015	**$549,045.65**

AA07009
TP05350

Your Financial Advisor:
SHELLEY M DUBIN
Telephone 702-731-1121/800-428-7573

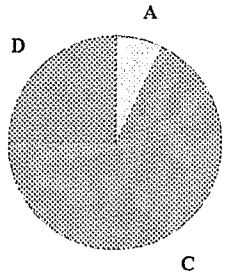
Your portfolio balance sheet

Summary of your assets

		Value on December 31 ($)	Percentage of your portfolio
A	Cash and money balances	38,750.04	7.06%
B	Cash alternatives	0.00	0.00%
C	Equities	373,255.77	67.98%
D	Fixed income	137,039.84	24.96%
E	Non-traditional	0.00	0.00%
F	Commodities	0.00	0.00%
G	Other	0.00	0.00%
Total assets		**$549,045.65**	**100.00%**

Value of your portfolio **$549,045.65**

Your current asset allocation



- *Cash and money balances* may include available cash balances, UBS Bank USA deposit account balances, UBS AG Stamford Branch deposit account balances and money market mutual fund sweep balances. See the *Important information about your statement* on the last two pages of this statement for details about those balances.

Eye on the markets

Index	Percentage change December 2015	Percentage change Year to date
S&P 500	-1.58%	1.38%
Russell 3000	-2.05%	0.48%
MSCI - Europe, Australia & Far East	-1.33%	-0.39%
Barclays Capital U.S. Aggregate Bond Index	-0.32%	0.55%

Interest rates on December 31, 2015
3-month Treasury bills: 0.17%
One-month LIBOR: 0.43%

AA07010
TP05351

COLUMBIA THREADNEEDLE INVESTMENTS

PINNACLE HEALTH SYSTEMS
DANKA K MICHAELS

Reporting Period
07/01/2015 - 09/30/2015

MB 01 005350 53118 B 21 C
DANKA K MICHAELS
9517 QUEEN CHARLOTTE DR
LAS VEGAS NV 89145-8673

Your Portfolio Overview

Change in Value Summary

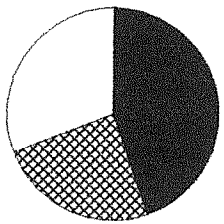
Portfolio Value on 07/01/2015	**$122,402.23**
+ Contibutions / Other Credits	$0.00
+ Earnings & Gain / (Loss)	($10,820.34)
- Distributions / Debits / Fees	($62.59)
Portfolio Value on 09/30/2015	**$111,519.30**

Participant Profile

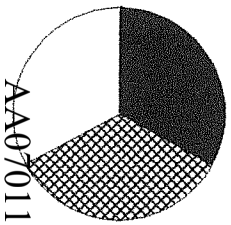
Plan Number R0003700

Your Portfolio Allocation

Current Investment Mix



Current Investment Allocation



Current Invest. Mix	Current Contrib. Allocation	Investment Type Fund Name	Number of Shares	Share Price	Actual Value on 09/30/2015
44.60%	**33.00%**	GROWTH			
44.60%	33.00%	COLUMBIA ACORN FUND-C	2,137.188	$23.2800	$49,753.74
24.40%	**34.00%**	INTERNATIONAL			
24.40%	34.00%	COLUMBIA GLOBAL EQUITY VALUE FUND-C	2,473.633	$11.0000	$27,209.96
31.00%	**33.00%**	VALUE			
31.00%	33.00%	COLUMBIA DIVIDEND INCOME FUND-C	2,041.086	$16.9300	$34,555.60
100%	**100%**	**Total**			**$111,519.30**

Questions?

Automated 24-hour Helpline
(800) 799-7526
Retirement Plan Services Representatives are available Monday - Friday 8:00 a.m. to 5:00 p.m. ET

Website
columbiathreadneedle.com/us
Visit our website for access to your account information 24 hours a day

Dealer's Name

FRANK/JASON AGUILAR/GAROFALO
TRICOR FINANCIAL, LLC
10501 W GOWAN RD STE 260
LAS VEGAS NV 89129-6603

AA07011
TP05352

BluePart Development Company Car

paid to date 3-25-16

$79,200.00 (estimated)

BANK OF THE WEST

>000091 4764472 0001 008230 10Z NC-B07-3CS
THOMAS A PICKENS
DANKA MICHAELS
9517 QUEEN CHARLOTTE DR
LAS VEGAS, NV 89145

December 02, 2014
New Loan # 384626474
2015 PORSCHE

Welcome to Bank of the West! We are delighted to provide financing for your recent purchase from GAUDIN JAGUAR PORSCHE OF LAS VEGAS. We are honored that more than 1.5 million customers have placed their trust in us and are pleased to offer our services to you. What sets Bank of the West apart from other banks is a spirit that drives us to do more for our customers. Bank of the West offers the stability of a company that has a 135 year history and is part of BNP Paribas, a European leader in global banking, financial services, and one of the six strongest banks in the world.

For your convenience, we offer online or mobile access to view your balance, payment amount and due date. It's fast, safe and free! To enroll, simply visit **bankofthewest.com**, go to "Online Banking", click "Enroll", "Other Account", and provide your information. You'll be ready to go in minutes.

Additionally, we make it easy for your payments to be deducted automatically from your checking or savings account, even if your accounts are not with Bank of the West. You can take advantage of this free service by completing the attached enrollment form, including a voided check and returning the information to the "*General Inquiry*" address listed below. If you prefer, you can schedule an automatic payment from your Bank's on-line bill pay service to be sent to your loan account at Bank of the West monthly.

Your first loan payment of $1,137.83 is due on January 06, 2015. You should be receiving a coupon book within two weeks. If you do not receive your coupon book in time to include with your first payment, you may send your payment electronically or send us a check, with your new loan number indicated on it, to the address listed below under "*Payments*."

If you are traveling, or simply need quick information about your loan, you may also call the "*General Inquiry*" phone number listed below to access your account information 24 hours a day, 7 days a week simply by entering your account number.

If you have not already done so, please contact your insurance representative and have Bank of the West added as "Loss Payee" to your policy covering this automobile. Proof of insurance should be mailed to the address listed below under "*Insurance*."

Bank of the West may report information about your account to credit bureaus. You are hereby advised that delinquency on this account may negatively impact your credit rating. Late payments, missed payments or other defaults on your account may be reflected in your credit report. If you need to contact us regarding any issues that may be impacting your ability to pay, or any other services with which we can assist you, please feel free to call the number listed below under "*General Inquiry*."

We are excited about the future and appreciate the opportunity to meet your financial needs.

General Inquiry
Bank of the West
PO Box 2078
Omaha, NE 68103-2078
800/827-7500
bankofthewest.com

Payments
Bank of the West
PO Box 4024
Alameda, CA 94501-0424
800/827-7500

Insurance
Bank of the West
Insurance Service Center
PO Box 513
Amelia, OH 45102
855/312-8722

STATE OF NEVADA
DEPARTMENT OF MOTOR VEHICLES

CERTIFICATE OF TITLE

VIN	YEAR	MAKE	MODEL	VEHICLE BODY	TITLE NUMBER
SALME1D40CA393530	2012	LNDR	RANGE ROVE	T4W	NV005887305

DATE ISSUED	ODOMETER MILES	FUEL TYPE	SALES TAX PD	EMPTY WT	GROSS WT	GVWR
01/14/2013	55	G				

VEHICLE COLOR

ODOMETER BRAND: ACTUAL MILES

BRANDS

OWNER(S) NAME AND ADDRESS
PICKENS THOMAS ALLEN
9517 QUEEN CHARLOTTE DR
LAS VEGAS NV 89145-8673

LIENHOLDER NAME AND ADDRESS
JPMORGAN CHASE BANK NA
PO BOX 901098
FORT WORTH TX 76101-2098

LIENHOLDER RELEASE - INTEREST IN THE VEHICLE DESCRIBED ON THIS TITLE IS HEREBY RELEASED:

Trans Proc Sr. Specialist — NOV 18 2015

SIGNATURE OF AUTHORIZED AGENT — DATE

Lucy Kimani — JPMorgan Chase Bank, N.A.

PRINTED NAME OF AGENT AND COMPANY

FEDERAL AND STATE LAW REQUIRES THAT YOU STATE THE MILEAGE IN CONNECTION WITH THE TRANSFER OF OWNERSHIP. FAILURE TO COMPLETE OR PROVIDING A FALSE STATEMENT MAY RESULT IN FINES AND/OR IMPRISONMENT.

The undersigned hereby certifies the vehicle described in this title has been transferred to the following buyer(s):

Printed Full Legal Name of Buyer — Nevada Driver's License Number or Identification Number — ☐ AND ☐ OR

Printed Full Legal Name of Buyer — Nevada Driver's License Number or Identification Number

Address — City — State — Zip Code

I certify to the best of my knowledge the odometer reading is the actual mileage of the vehicle unless one of the following statements is checked.

ODOMETER READING (NO TENTHS)

☐ The mileage stated is in excess of its mechanical limits.
☐ The odometer reading is not the actual mileage. WARNING: ODOMETER DISCREPANCY.
☐ Exempt - Model year over 9 years old.

Signature of Seller(s)/Agent/Dealership — Printed Name of Seller(s)/Agent/Dealership

I am aware of the above odometer certification made by the seller/agent. ☐ — Dealer's License Number — Date of Sale

Signature of Buyer — Printed Full Legal Name of Buyer

ACCORDING TO THE RECORDS OF THE DEPARTMENT OF MOTOR VEHICLES, THE PERSON NAMED HEREON IS THE OWNER OF THE VEHICLE DESCRIBED ABOVE, SUBJECT TO LIEN AS SHOWN.

CONTROL NO. 98666JC

(THIS IS NOT A TITLE NO.)

VP-2 (Rev. 8/10)

STATE OF NEVADA

ALTERATION OR ERASURE VOIDS THIS TITLE

UBS Financial Services Inc.
10801 W Charleston Boulevard
4th Floor
Las Vegas NV 89135-1200

CPZ3001990063 0216 X1 KV 0

Retirement Account

Mgd Port of Global Selections

February 2016

Your Financial Advisor:
SHELLEY M DUBIN
Phone: 702-731-1121/800-428-7573

Visit our website:
www.ubs.com/financialservices

Account name: THOMAS PICKENS
ROLLOVER IRA
Account type: IRA Rollover
Account number: KV 11693 DW

Your investment objectives:
You have identified the following investment objectives for this account. If you have questions about these objectives, disagree with them, or wish to change them, please contact your Financial Advisor or Branch Manager. You can find a full description of the alternative investment objectives in *Important information about your statement* at the end of this document.

Your return objective:
Capital appreciation
Your risk profile:
Primary - Moderate
Investment eligibility consideration - None selected

Value of your account

	on January 29 ($)	on February 29 ($)
Your assets	198,918.19	198,320.25
Your liabilities	0.00	0.00
Value of your account	**$198,918.19**	**$198,320.25**

Your account instructions
- Your account is managed by MP GS Mod Aggressive.
- UBS Financial Services Inc. is your IRA custodian.
- Your account cost basis default closing method is FIFO, First In, First Out.

Change in the value of your account

	February 2016 ($)	Year to date ($)
Opening account value	**$198,918.19**	**$207,635.88**
Withdrawals and fees, including investments transferred out	0.00	-929.26
Dividend and interest income	215.96	436.14
Change in market value	-813.90	-8,822.51
Closing account value	**$198,320.25**	**$198,320.25**

AA07014
TP05359

UBS

UBS Financial Services Inc.
10801 W Charleston Boulevard
4th Floor
Las Vegas NV 89135-1200

APZ3000919013 0617 X125 KV 0

Retirement Account

UBS Managed Portfolio

June 2017

THOMAS PICKENS
ROLLOVER IRA
3320 N BUFFALO
#208
LAS VEGAS NV 89129-7411

Account name: THOMAS PICKENS
ROLLOVER IRA
Account type: IRA Rollover
Account number: KV 11693 DW

Your Financial Advisor:
SHELLEY M DUBIN
Phone: 702-731-1121/800-428-7573

Visit our website:
www.ubs.com/financialservices

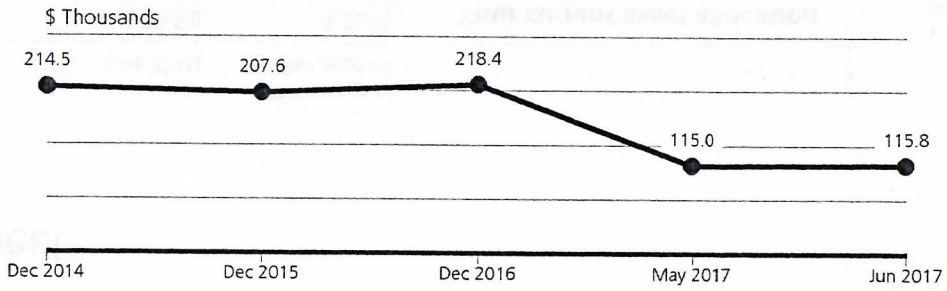
Items for your attention

- For information about our fees, charges and compensation, please see ubs.com/guidetofees and ubs.com/accountdisclosures.

Value of your account

	on May 31 ($)	on June 30 ($)
Your assets	115,027.71	115,826.38
Your liabilities	0.00	0.00
Value of your account	**$115,027.71**	**$115,826.38**

Tracking the value of your account



Sources of your account growth during 2017

Value of your account at year end 2016	$218,389.98
Net deposits and withdrawals	-$114,664.81
Your investment return:	
Dividend and interest income	$1,358.12
Change in market value	$10,743.09
Value of your account on Jun 30, 2017	**$115,826.38**

AA07015
TP05421

UBS

UBS Financial Services Inc.
10801 W Charleston Boulevard
4th Floor
Las Vegas NV 89135-1200

APZ3000875489 1217 X123 KV 0

Retirement Account

Oct. 2017 - Dec. 2017

0015608 03 AB 0.400 03 TR 00090 B301B022 111000 edg
THOMAS PICKENS
ROLLOVER IRA
3320 N BUFFALO
#208
LAS VEGAS NV 89129-7411

Account name: THOMAS PICKENS
ROLLOVER IRA
Account type: IRA Rollover
Account number: KV 11693 DW

Your Financial Advisor:
SHELLEY M DUBIN
Phone: 702-731-1121/800-428-7573

Visit our website:
www.ubs.com/financialservices

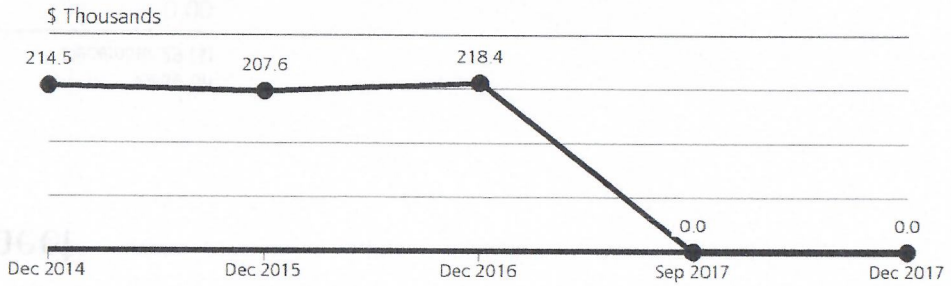
Items for your attention

- Help protect yourself from fraud and review bank, credit card, and brokerage statements regularly. Also, get your free credit report annually from www.annualcreditreport.com.

Value of your account

	on September 29 ($)	on December 29 ($)
Your assets	25.24	0.00
Your liabilities	0.00	0.00
Value of your account	**$25.24**	**$0.00**

Tracking the value of your account



Sources of your account growth during 2017

Value of your account at year end 2016	$218,389.98
Net deposits and withdrawals	-$232,671.14
Your investment return:	
Dividend and interest income	$1,560.60
Change in market value	$12,720.56
Value of your account on Dec 29, 2017	**$0.00**

Docket 83491 Document 2022-05316
AA07016
TP05422

J.P.Morgan

Statement Period
August 31 - September 30, 2019

Account Number
959-66373

Investment Statement

69937 BDS 001 003 27319 - NNNNNNNNNNN

DANKA K MICHAELS IRA
JPMS LLC CUST.
9517 QUEEN CHARLOTTE DR
LAS VEGAS NV 89145-8673

Account Value

Account Description	Previous Period	This Period
Retirement Managed	414,576.62	420,882.29
ACCOUNT VALUE [3]	**$414,576.62**	**$420,882.29**

See page 3 for footnotes and more detail.

Questions?

For Full Service Accounts, Call Private Client Advisor

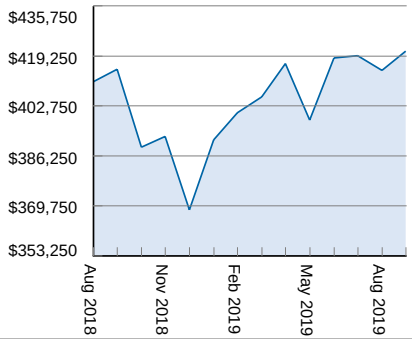
(702) 352 0525 Jessica Arana

Customer Service
(888) 994 5626
Branch Address
6920 Arroyo Crossing Pwky
Las Vegas, NV, 89113

www.chase.com

More contact information on page 21

Account Value
(August 2018 to September 2019)



If you have any questions about your statement or concerns about your account, please call us at the toll free number provided above.

INVESTMENT AND INSURANCE PRODUCTS ARE: · NOT FDIC INSURED · NOT INSURED BY ANY FEDERAL GOVERNMENT AGENCY
· NOT A DEPOSIT OR OTHER OBLIGATION OF, OR GUARANTEED BY, JPMORGAN CHASE BANK, N.A. OR ANY OF ITS AFFILIATES
· SUBJECT TO INVESTMENT RISKS, INCLUDING POSSIBLE LOSS OF THE PRINCIPAL AMOUNT INVESTED

Account is held at J.P. Morgan Securities LLC (JPMS), member Financial Industry Regulatory Authority (FINRA) and Securities Investor Protection Corporation (SIPC). **This statement summary is provided for convenience purposes only**. For information about your JPMS account(s), please refer to your official JPMS account statement(s), which follows this statement summary. **Neither this statement summary nor your official JPMS account statement(s) should be used for tax reporting purposes.**

STATEMENT SUMMARY | RETIREMENT MANAGED | IMPORTANT INFORMATION

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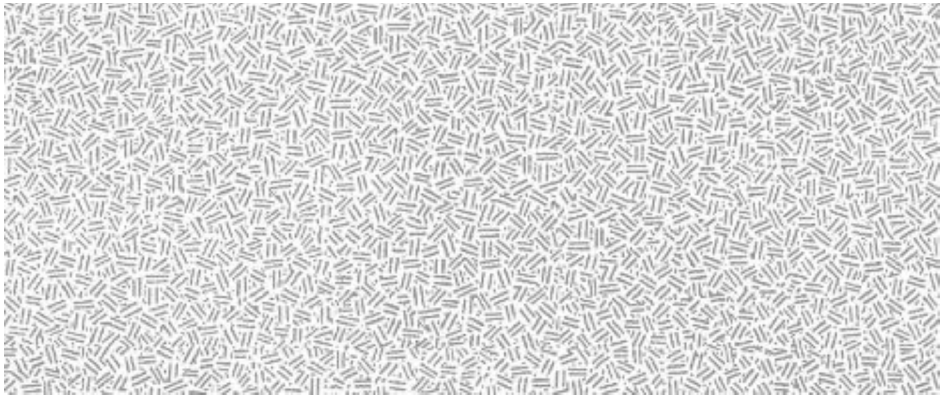


J.P.Morgan

Statement Period
August 31 - September 30, 2019
Last Statement: August 30, 2019

Account Number
959-66373

DANKA K MICHAELS IRA
JPMS LLC CUST.
9517 QUEEN CHARLOTTE DR
LAS VEGAS NV 89145-8673

Account Value: **$420,882.29**

JPMS LLC IRA

JPMorgan Core Advisory Portfolio (JPMCAP)

Growth Liq Alts - Retirement

Account Activity Summary

Deposits and Withdrawals may differ from your Retirement Contributions and Distributions. See details on the next page.

Description	This Period	Year-to-Date
Beginning Account Value	**$414,576.62**	**$368,535.33**
Deposits (Cash & Securities)	0.00	0.00
Withdrawals (Cash & Securities)	0.00	0.00
Net Deposits / Withdrawals	**$0.00**	**$0.00**
Income (Posted to your account)	328.44	3,808.31
Fees [1]	(407.49)	(3,490.22)
Change In Investment Value	6,384.72	52,028.87
ENDING ACCOUNT VALUE [3]	**$420,882.29**	**$420,882.29**
Net Accrued Income	0.00	0.00
Account Value With Accruals	**$420,882.29**	**$420,882.29**

1 *Account fees, management fees, and debit interest are included. Trade related fees charged by brokers and commissions impact the total cost or proceeds of your trades and are not included here.*

3 *Important information regarding Alternative Assets including pricing and source of valuations is provided in the "Messages" section of Important Information.*

Month End Closing Method: First In, First Out (FIFO)

Your Broker/Dealer is J.P. MORGAN SECURITIES LLC, 4 Chase Metrotech Center, Brooklyn, New York 11245-0001

INVESTMENT AND INSURANCE PRODUCTS ARE: · NOT FDIC INSURED · NOT INSURED BY ANY FEDERAL GOVERNMENT AGENCY
· NOT A DEPOSIT OR OTHER OBLIGATION OF, OR GUARANTEED BY, JPMORGAN CHASE BANK, N.A. OR ANY OF ITS AFFILIATES
· SUBJECT TO INVESTMENT RISKS, INCLUDING POSSIBLE LOSS OF THE PRINCIPAL AMOUNT INVESTED

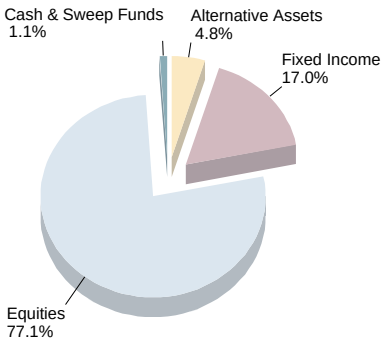
JPMorgan Chase Bank, N.A. and its affiliates (collectively "JPMCB") offer investment products, which may include bank managed accounts and custody, as part of its trust and fiduciary services. Other investment products and services, such as brokerage and advisory accounts, are offered through **J.P. Morgan Securities LLC** (JPMS), a member of FINRA and SIPC. Annuities are made available through Chase Insurance Agency, Inc. (CIA), a licensed insurance agency, doing business as Chase Insurance Agency Services, Inc. in Florida. JPMCB, JPMS and CIA are affiliated companies under the common control of JPMorgan Chase & Co. Products not available in all states. For information about your account, please refer to your official JPMS account statement **which should not be used for tax reporting purposes**. Please read the important disclosures at the end of the statement. For questions, please call (888) 994 5626.

JPMorgan Core Advisory Portfolio (JPMCAP)

Asset Allocation Summary

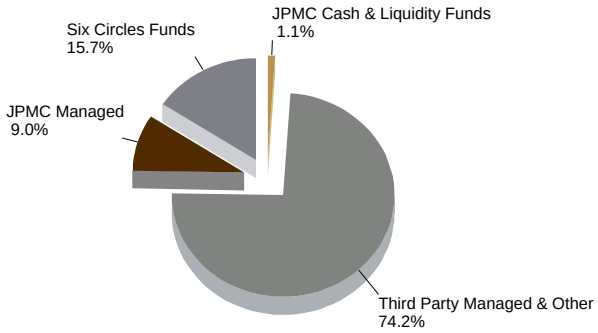
Description	Market Value Previous Period	Market Value This Period	Total Change ($)	Total Change (%)
Cash & Sweep Funds	5,999.74	4,556.65	(1,443.09)	-24.05
Equities	317,622.10	324,269.99	6,647.89	+2.09
Fixed Income	70,694.23	71,674.57	980.34	+1.38
Alternative Assets	20,260.55	20,381.08	120.53	+0.59
TOTAL ACCOUNT VALUE	**$414,576.62**	**$420,882.29**	**$6,305.67**	**+1.52**

Asset Allocation



The allocation percentage is derived from net positive market values only.

Manager Allocation



For additional information, please see the Manager Allocation message within Important Information at the end of the statement.

JPMorgan Core Advisory Portfolio (JPMCAP)

Retirement Contribution and Distribution Summary

Description	Tax Year 2018 (Year-to-Date)	Tax Year 2019 (Year-to-Date)
Contributions	0.00	0.00
Rollovers	0.00	0.00
Distributions	0.00	0.00
Federal Tax Withheld	0.00	0.00
State Tax Withheld	0.00	0.00

Assets and Liabilities Summary

Description	Previous Period	This Period
Long Cash and Sweep Funds	5,999.74	4,556.65
Long Market Value	408,576.88	416,325.64
Total Assets	**$414,576.62**	**$420,882.29**
Total Liabilities	**$0.00**	**$0.00**
TOTAL ACCOUNT VALUE	**$414,576.62**	**$420,882.29**
Total Account Value with Accruals	**$414,576.62**	**$420,882.29**

Income Summary

Description	This Period	Year-to-Date
Dividends	318.82	3,514.12
Interest	9.62	80.96
Distributions	0.00	213.23
Total Income from Taxable Investments	**$328.44**	**$3,808.31**
Total Income from Non-Taxable Investments	**$0.00**	**$0.00**
TOTAL INCOME	**$328.44**	**$3,808.31**

Taxable and Non-taxable income classifications are based on the characteristics of the underlying securities and not the taxable status of the account.

Cash Flow Summary

Description	This Period	Year-to-Date
Opening Cash Balance	**$5,999.74**	**$3,135.43**
Trade and Investment Activity	9,342.70	71,677.42
Income	328.44	3,808.31
Fees [1]	4.48	55.78
Total Credits	**$9,675.62**	**$75,541.51**
Trade and Investment Activity	(10,706.74)	(70,574.29)
Fees [1]	(411.97)	(3,546.00)
Total Debits	**($11,118.71)**	**($74,120.29)**
Net Cash Activity	**($1,443.09)**	**$1,421.22**
CLOSING CASH BALANCE	**$4,556.65**	**$4,556.65**

"Opening Cash Balance" and "Closing Cash Balance" include Sweep Funds.

1 *Account fees, management fees, and debit interest are included. Trade related fees charged by brokers and commissions impact the total cost or proceeds of your trades and are not included here.*

JPMorgan Core Advisory Portfolio (JPMCAP)

Unrealized Gain / Loss Summary

Description	This Period
Short-Term Gain	6,571.60
Short-Term Loss	(245.52)
Short-Term Net Gain / Loss	**$6,326.08**
Long-Term Gain	7,609.34
Long-Term Loss	(420.51)
Long-Term Net Gain / Loss	**$7,188.83**
TOTAL UNREALIZED GAIN / LOSS	**$13,514.91**

Unrealized Gain / Loss represents Gain / Loss data since the date of acquisition.

Realized Gain / Loss Summary

Description	This Period	Year-to-Date
Short-Term Gain	95.29	189.05
Short-Term Loss	0.00	(1,686.70)
Short-Term Net Gain / Loss	**$95.29**	**($1,497.65)**
Long-Term Gain	298.41	298.41
Long-Term Net Gain / Loss	**$298.41**	**$298.41**
TOTAL REALIZED GAIN / LOSS	**$393.70**	**($1,199.24)**

Realized gain/loss information is provided for transactions in your account as of the trade date and excludes transactions where cost basis information has not been provided or is unavailable.

Gain/loss calculations do not include adjustments for wash sales that may have occurred on the last business day of this statement period. These wash sale adjustments, if any, will be reflected on your next statement.

Cost basis and realized gain/loss on statements are provided for informational purposes only and should not be used for tax purposes or otherwise relied upon without assistance of your tax advisor.

JPMorgan Core Advisory Portfolio (JPMCAP)

Holdings

The total cost basis for each security position and the unrealized gain/loss are provided solely for your convenience and may not be used for tax purposes or otherwise relied upon. If you have questions related to the tax treatment of your investments, please consult your tax advisor. Unrealized gain/loss total reflects only those positions for which a cost basis is available or has been provided. J.P. Morgan has not, and cannot, validate the cost basis of positions reported by you or your agent, and are displayed solely for your convenience. Information on this statement related to cost and gain/loss calculations does not include adjustments for wash sales that may have occurred on transactions pending settlement. These wash sale adjustments, if any, will be reflected on your next statement.

CASH & SWEEP FUNDS

Description	Acquisition Date	Quantity	Price	Market Value	Unit Cost	Cost Basis	Unrealized Gain/Loss	Accrued Income / Est. Annual Inc.
JPMORGAN IRA DEPOSIT		4,556.65	1	**4,556.65**				-- / --
SWEEP MGD JPMORGAN CHASE BANK NA EST. 30 DAY AVG YIELD 1.78% FDIC-INSURED SUBJECT TO APPLICABLE LIMITS NOT COVERED BY SIPC Symbol: QBERQ								
TOTAL CASH & SWEEP FUNDS				**$4,556.65**				-- / --

EQUITIES

Description	Acquisition Date		Quantity	Price	Market Value	Unit Cost		Cost Basis	Unrealized Gain/Loss		Accrued Income / Est. Annual Inc.
FIDELITY SALEM STR TR			*1,680.535	103.92	**174,641.20**	100.49	A	168,877.40	5,763.80		-- / 3,174.53
FIDELITY 500 INDEX FUND EST YIELD: 1.82% DIV & CAP	Long Term	N	1,549.696		161,044.41	100.49		155,729.36	5,315.05	LT	
GAIN REINVEST Symbol: FXAIX	Short Term	N	130.839		13,596.79	100.49		13,148.04	448.75	ST	
FIDELITY SALEM STR TR			*1,214.821	40.99	**49,795.51**	41.12	A	49,949.30	(153.79)		-- / 1,297.43
INTERNATIONAL INDEX FUND EST YIELD: 2.61% DIV & CAP	Long Term	N	1,074.426		44,040.72	41.12		44,176.74	(136.02)	LT	
GAIN REINVEST Symbol: FSPSX	Short Term	N	140.395		5,754.79	41.12		5,772.56	(17.77)	ST	
J P MORGAN EXCHANGE			507	25.02	**12,685.14**	23.73		12,033.43	651.71		-- / 302.17
TRADED FD TR BETABUILDERS CDA ETF EST YIELD: 2.38%	06 Sep 2018	N	168		4,203.36	24.19		4,063.55	139.81	LT	

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See additional footnotes on the last page of the Holdings section.

JPMorgan Core Advisory Portfolio (JPMCAP)

EQUITIES (continued)

Description	Acquisition Date		Quantity	Price	Market Value	Unit Cost		Cost Basis	Unrealized Gain/Loss		Accrued Income / Est. Annual Inc.
J P MORGAN EXCHANGE											
Symbol: BBCA	24 Oct 2018	N	173		4,328.46	22.56		3,902.88	425.58	ST	
	10 Apr 2019	N	166		4,153.32	24.5		4,067.00	86.32	ST	
J P MORGAN EXCHANGE	06 Sep 2018	N	167	24.71	**4,126.57**	24.32		4,061.89	64.68	LT	--
TRADED FD TR BETABUILDERS DEVELOPED ASIA EX JAPAN ETF EST YIELD: 4.05%											167.00
Symbol: BBAX											
J P MORGAN EXCHANGE			359	23.52	**8,443.68**	24.15		8,670.57	(226.89)		--
TRADED FD TR BETABUILDERS											278.58
EUROPE ETF EST YIELD:	06 Sep 2018	N	16		376.32	23.98		383.69	(7.37)	LT	
3.30%	10 Apr 2019	N	343		8,067.36	24.16		8,286.88	(219.52)	ST	
Symbol: BBEU											
J P MORGAN EXCHANGE			533	23.74	**12,653.42**	23.17		12,347.64	305.78		--
TRADED FD TR BETABUILDERS											73.55
JAPAN ETF EST YIELD: 0.58%	06 Sep 2018	N	371		8,807.54	23.5		8,718.84	88.70	LT	
Symbol: BBJP	24 Oct 2018	N	162		3,845.88	22.4		3,628.80	217.08	ST	
SIX CIRCLES TR		N	*2,175.348	9.29	**20,208.98**	8.88	A	19,310.61	898.37	ST	--
INTL UNCONSTRAINED EQUITY FD EST YIELD: 0.18% DIV & CAP GAIN REINVEST											36.44
Symbol: CIUEX											
SIX CIRCLES TR		N	*4,014.965	10.39	**41,715.49**	9.62	A	38,640.72	3,074.77	ST	--
U S UNCONSTRAINED EQUITY FD EST YIELD: 0.34% DIV & CAP GAIN REINVEST											142.93
Symbol: CUSUX											
TOTAL EQUITIES					**$324,269.99**			**$313,891.56**	**$10,378.43**		**--** **$5,472.64**

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JPMorgan Core Advisory Portfolio (JPMCAP)

FIXED INCOME

Description	Acquisition Date		Quantity	Price	Market Value	Unit Cost		Cost Basis	Unrealized Gain/Loss		Accrued Income / Est. Annual Inc.
ISHARES 20 PLUS YEAR TREASURY BOND ETF EST YIELD: 2.24% Symbol: TLT	23 Sep 2019	N	30	143.08	**4,292.40**	142.17	A	4,265.10	27.30	ST	-- / 96.09
ISHARES TRUST ISHARES 7 10 YEAR TREASURY BOND ETF EST YIELD: 2.21% Symbol: IEF	14 Feb 2019	N	38	112.47	**4,273.86**	104.48	A	3,970.24	303.62	ST	-- / 94.32
ISHARES TRUST ISHARES MBS ETF EST YIELD: 2.77% Symbol: MBB	05 Feb 2019	N	38	108.3	**4,115.40**	104.94	A	3,987.72	127.68	ST	-- / 113.85
LORD ABBETT INVT TR SHORT DURATION INCOME FD CL F3 EST YIELD: 4.00% DIV & CAP GAIN REINVEST Symbol: LOLDX		N	*1,981.315	4.22	**8,361.15**	4.15		8,225.13	136.02	ST	-- / 334.84
SIX CIRCLES TR ULTRA SHORT DURATION FD EST YIELD: 1.90% DIV & CAP GAIN REINVEST Symbol: CUSDX		N	*401.153	10	**4,011.53**	10.01	A	4,015.41	(3.88)	ST	-- / 76.22
VANGUARD BOND INDEX FD INC TOTAL BD MARKET IDX FDADMIRAL EST YIELD: 2.74% DIV & CAP GAIN REINVEST Symbol: VBTLX			*1,144.692	11.12	**12,728.98**	10.38	A	11,876.36	852.62		-- / 349.13
	Long Term	N	730.566		8,123.89	10.38		7,579.74	544.15	LT	
	Short Term	N	414.126		4,605.08	10.38		4,296.62	308.46	ST	
VANGUARD TOTAL INTERNATIONAL BOND ETF EST YIELD: 2.84% Symbol: BNDX			504	58.83	**29,650.32**	55.62		28,033.07	1,617.25		-- / 843.19
	06 Sep 2018	N	298		17,531.34	54.72		16,306.78	1,224.56	LT	
	05 Feb 2019	N	98		5,765.34	54.79		5,369.41	395.93	ST	
	23 Sep 2019	N	108		6,353.64	58.86		6,356.88	(3.24)	ST	

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JPMorgan Core Advisory Portfolio (JPMCAP)

FIXED INCOME (continued)

Description	Acquisition Date		Quantity	Price	Market Value	Unit Cost		Cost Basis	Unrealized Gain/Loss		Accrued Income / Est. Annual Inc.
WELLS FARGO FDS TR			*318.867	13.3	**4,240.93**	12.53	A	3,994.03	246.90		--
TOTAL RETURN BD FD CL R6											116.39
EST YIELD: 2.74% DIV & CAP	Long Term	N	300.135		3,991.80	12.53		3,759.41	232.39	LT	
GAIN REINVEST	Short Term	N	18.732		249.14	12.53		234.62	14.52	ST	
Symbol: WTRIX											
TOTAL FIXED INCOME					**$71,674.57**			**$68,367.06**	**$3,307.51**		--
											$2,024.02

ALTERNATIVE ASSETS

Please note: Important information regarding Alternative Assets including pricing and source of valuations is provided in the "Messages" section of Important Information. This security is classified as indicated based on best efforts by J.P. Morgan for convenience and informational purposes only and J.P. Morgan does not warrant the accuracy of these classifications. Please refer to investment documentation for a more accurate classification.

Description	Acquisition Date		Quantity	Price	Market Value	Unit Cost		Cost Basis	Unrealized Gain/Loss		Accrued Income / Est. Annual Inc.
BLACKSTONE ALTRNTV INVT		N	*1,150.552	10.77	**12,391.45**	10.67	A	12,281.01	110.44	ST	--
FDS ALTRNTV MULTI STRTGY FD											157.63
CL Y EST YIELD: 1.27% DIV											
& CAP GAIN REINVEST											
Symbol: BXMYX											
CRM MUT FD TR			*384.346	10.34	**3,974.14**	10.77	A	4,138.35	(164.21)		--
LNG SHT OPPORTUNITIES FD											--
INSTL DIV & CAP GAIN	Long Term	N	377.827		3,906.73	10.77		4,068.16	(161.43)	LT	
REINVEST	Short Term	N	6.519		67.41	10.77		70.19	(2.78)	ST	
Symbol: CRIHX											
EQUINOX FDS TR			*416.977	9.63	**4,015.49**	9.91	A	4,132.75	(117.26)		--
IPM SYSTEMATIC MACRO FD CL											56.71
I EST YIELD: 1.41% DIV &	Long Term	N	411.377		3,961.56	9.91		4,077.25	(115.69)	LT	
CAP GAIN REINVEST	Short Term	N	5.6		53.93	9.91		55.50	(1.57)	ST	
Symbol: EQIPX											
TOTAL ALTERNATIVE ASSETS [3]					**$20,381.08**			**$20,552.11**	**($171.03)**		--
											$214.33

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Holdings (continued)

Total Account Value : $420,882.29 [3]

Unless otherwise noted, all positions are held in your cash account. F - TEFRA Account G - Good Faith Account I - Income Account L - Non Purpose Loan Account M - Margin Account R - DVP/RVP Account S - Short Account

AI Pricing Method: a – Net Investment b – Appraised Value c – The firm did not receive price information compliant with applicable reporting requirements.

A - Average Cost B - Adjusted for Amortization or Accretion D - Acquisition Date = Date of Death E - Adjusted for Option Exercise or Assignment K - Gifted Security LT - Long Term MT - Mixed Term N - Noncovered Provide - Please provide this information ST - Short Term T - Cost Basis provided by Third Party W - Adjusted for Wash Sale

3 *Important information regarding Alternative Assets including pricing and source of valuations is provided in the "Messages" section of Important Information.*

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Activity

TRADE AND INVESTMENT ACTIVITY

For transaction descriptions that direct you to "See Note on Back", the notes will be located in the "Messages" section within "Important Information".

Trade Date / Settle Date		Transaction / Closing Method	Description	Quantity	Price	Cost	Proceeds	Cost Basis	Realized Gain/Loss
03 Sep 2019 03 Sep 2019		REINVEST	**LORD ABBETT INVT TR** SHORT DURATION INCOME FD CL F3 REINVEST PRICE $ 4.23 Symbol: LOLDX	6.232		(26.36)			
03 Sep 2019 03 Sep 2019		REINVEST	**VANGUARD BOND INDEX FD** INC TOTAL BD MARKET IDX FDADMIRAL REINVEST PRICE $ 11.21 Symbol: VBTLX	2.67		(29.93)			
03 Sep 2019 03 Sep 2019		REINVEST	**WELLS FARGO FDS TR** TOTAL RETURN BD FD CL R6 REINVEST PRICE $ 13.39 Symbol: WTRIX	1.477		(19.78)			
23 Sep 2019 24 Sep 2019	N A	SELL FIFO	**VANGUARD BOND INDEX FD** INC TOTAL BD MARKET IDX FDADMIRAL SOLICITED TAG NUMBER 90184 LT GAIN 37.09 Symbol: VBTLX CAPACITY C1	(51.1680)	11.1 Principal		567.97 567.97	530.88	37.09
23 Sep 2019 24 Sep 2019	N A	SELL FIFO	**WELLS FARGO FDS TR** TOTAL RETURN BD FD CL R6 SOLICITED TAG NUMBER 90248 LT GAIN 261.32 Symbol: WTRIX CAPACITY C1	(351.1020)	13.27 Principal		4,659.12 4,659.12	4,397.80	261.32
23 Sep 2019 25 Sep 2019		BUY	**ISHARES 20 PLUS YEAR** TREASURY BOND ETF OFFERING MATERIALS ENCLOSED OR TO FOLLOW VIA E-MAIL FOR ONLINE DELIVERY OR VIA POSTAL SERVICE AVG PRICE SHOWN- SEE DISCLOSURE ON REVERSE*** ROME: WHIPANYAAL19092364785 TAG NUMBER 67258 Symbol: TLT CAPACITY C8	30	142.17 Principal	(4,265.10) (4,265.10)			

See additional footnotes on the last page of this account.

JPMorgan Core Advisory Portfolio (JPMCAP)

TRADE AND INVESTMENT ACTIVITY (continued)

Trade Date / Settle Date		Transaction / Closing Method	Description	Quantity	Price	Cost	Proceeds	Cost Basis	Realized Gain/Loss
23 Sep 2019 25 Sep 2019	N A	SELL FIFO	**VANGUARD SHORT TERM BOND** ETF AVG PRICE SHOWN- SEE DISCLOSURE ON REVERSE*** ROME: WHIPANYAAH19092322374 TAG NUMBER H7439 ST GAIN 95.29 Symbol: BSV CAPACITY C8	(51.0)	80.7 Principal SEC Fee		4,115.61 4,115.70 (0.09)	4,020.32	95.29
23 Sep 2019 25 Sep 2019		BUY	**VANGUARD TOTAL** INTERNATIONAL BOND ETF OFFERING MATERIALS ENCLOSED OR TO FOLLOW VIA E-MAIL FOR ONLINE DELIVERY OR VIA POSTAL SERVICE AVG PRICE SHOWN- SEE DISCLOSURE ON REVERSE*** ROME: WHIPANYAAD19092367298 TAG NUMBER N5878 Symbol: BNDX CAPACITY C8	108	58.86 Principal	(6,356.88) (6,356.88)			
30 Sep 2019 30 Sep 2019		REINVEST	**SIX CIRCLES TR** ULTRA SHORT DURATION FD REINVEST PRICE $ 10.00 Symbol: CUSDX	0.869		(8.69)			
Total Securities Bought & Sold						**($10,621.98)**	**$9,342.70**		
Total Other Investment Activity						**($84.76)**			
TOTAL TRADE AND INVESTMENT ACTIVITY						**($10,706.74)**	**$9,342.70**		

INCOME

Taxable and non-taxable income classifications are based on the characteristics of the underlying securities and not the taxable status of the account.

Income from Taxable Investments

Date	Transaction	Description	Quantity	Rate	Debit Amount	Credit Amount	Net Amount
03 Sep 2019	DIVIDEND	**LORD ABBETT INVT TR** SHORT DURATION INCOME FD CL F3 RECORD 08/30/19 PAY				26.36	26.36

JPMorgan Core Advisory Portfolio (JPMCAP)

Income from Taxable Investments (continued)

Date	Transaction	Description	Quantity	Rate	Debit Amount	Credit Amount	Net Amount
		LORD ABBETT INVT TR 08/30/19 Symbol: LOLDX					
03 Sep 2019	DIVIDEND	**VANGUARD BOND INDEX FD** INC TOTAL BD MARKET IDX FDADMIRAL RECORD 08/31/19 PAY 08/30/19 Symbol: VBTLX				29.93	29.93
03 Sep 2019	DIVIDEND	**WELLS FARGO FDS TR** TOTAL RETURN BD FD CL R6 RECORD 08/30/19 PAY 08/30/19 Symbol: WTRIX				19.78	19.78
06 Sep 2019	DIVIDEND	**VANGUARD SHORT TERM BOND** ETF CASH DIV ON 51 SHS REC 09/04/19 PAY 09/06/19 Symbol: BSV	51	0.1557		7.94	7.94
06 Sep 2019	DIVIDEND	**VANGUARD TOTAL** INTERNATIONAL BOND ETF CASH DIV ON 396 SHS REC 09/04/19 PAY 09/06/19 Symbol: BNDX	396	0.0534		21.15	21.15
09 Sep 2019	DIVIDEND	**ISHARES TRUST** ISHARES 7 10 YEAR TREASURY BOND ETF CASH DIV ON 38 SHS REC 09/04/19 PAY 09/09/19 Symbol: IEF	38	0.1902		7.23	7.23
09 Sep 2019	DIVIDEND	**ISHARES TRUST** ISHARES MBS ETF CASH DIV ON 38 SHS REC 09/04/19 PAY 09/09/19 Symbol: MBB	38	0.2651		10.08	10.08
27 Sep 2019	DIVIDEND	**J P MORGAN EXCHANGE** TRADED FD TR BETABUILDERS CDA ETF CASH DIV ON 507 SHS REC 09/25/19 PAY 09/27/19 Symbol: BBCA	507	0.1637		83.02	83.02

See additional footnotes on the last page of this account.

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JPMorgan Core Advisory Portfolio (JPMCAP)

Income from Taxable Investments (continued)

Date	Transaction	Description	Quantity	Rate	Debit Amount	Credit Amount	Net Amount
27 Sep 2019	DIVIDEND	**J P MORGAN EXCHANGE** TRADED FD TR BETABUILDERS DEVELOPED ASIA EX JAPAN ETF CASH DIV ON 167 SHS REC 09/25/19 PAY 09/27/19 Symbol: BBAX	167	0.3133		52.34	52.34
27 Sep 2019	DIVIDEND	**J P MORGAN EXCHANGE** TRADED FD TR BETABUILDERS EUROPE ETF CASH DIV ON 359 SHS REC 09/25/19 PAY 09/27/19 Symbol: BBEU	359	0.1456		52.30	52.30
30 Sep 2019	DIVIDEND	**SIX CIRCLES TR** ULTRA SHORT DURATION FD RECORD 09/26/19 PAY 09/30/19 Symbol: CUSDX				8.69	8.69
Total Dividends						**$318.82**	**$318.82**
TOTAL INCOME FROM TAXABLE INVESTMENTS						**$318.82**	**$318.82**

Total Income	**$318.82**	**$318.82**

FEES

Date	Description	Debit Amount	Credit Amount
23 Sep 2019	**Advisory Fee**	(411.97)	
23 Sep 2019	**ERISA Manager Fee Rebate**		4.13
30 Sep 2019	**MANAGED RETIREMENT ACCT** CREDIT FOR 07/2019		0.09
30 Sep 2019	**MANAGED RETIREMENT ACCT** CREDIT FOR 08/2019		0.26
TOTAL FEES [1]		**($411.97)**	**$4.48**

1 *Account fees, management fees, and debit interest are included. Trade related fees charged by brokers and commissions impact the total cost or proceeds of your trades and are not included here.*

See additional footnotes on the last page of this account.

JPMorgan Core Advisory Portfolio (JPMCAP)

SWEEP PROGRAM ACTIVITY

JPMORGAN IRA DEPOSIT SWEEP MGD, JPMORGAN CHASE BANK NA, Symbol: QBERQ

Date	Transaction	Description	Quantity	Price	Debit Amount	Credit Amount
OPENING BALANCE			5,999.74	1		
03 Sep 2019	REINVEST	MONTHLY INTEREST REINVESTED	9.62		(9.62)	
06 Sep 2019	PURCHASE	INTRA-DAY DEPOSIT	29.09		(29.09)	
09 Sep 2019	PURCHASE	INTRA-DAY DEPOSIT	17.31		(17.31)	
24 Sep 2019	PURCHASE	INTRA-DAY DEPOSIT	4,819.25		(4,819.25)	
25 Sep 2019	REDEMPTION	INTRA-DAY WITHDRWAL	(6,506.370)			6,506.37
27 Sep 2019	PURCHASE	INTRA-DAY DEPOSIT	187.66		(187.66)	
30 Sep 2019	PURCHASE	INTRA-DAY DEPOSIT	0.35		(0.35)	
CLOSING BALANCE			**4,556.65**	**1**		
SWEEP PROGRAM ACTIVITY					**($5,063.28)**	**$6,506.37**

JPMORGAN IRA DEPOSIT SWEEP MGD, JPMORGAN CHASE BANK NA, Symbol: QBERQ

Date	Transaction	Description	Quantity	Price	Debit Amount	Credit Amount
03 Sep 2019	INTEREST	MONTHLY INTEREST 08/01-08/30				9.62
Sweep Program Dividend/Interest						**$9.62**

Total Sweep Program Activity	**($5,063.28)**	**$6,506.37**

JPMorgan Core Advisory Portfolio (JPMCAP)

Realized Gain / Loss Detail - Year To Date

Cost Basis, Realized Gain / Loss, and holding period information may not reflect all adjustments necessary for tax reporting purposes. Tax payers should verify such information against their own records when calculating reportable gain or loss resulting from a sale, redemption or exchange. Please contact your tax advisor for additional information as neither J.P. Morgan nor any of its affiliates provides tax advice related to the accounts referenced in these statement(s). J.P. Morgan makes no warranties with respect to and specifically disclaims any liability arising out of a customer's use of or any tax position taken in reliance upon such information. Proceeds information excludes accrued interest.

Information on this statement related to cost and gain/loss calculations does not include adjustments for wash sales that may have occurred on the last business day of this statement period. These wash sale adjustments, if any, will be reflected on your next statement. Cost Basis and Realized Gain / Loss on statements are provided for informational purposes only and should not be used for tax purposes or otherwise relied upon without the assistance of your tax advisor.

SHORT TERM GAIN / LOSS DETAILS

Acquisition Date / Date Sold		Closing Method	Description	Quantity	Proceeds	Cost Basis		Realized Gain/Loss
06 Sep 2018 14 Feb 2019	N	FIFO	**CAUSEWAY CAP MGMT TR** INTL VALUE FD INSTL CL Symbol: CIVIX	113.828	1,669.86	1,813.56	A	(143.70)
06 Sep 2018 10 Apr 2019	N	FIFO	**CAUSEWAY CAP MGMT TR** INTL VALUE FD INSTL CL Symbol: CIVIX	388.236	5,936.13	6,185.57	A	(249.44)
06 Sep 2018 10 Apr 2019	N	FIFO	**FIDELITY SALEM STR TR** FIDELITY 500 INDEX FUND Symbol: FXAIX	157.655	15,823.86	15,840.79	A	(16.93)
06 Sep 2018 10 Apr 2019	N	FIFO	**HARRIS ASSOC INVT TR** OAKMARK INTL FD INSTL CL Symbol: OANIX	155.536	3,633.32	3,896.82	A	(263.50)
06 Sep 2018 05 Feb 2019	N	FIFO	**HARRIS ASSOC INVT TR** OAKMARK INTL FD INSTL CL Symbol: OANIX	80.804	1,816.48	2,024.48	A	(208.00)
06 Sep 2018 14 Feb 2019	N	FIFO	**HARRIS ASSOC INVT TR** OAKMARK INTL FD INSTL CL Symbol: OANIX	87.889	1,922.14	2,201.98	A	(279.84)
06 Sep 2018 26 Aug 2019	N	FIFO	**J P MORGAN EXCHANGE** TRADED FD TR BETABUILDERS EUROPE ETF Symbol: BBEU	153	3,480.67	3,669.04		(188.37)
06 Sep 2018 04 Mar 2019	N	FIFO	**J P MORGAN EXCHANGE** TRADED FD TR BETABUILDERS	148	3,338.85	3,478.13		(139.28)

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JPMorgan Core Advisory Portfolio (JPMCAP)

SHORT TERM GAIN / LOSS DETAILS (continued)

Acquisition Date / Date Sold		Closing Method	Description	Quantity	Proceeds	Cost Basis		Realized Gain/Loss
			J P MORGAN EXCHANGE JAPAN ETF Symbol: BBJP					
06 Sep 2018 05 Feb 2019	N	FIFO	**VANGUARD FIXED INCOME** SECS INTER TERM INVT GRADE FD ADMIRAL CL Symbol: VFIDX	864.633	8,214.02	8,152.79	A	61.23
06 Sep 2018 05 Feb 2019	N	FIFO	**WCM FOCUSED INTERNATIONAL** GROWTH CL INSTITUTIONAL Symbol: WCMIX	139.471	2,101.83	2,248.10	A	(146.27)
06 Sep 2018 10 Apr 2019	N	FIFO	**WCM FOCUSED INTERNATIONAL** GROWTH CL INSTITUTIONAL Symbol: WCMIX	375.142	6,051.04	6,046.84	A	4.20
01 Oct 2018 05 Feb 2019	N	FIFO	**VANGUARD FIXED INCOME** SECS INTER TERM INVT GRADE FD ADMIRAL CL Symbol: VFIDX	1.9	18.05	17.92	A	0.13
30 Oct 2018 05 Feb 2019	N	FIFO	**VANGUARD FIXED INCOME** SECS INTER TERM INVT GRADE FD ADMIRAL CL Symbol: VFIDX	2.04	19.38	19.24	A	0.14
01 Nov 2018 05 Feb 2019	N	FIFO	**VANGUARD FIXED INCOME** SECS INTER TERM INVT GRADE FD ADMIRAL CL Symbol: VFIDX	0.512	4.86	4.83	A	0.03
16 Nov 2018 14 Jun 2019	N	FIFO	**DIAMOND HILL FDS** LONG SHORT FD CL Y Symbol: DIAYX	118.68005	3,131.97	3,120.63	A	11.34
03 Dec 2018 05 Feb 2019	N	FIFO	**VANGUARD FIXED INCOME** SECS INTER TERM INVT GRADE FD ADMIRAL CL Symbol: VFIDX	2.595	24.65	24.47	A	0.18
07 Dec 2018 10 Apr 2019	N	FIFO	**WCM FOCUSED INTERNATIONAL** GROWTH CL INSTITUTIONAL Symbol: WCMIX	18.447	297.55	297.35	A	0.20

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JPMorgan Core Advisory Portfolio (JPMCAP)

SHORT TERM GAIN / LOSS DETAILS (continued)

Acquisition Date / Date Sold		Closing Method	Description	Quantity	Proceeds	Cost Basis		Realized Gain/Loss
07 Dec 2018 10 Apr 2019	N	FIFO	**WCM FOCUSED INTERNATIONAL** GROWTH CL INSTITUTIONAL Symbol: WCMIX	0.62	10.00	9.99	A	0.01
07 Dec 2018 10 Apr 2019	N	FIFO	**WCM FOCUSED INTERNATIONAL** GROWTH CL INSTITUTIONAL Symbol: WCMIX	1.891	30.50	30.48	A	0.02
14 Dec 2018 14 Jun 2019	N	FIFO	**DIAMOND HILL FDS** LONG SHORT FD CL Y Symbol: DIAYX	5.18112	136.73	136.23	A	0.50
14 Dec 2018 10 Apr 2019	N	FIFO	**HARRIS ASSOC INVT TR** OAKMARK INTL FD INSTL CL Symbol: OANIX	7.741	180.83	193.95	A	(13.12)
14 Dec 2018 10 Apr 2019	N	FIFO	**HARRIS ASSOC INVT TR** OAKMARK INTL FD INSTL CL Symbol: OANIX	15.758	368.11	394.80	A	(26.69)
17 Dec 2018 04 Jan 2019	N	FIFO	**VANGUARD SHORT TERM BOND** ETF Symbol: BSV	48	3,773.71	3,758.40	A	15.31
21 Dec 2018 10 Apr 2019	N	FIFO	**CAUSEWAY CAP MGMT TR** INTL VALUE FD INSTL CL Symbol: CIVIX	13.956	213.39	222.36	A	(8.97)
21 Dec 2018 10 Apr 2019	N	FIFO	**CAUSEWAY CAP MGMT TR** INTL VALUE FD INSTL CL Symbol: CIVIX	4.031	61.63	64.22	A	(2.59)
31 Dec 2018 14 Jun 2019	N	FIFO	**DIAMOND HILL FDS** LONG SHORT FD CL Y Symbol: DIAYX	0.98683	26.04	25.95	A	0.09
02 Jan 2019 05 Feb 2019	N	FIFO	**VANGUARD FIXED INCOME** SECS INTER TERM INVT GRADE FD ADMIRAL CL Symbol: VFIDX	2.667	25.34	25.14	A	0.20
01 Feb 2019 05 Feb 2019	N	FIFO	**VANGUARD FIXED INCOME** SECS INTER TERM INVT GRADE	2.503	23.78	23.60	A	0.18

See additional footnotes on the last page of this account.

Please read the important disclosures at the end of the statement. For questions, please contact us using the information provided on the front of this statement.

JPMorgan Core Advisory Portfolio (JPMCAP)

SHORT TERM GAIN / LOSS DETAILS (continued)

Acquisition Date / Date Sold		Closing Method	Description	Quantity	Proceeds	Cost Basis		Realized Gain/Loss
			VANGUARD FIXED INCOME FD ADMIRAL CL Symbol: VFIDX					
04 Mar 2019 23 Sep 2019	N	FIFO	**VANGUARD SHORT TERM BOND** ETF Symbol: BSV	51	4,115.61	4,020.32	A	95.29
TOTAL SHORT TERM GAIN / LOSS					**$66,450.33**	**$67,947.98**		**($1,497.65)**

LONG TERM GAIN / LOSS DETAILS

Acquisition Date / Date Sold		Closing Method	Description	Quantity	Proceeds	Cost Basis		Realized Gain/Loss
06 Sep 2018 23 Sep 2019	N	FIFO	**VANGUARD BOND INDEX FD** INC TOTAL BD MARKET IDX FDADMIRAL Symbol: VBTLX	51.168	567.97	530.88	A	37.09
06 Sep 2018 23 Sep 2019	N	FIFO	**WELLS FARGO FDS TR** TOTAL RETURN BD FD CL R6 Symbol: WTRIX	351.102	4,659.12	4,397.80	A	261.32
TOTAL LONG TERM GAIN / LOSS					**$5,227.09**	**$4,928.68**		**$298.41**

Total Realized Gain / Loss	**$71,677.42**	**$72,876.66**	**($1,199.24)**

Capacity
C1, C2, C3, C4, C5, C8, C9 - JPMS, as indicated on this statement, acted as Agent for your account unless otherwise indicated.
C6 - JPMS, as indicated on this statement, acted as Agent for both buyer and seller, charging a commission or commission equivalent to both parties. The source and any remuneration charged in the transaction will be furnished upon written request.
C7 -JPMS, as indicated on this statement, acted as Principal.
CA -This trade was executed by your broker with JPMS acting as your prime broker. Contact your executing broker for trade details.

A - Average Cost B - Adjusted for Amortization or Accretion D - Acquisition Date = Date of Death E - Adjusted for Option Exercise or Assignment K - Gifted Security LT - Long Term MT - Mixed Term N - Noncovered Provide - Please provide this information ST - Short Term T - Cost Basis provided by Third Party W - Adjusted for Wash Sale

Closing Methods: MLMG - Maximum Loss, Minimum Gain LIFO - Last In, First Out FIFO - First In, First Out HC - High Cost LC - Low Cost LTHC - Long Term, High Cost PRO - Pro Rata VSP - Specific Match (the closing transaction was specifically matched to this lot)

Additional Contact Information

Account(s)	Contact	Custodian
JPMS LLC IRA (95966373)	**Jessica Arana** (Private Client Advisor) (702) 352 0525	**J.P. Morgan Securities LLC** **Member FINRA and SIPC** 131 South Dearborn Street, IL1-0291 4th FLOOR Chicago, IL, 60603-5506 (888) 994 5626 www.chase.com

Messages

ALTERNATIVE INVESTMENTS

Investments referred to as "Alternative Investments" include, but are not limited to, direct participation programs, private equity investments, pooled private investments (such as limited partnerships and limited liability companies), non-publically traded real estate investment trusts, private debt and hedge funds. While these investment types are each different, they do share some common characteristics such as: they are generally illiquid securities that are not listed on any exchange; there is a limited or no secondary trading market for these securities; and, there are typically restrictions on the timing and availability for redemptions. Additionally, private investment contracts, which would include most Alternative Investments, are ineligible for SIPC protection. Valuations of these investments are difficult to obtain and verify. The valuations of these investments presented on this statement have been obtained, unless otherwise noted, from the management, administrator or sponsor of each program (collectively, "Management"), or from a third-party vendor. These valuations have not been independently verified by J.P. Morgan Securities LLC ("JPMS") and do not represent the actual terms at which transactions or securities could be bought or sold or new transactions could be entered into or the actual terms on which existing transactions could be liquidated as of the date of this statement. Values are estimates only and may represent a value as of a date no greater than 18 months prior to the date of this statement. If an estimated value is not provided, valuation information is not available. In some instances, the valuations reflected on this statement may represent original cost, which information may or may not have been provided by Management or the third-party vendor. Valuations are provided for information purposes only and are intended solely for your own use. Please contact us if you wish to obtain additional or more specific information regarding the source(s) of the valuations. Alternative Investments may be reflected on your statement even though they may be held by a third party unaffiliated with JPMS. In such cases, unless JPMS otherwise agrees, JPMS has no responsibility for the verification, valuation, safekeeping or management of those assets.

In as much valuations may have been provided by Management of any program, you should review the operative documentation for each investment for the specific valuation methodology used by Management of that investment. JPMS expressly disclaims any responsibility for (1) the accuracy of the information and the methodology used by the Management in deriving valuations; (2) any errors or omissions in compiling or disseminating the valuations; and, (3) any use to which the valuations are put.

SPECIFIC NOTICE FOR RETIREMENT ACCOUNTS: In the case of Alternative Investments, the annual fair market valuations ("FMV") of your account assets are reported by JPMS based on the best information available to JPMS (or its vendor) as of December 31 of the reporting year. If a more accurate valuation is subsequently obtained, the information reported to the IRS may differ from that reported to you on the earlier date and the adjusted value may affect various calculations including, but not limited to, possible required minimum distributions ("RMD"). If you are subject to a RMD, JPMS may notify you of the adjusted value. Additionally, certain Alternative Investments (e.g., private equity funds) may require capital calls of their investors. If capital calls are required in connection with assets held by your retirement account, the funds to meet such calls must be paid from your retirement account. The preceding information should not be construed as tax or investment advice. Please consult your tax or investment advisor for questions concerning your tax or financial situation, including any questions regarding the effect of these characteristics of Alternative Investments.

Special Notice for DPP and REIT Securities: DPP or REIT securities are not listed on a national securities exchange, are generally illiquid and, even if a customer is able to sell the securities, the price received may be less than the per share estimated value provided in the account statement.

Messages (continued)

TRADE AND INVESTMENT ACTIVITY DESCRIPTION NOTES

"S" The transaction described is subject to the U.S Treasury or Agency Debt and Agency MBS fails charge trading practice published by TMPG and SIFMA at 'http://www.sifma.org/capital_markets/docs/Fails-Charge-Trading-Practice.pdf' and 'http://www.sifma.org/Services/Standard-Forms-and-Documentation/Securitized-Products/Securitized-Products-Fails-Charge-Trading-Practice'

"I" J.P.Morgan Securities LLC (JPMS) receives compensation for directing customer orders for equity securities. The source and nature of such compensation received on this transaction, if any, will be furnished to you upon written request.

"U" You may be eligible for breakpoint discounts based on the size of your purchase, current holdings or future purchases. The sales charge you paid may differ slightly from the Prospectus disclosed rate due to rounding calculations. Please refer to the Prospectus, Statement of Additional Information or contact us for further information.

"V" A paper copy of the offering document relating to this transaction is available, upon request, by calling 1-866-803-9204 during normal business hours.

"W" The securities have not been registered under the US Securities Act of 1933, any may only be offered and sold pursuant to registration under the 1933 Act or an available exemption therefrom or in accordance with Regulation S.

"X" These securities have not been registered under the US Securities Act of 1933, and were issued pursuant to the exemption provided by Section 3(c)(7) of the Investment Company Act of 1940. The securities may only be offered and sold (i) pursuant to registration under the 1933 Act of an exemption there from and (ii) in compliance with the provisions of Section 3(c)(7).

"Y" To obtain a paper copy of the official statement, please call 877-430-3544 for domestic accounts or 347-643-6233 for international accounts. Alternatively, you may call the number on this statement.

"Z" JPMS or an affiliate is a market maker in the security. As a market maker, JPMS or its affiliate may have acted as principal, may have had a long or short position in the security, and may have profited or lost in connection with the transaction.

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Messages (continued)

MANAGER ALLOCATION

JPMorgan Chase & Co. and its affiliates are referred to below as JPMC.

JPMC Managed Products include mutual funds, exchange-traded funds, other registered funds and hedge funds managed by J.P. Morgan and structured products issued by J.P. Morgan (excludes Six Circles Funds and J.P. Morgan Cash and Liquidity Products).

Six Circles Funds are mutual funds managed by J.P. Morgan and sub-advised by third parties, and for which J.P. Morgan does not retain a fee for fund management or other fund services.

JPMC Separately Managed Accounts include fixed income, equity, and alternative separately managed accounts managed by J.P. Morgan.

Third-Party Managed & Other include mutual funds, exchange traded funds, hedge funds, and separately managed accounts managed by parties other than J.P. Morgan; separately managed accounts managed by J.P. Morgan where a party other than J.P. Morgan is the appointed investment advisor; structured products and exchange traded notes issued by parties other than J.P. Morgan; investment conduits investing in non-J.P. Morgan managed hedge funds, where J.P. Morgan is solely administrator to the conduit; and other investments not managed or issued by J.P. Morgan.

JPMC Cash & Liquidity Funds include cash, J.P. Morgan deposit sweeps and J.P. Morgan money market mutual funds.

Manager Allocation for certain advisory accounts in which J.P. Morgan has the discretion to employ J.P. Morgan and third party investment portfolios will reflect the expected targeted allocations for each investment portfolio, rather than the actual allocations. While these targets are generally indicative of actual holdings, differences may arise due to factors such as relative asset performance prior to portfolio rebalancing. J.P. Morgan Core Advisory Portfolio (JPMCAP) models that contain a Separately Managed Account (SMA) component and Select Advisory Strategies (SAS) model-based strategies utilize the expected target allocations for each investment portfolio.

FRACTIONAL SHARES

Fractional Shares will not be adjusted for certain corporate actions. Any remaining position less than 1 share will be liquidated.

WITHHOLDING NOTICE

The distributions you receive from your retirement account are subject to Federal income tax withholding unless you elect not to have withholding apply. You may elect not to have withholding apply to your distribution payments by completing the "Tax Withholding" section on the Retirement Account Distribution Form.

If you do not complete the "Withholding" section, Federal Income tax will be withheld from the amount withdrawn at a rate of 10%. If your account is a Qualified Plan, 20% withholding is required from any eligible rollover distribution. If you elect not to have withholding apply to your distribution payments or if you do not have enough Federal income tax withheld from your distribution, you may be responsible for payment of estimated tax. You may incur penalties and interest under the estimated tax rules, if withholding and estimated tax payments are not sufficient.

Your withholding election shall remain in effect until revoked by submitting a new withholding election on a new Retirement Account Distribution Form.

If you have requested a recurring or future-dated distribution, you may be eligible to receive partial payments in the event of insufficient funds. Withholding on any partial payment will be made in accordance with the withholding election for your recurring or future-dated distribution except that if you elected to withhold a dollar amount, this amount will be adjusted to equal the partial payment times your original withholding ratio (your elected withholding amount divided by the gross amount of your recurring or future-dated distribution).

Please consult your tax advisor regarding how your withholding election might affect your personal taxation.

IMPORTANT INFORMATION REGARDING PURCHASES INDICATED AS AVERAGE PRICE

*** Your orders are processed in either (1) one execution at the confirmed price or (2) more than one execution, in which case the confirmed price is an average price. Details regarding the actual prices are available by your J.P. Morgan representative.

Messages (continued)

EMPLOYEE COMPENSATION

Employees of JPMorgan Chase Bank, N.A. may be eligible to receive compensation when they refer clients to J.P. Morgan Securities LLC (JPMS). Additionally, other JPMS employees who assist or consult with your advisor may be compensated when you make certain investment purchases. These compensation payments, if made, will not increase your account fees.

MARGIN ACCOUNTS

Securities and other assets in your account are the firm's collateral for any margin loan made to you. If the securities and other assets in your account decline in value, so does the value of the collateral supporting your loan, and, as a result, the firm can take action, such as issue a margin call and/or sell securities or other assets in any of your accounts held with the member, in order to maintain the required equity in the account. It is important that you fully understand the risks involved in trading securities on margin. These risks include the following:

- You can lose more funds than you deposit in the margin account.
- The firm can force the sale of securities or other assets in your account(s).
- The firm can sell your securities or other assets without contacting you.
- You are not entitled to choose which securities or other assets in your account(s) are liquidated or sold to meet a margin call.
- The firm can increase its "house" maintenance margin requirements at any time and is not required to provide you advance written notice.
- You are not entitled to an extension of time on a margin call.

Further, if you have a margin account with us, as permitted by law we may use certain securities in your account for, among other things, settling short sales and lending the securities for short sales, and as a result may receive compensation in connection therewith.

LARGE TRADE REPORTING

The U.S. Securities and Exchange Commission ("SEC") Rule 13h-1 Large Trader Reporting System requires U.S. and non-U.S. market participants who meet the definition of "Large Trader"* as of October 3, 2011, or at any point thereafter to:
(i) File an electronic Form 13H with the SEC (via EDGAR) to obtain a large trader identification number (LTID); and
(ii) Promptly disclose to U.S. broker-dealers that execute trades or carry accounts for the Large Trader, their LTIDs and the accounts to which the LTIDs apply.
*A "Large Trader" is a legal entity or natural person who, directly or indirectly, through the exercise of investment discretion, effects transactions in NMS securities that equal or exceed either: (i) 2 million shares or $20 million during any calendar day; OR (ii) 20 million shares or $200 million over any calendar month.
If you are a "Large Trader" and have completed a Form 13H, you will receive an LTID from the SEC. In order to ensure that LTID's are captured and reported as required under the Rule, you are required to promptly report your LTID to your broker and identify each account to which the LTID should be applied. If you have any questions, please call the appropriate number on the front of this statement.

ELECTRONIC FUNDS TRANSFER NOTICE

In case of errors or questions about electronic fund transfers to/from your account (via the Automated Clearing House (ACH) Network), your account statement or transaction record, please call us at 1-800-392-5749 or write to us at J.P. Morgan Securities LLC, Mail Code: IL1-0291, 4th Floor, 131 South Dearborn, Chicago, IL 60603-5506.
Please provide the following information:
1. Your name and account number,
2. The dollar amount of the suspected error, and
3. A description of the error or the transfer you are unsure about; please explain as clearly as you can why you believe it is an error or why you need more information.

Please note:
We must hear from you no later than 60 days after we sent the first account statement on which the problem or error appeared. If you tell us verbally, we may require that you send us your complaint or question in writing within 10 business days. We will determine whether an error occurred within 10 business days after we hear from you and will correct any error promptly. If we need more time, however, we may take up to 45 days to investigate your complaint or question; for errors involving new accounts or foreign-initiated transactions, we may take up to 90 days to investigate. If we decide to do this, we will credit your account within 10 business days for the amount you think is in error (new accounts may take up to 20 days). However, if we ask you to put your complaint or question in writing and we do not receive it within 10 business days, we may not credit your account. If we determine at the conclusion of the investigation that there was no error, we will charge your account for the credited amount. We will tell you the results within three business days after completing our investigation. If we decide that there was no error, we will send you a written explanation. You may ask for copies of the documents that we used in our investigation.

Messages (continued)

J.P. MORGAN SECURITIES LLC NET CAPITAL REQUIREMENTS

As of July 31, 2019, J.P. Morgan Securities LLC's net capital of $20.6 billion exceeded the minimum regulatory net capital requirement of $3.5 billion by $17.1 billion.

If you wish to obtain the June 30, 2019, unaudited Statement of Financial Condition, the document may be viewed by accessing http://investor.shareholder.com/jpmorganchase/financial-condition.cfm, or call 1.212.622.6350 to request the document be mailed to you at no cost.

COMPENSATION RECEIVED IN CONNECTION WITH MUTUAL FUND TRANSACTIONS

Advisors, distributors or other affiliates of certain mutual funds (which include money market and non-money market funds) may enter into arrangements to pay brokers that distribute their shares for administrative, technological or other services, including marketing and other support services provided to such funds or their affiliates. These fees, commonly referred to as "revenue sharing," are separate from, and in addition to, any shareholder servicing or distribution fees that a mutual fund pays out of its own assets pursuant to its Rule 12b-1 plan and other expenses which are described in a fund's prospectus fee table. Revenue sharing fees are paid out of the assets of the fund affiliate and not from the fund's assets and, therefore, have no impact on a fund's expense ratio or yield.

J.P. Morgan Securities LLC ("JPMS") receives compensation from fund families or their affiliates for providing certain administrative and clearing services. These payments are calculated either based on a percentage of the average dollar value of the fund assets held by JPMS in customer accounts or based on the number of mutual fund positions in the accounts. These fees may be paid from fund assets or may be subsidized in whole or in part by the advisor, distributor or other affiliates of the fund through revenue sharing. Revenue sharing payments are negotiated separately with each fund family and not all fund families pay the same amount or pay according to the same formula. There is, therefore, a potential conflict of interest in the form of an additional financial incentive to J.P. Morgan for making available to customer mutual funds whose affiliates enter into revenue sharing arrangements.

For the administrative and clearing services noted above, JPMS may receive revenue sharing payments of up to 0.50% per year or the average daily assets of fund shares carried in customer's accounts at JPMS and/or a rate of up to $21 per year per mutual fund position in each account, as applicable. To establish such arrangements with a fund company, JPMS has either entered into an agreement directly with the fund company or has entered into an agreement with a service provider which, in turn, has entered into an agreement directly with the fund company. Please note that the actual amount received by JPMS may be subject to periodic waiver by fund families and such waivers may reduce the actual amount received by JPMS. Funds whose affiliates do not make such revenue sharing payments to JPMS are generally not offered or recommended by JPMS, and in some cases, have higher returns or yields than funds whose affiliates do make revenue sharing payment. Compensation JPMS receives under these arrangements may be passed on to affiliates or non-affiliates of JPMS.

In addition to these payments, JPMS may receive additional revenue sharing payments from certain fund families. Most funds offered by JPMS make these additional revenue sharing payments based upon the percentage of a client's total purchase amount in one of these funds. Percentage payments to JPMS generally range from 0.08% to 0.25%. If, for example, a client invested $10,000 in a fund that paid 0.25%, the fund's advisor, distributor or other entity would pay JPMS $25. In addition, for any fund held in a client's account, and for as long as the client holds that fund, JPMS will receive an additional payment, paid quarterly, as a percentage per year of the amount held. Percentage payments generally range from 0.02% to 0.08%. For example, on a $10,000 holding, 0.08% is $8. Additionally, JPMS may receive an annual payment of up to $290,000. Lastly, JPMS may be reimbursed by or on behalf of mutual funds for expenses incurred for various sales meetings, seminars and conferences held in the normal course of business. Financial Advisors do not receive additional compensation from these revenue sharing payments made to JPMS.

The amounts listed above have been updated from those previously provided to you. The prospectus and Statement of Additional Information of mutual funds available through J.P. Morgan or your broker contain information regarding revenue sharing payments made by affiliates of the fund companies. In addition, information regarding revenue sharing can be found at www.Chase.com or related websites.

MARGIN ACCOUNT

If you are a customer with a margin account, you consent to JP Morgan's right (to the extent permitted by applicable law) to use, lend or pledge any securities held by J.P. Morgan Securities LLC in your margin account. In certain circumstances, such loans or other use may limit, in whole or in part, your ability to receive dividends directly from the issuing company and/or your right to exercise voting and other attendant rights of ownership with respect to the loaned, sold or pledged securities. Such circumstances include, but are not limited to, loans of securities that you own in your margin account that continue over record dates for voting purposes and ex-dividend dates for dividend distributions. If you do not receive dividends directly from the issuing company, you may receive payments-in-lieu of dividends which could cause you to lose the benefit of the preferential tax treatment accorded to dividends.

INVESTING IN MUTUAL FUNDS AND EXCHANGE-TRADED PRODUCTS

Please visit chase.com/mutualfunds and chase.com/NTfunds to view our Guides to investing in mutual and non-traditional funds. We encourage you to review each product's prospectus and term sheet for important information regarding investment objectives, risks, charges, expenses and other details.

Messages (continued)

INVESTOR EDUCATION AND PROTECTION

J.P. Morgan Securities LLC is registered with the Municipal Securities Rulemaking Board (MSRB) and the U.S. Securities and Exchange Commission (SEC). The MRSB provides investor information and educational documents online at msrb.org, including their "Information for Municipal Securities Investors" brochure, also referred to as their "Investor Brochure," which summarizes key principles of their rules that are designed to help protect investors who trade municipal securities. It also includes instructions on how to file a complaint against a registered brokerage firm or individuals associated with them.

INVESTMENT RESTRICTIONS IN MANAGED ACCOUNTS

You can choose not to invest in certain trades, industries or securities. If you would like to add, change or remove a "Do Not Buy" investment restriction in your managed account, please call the appropriate number on the front of this statement.

EXTENDED HOURS TRADING RISK DISCLOSURE

You should consider the following points before engaging in extended hours trading. "Extended hours trading" means trading outside of "regular trading hours." "Regular trading hours" generally means the time between 9:30 a.m. and 4:00 p.m. Eastern Standard Time.

Risk of Lower Liquidity. Liquidity refers to the ability of market participants to buy and sell securities. Generally, the more orders that are available in a market, the greater the liquidity. Liquidity is important because with greater liquidity it is easier for investors to buy or sell securities, and as a result, investors are more likely to pay or receive a competitive price for securities purchased or sold. There may be lower liquidity in extended hours trading as compared to regular market hours. As a result, your order may only be partially executed, or not at all.

Risk of Higher Volatility. Volatility refers to the changes in price that securities undergo when trading. Generally, the higher the volatility of a security, the greater its price swings. There may be greater volatility in extended hours trading than in regular market hours. As a result, your order may only be partially executed, or not at all, or you may receive an inferior price in extended hours trading than you would during regular market hours.

Risk of Changing Prices. The prices of securities traded in extended hours trading may not reflect the prices either at the end of regular market hours, or upon the opening the next morning. As a result, you may receive an inferior price in extended hours trading than you would during regular market hours.

Risk of Unlinked Markets. Depending on the extended hours trading system or the time of day, the prices displayed on a particular extended hours trading system may not reflect the prices in other concurrently operating extended hours trading systems dealing in the same securities. Accordingly, you may receive an inferior price in one extended hours trading system than you would in another extended hours trading system.

Risk of News Announcements. Normally, issuers make news announcements that may affect the price of their securities after regular trading hours. Similarly, important financial information is frequently announced outside of regular trading hours. In extended hours trading, these announcements may occur during trading, and if combined with lower liquidity and higher volatility, may cause an exaggerated and unsustainable effect on the price of a security.

Risk of Wider Spreads. The spread refers to the difference in price between what you can buy a security for and what you can sell it for. Lower liquidity and higher volatility in extended hours trading may result in wider than normal spreads for a particular security.

FINRA BROKERCHECK PROGRAM

As part of the Financial Industry Regulatory Authority (FINRA) Investor Education Program, BrokerCheck provides investors with the ability to research the professional backgrounds, business practices, and conduct of FINRA-registered brokerage firms and brokers. In connection with this program, investors may call the BrokerCheck Hotline at 800.289.9999, and visit the FINRA website at http://brokercheck.finra.org/. An investor brochure that includes information describing the FINRA BrokerCheck Program is available from either of these sources.

PAYMENT FOR ORDER FLOW

JPMS may pay from time to time for certain order flow in the form of discounts, rebates, reductions of fees or credits. As a result of sending orders to certain trading centers, JPMS receives payment for order flow in the form of discounts, rebates, reductions of fees or credits. Under some circumstances, the amount of such remuneration may exceed the amount that JPMS is charged by such trading centers. This does not alter JPMS´ policy to route customer orders to the trading center where it believes clients will receive the best execution, taking into account price, reliability, market depth, quality of service, speed and efficiency. Additional details are available upon request.

Messages (continued)

NOTICE OF ESCHEATMENT PROCESS FOR UNCLAIMED PROPERTY

Under state law, if no account activity occurs within your investment account for a period of years (as defined by your state) or if your account statement is returned to us as undeliverable, your account will be considered inactive. If this occurs, we will notify you of the action you need to take to reactivate your account. If you do not take action as requested, your account may be deemed "unclaimed" or "abandoned." This starts a process called escheatment in which we are required to transfer your account to your last known state of residence. If your account is escheated, you will have to work with your state to get your assets back. To avoid escheatment, please ensure that your account remains active and that your contact information is up-to-date.

BUSINESS RECOVERY AND CONTINUITY

JPMS maintains a business recovery and continuity plan, including alternate processing and data centers, which will allow us to resume normal business operations including relocating technology and personnel to alternate facilities within 24 hours, in the event of an extended business disruption. The recovery time objective is 24 hours. The plan is reviewed annually, tested throughout the year, and updated as necessary. Investors will be able to obtain information about their accounts at their local Chase branch, by contacting us at the phone number listed on the front of this statement, or by visiting www.chase.com. Every effort will be made to provide investors with timely and accurate information.

EDELIVERED TRADE CONFIRMATIONS

As a reminder, if you've elected to receive trade confirmations by electronic delivery, you can find current and past copies online in the Trade Confirmations section under Statements & Documents. You can also find disclosures and important information about those trades, via a link on that page titled "See important disclosures for your confirmations".

CUSTOMER FREE CREDIT BALANCES

For accounts that are held at JPMS, customer free credit balances may be used in this firm's business subject to the limitation of 17CFR Section 240.15c3-3 under the Securities Exchange Act of 1934. You have the right to receive from us in the course of normal business operation, upon demand, the delivery of:

1. any free credit balances to which you are entitled
2. any fully-paid securities to which you are entitled
3. any securities purchased on margin upon full payment of any indebtedness to us

If this is a margin account and we maintain a special memorandum account for you, this is a combined statement of your general account and a special memorandum account maintained for you under Section 220.6 of Regulation T issued by the Board of Governors of the Federal Reserve System. The permanent record of this separate account, as required by Regulation T, is available for your inspection.

Unless we hear from you to the contrary, it is our understanding that any free credit balances in your account are being maintained to facilitate your intention to invest such amounts through us.

FUND MANAGER DISCLOSURE INFORMATION AVAILABLE UPON REQUEST

If you have an investment account that is managed by an SEC-Registered Investment Advisor, JPMS will provide a copy of the advisor's Form ADV Part 2A Firm Brochure upon written request.

STATEMENT FREQUENCY

We send statements when your account has activity during the statement period that affects your balances and/or security positions. Delivery Versus Payment clients receive statements on a quarterly basis as long as there is a balance, regardless of activity. All other clients receive statements at least quarterly provided their account has a balance or security position.

Messages (continued)

IMPORTANT INFORMATION ABOUT YOUR INVESTMENTS AND POTENTIAL CONFLICTS OF INTEREST

Conflicts of interest will arise whenever J.P. Morgan Chase & Co. or any of its affiliates (together, "J.P. Morgan") has an actual or perceived economic or other incentive in its management of clients' portfolios to act in a way that benefits J.P. Morgan. Conflicts will result, for example (to the extent the following activities are permitted in the account): (1) when J.P. Morgan invests in an investment product, such as a mutual fund, exchange-traded fund ("ETF"), structured product, separately managed account or hedge fund issued or managed by an affiliate, such as J.P. Morgan Investment Management Inc. ("JPMIM"); (2) when a J.P. Morgan entity obtains services, including trade execution and trade clearing, from an affiliate; (3) when J.P. Morgan receives payment as a result of purchasing an investment product for a client's account; or (4) when J.P. Morgan receives payment for providing services (including shareholder servicing, recordkeeping or custody) with respect to investment products purchased for a client's portfolio. Other conflicts will result because of relationships that J.P. Morgan has with other clients or when J.P. Morgan acts for its own account.

JPMIM or its affiliates may be sponsors or managers of ETFs and other registered funds ("J.P. Morgan Funds") that J.P. Morgan purchases for the client's portfolio. In such case, JPMIM or its affiliates receive a fee for managing the J.P. Morgan Funds. Because fees paid to JPMIM and its affiliates will be offset against the advisory account fee, J.P. Morgan will keep no more revenue when the client's portfolio is invested in J.P. Morgan Funds than when it is invested in third party funds.

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Messages (continued)

Investment Advisory Accounts (Other Than You Invest Portfolios)
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As a general matter, we prefer J.P. Morgan managed strategies. We expect the proportion of J.P. Morgan managed strategies will be high (in fact, up to 100 percent) in strategies such as, for example, cash and high-quality fixed income, subject to applicable law and any account-specific considerations.

While our internally managed strategies generally align well with our forward looking views, and we are familiar with the investment processes as well as the risk and compliance philosophy of the firm, it is important to note that J.P. Morgan receives more overall fees when internally managed strategies are included. We offer the option of choosing to exclude J.P. Morgan managed strategies (other than cash and liquidity products) in certain portfolios.

The Six Circles Funds are mutual funds managed by J.P. Morgan and sub-advised by third parties. Although considered internally managed strategies, J.P. Morgan does not retain a fee for fund management or other fund services.

You Invest Portfolios Accounts
When selecting ETFs for this program, this program's portfolio manager limits its selection to J.P. Morgan ETFs. As a result, this program's portfolio manager will choose J.P. Morgan ETFs even in cases where there are third party ETFs that are less expensive, or that have longer track records or superior historical returns. J.P. Morgan has a conflict of interest when it determines the portfolio's target asset classes, asset allocation goals or ongoing allocations, because it will allocate only to asset classes where J.P. Morgan ETFs are available.

The clients' portfolios will contain 100% J.P. Morgan ETFs. You should not invest in this program if you are not comfortable holding an investment portfolio that is comprised of 100% J.P. Morgan ETFs. It is important to note that J.P. Morgan will receive more overall fees when J.P. Morgan ETFs are used. Additionally, the J.P. Morgan ETFs in this program are not required to be reviewed or approved by the research process applicable to other programs for which J.P. Morgan Securities LLC ("JPMS") serves as investment adviser. Consequently, investment decisions regarding J.P. Morgan ETFs for the program will be different from, and may, in certain circumstances, be inconsistent with, the investment decisions made by J.P. Morgan for other advisory programs. Furthermore, the J.P. Morgan ETFs used in this program may or may not be approved for solicitation in the JPMS full service brokerage platform.

These conflicts may be heightened by the collaboration of this program's portfolio manager and the portfolio managers of the J.P. Morgan Funds in designing portfolios for this program.

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J.P. Morgan makes no representation, warranty or guarantee, express or implied, that any quoted value represents the actual terms at which securities could be bought or sold or new transactions could be entered into, or the actual terms on which existing transactions or securities could be liquidated. Such values are only indicative.

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Pricing estimates may be based on bids, prices within the bid offer spread, closing prices or matrix methodology that uses data relating to other securities whose prices are more ascertainable to produce a hypothetical price based on the estimated yield spread relationship between the securities. Pricing estimates do not constitute bids for any securities. Actual prices realized at sale may be more or less than those shown on your statement.

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You may hold positions where the original cost basis has been adjusted to reflect amortization or accretion.

For Regulated Investment Companies or Dividend Reinvestment Plan sales, for which the average price method has been chosen, positions are closed out on a First-In-First-Out (FIFO) basis.

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In your written communication, please provide the following information: (1) your name and account number; (2) the dollar amount of the suspected error; and (3) a description of the error. Please note that we must receive your written communication no later than 30 days after the statement on which the error appeared is sent or made available. If you do not notify us, you agree that the statement activity and account balances are correct.

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INFORMATION AVAILABLE UPON REQUEST: The date and time of the transaction and the name of the person from whom the security was purchased, or to whom it was sold will be furnished upon request.

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From: **Danka Michaels** dankashen@icloud.com
Subject: office management
Date: April 3, 2014 at 9:47 PM
To: Roberto Carillo APN carterfan777@gmail.com, Felicitas Carillo felicigas@aol.com, Ireri Paque irerijpaque@hotmail.com, Kari Redlich kari_lynn001@yahoo.com, Kim Shaw kshaw2010@hotmail.com, Kisha Greer mikeyshagreer@yahoo.com, Stephanie Ashman MD stephrichheimer@yahoo.com, Dolores Wolf wolfrb@ymail.com, nmbr1angel1106@gmail.com
Cc: christiewanamaker@yahoo.com, Nicole Omps nicoleompscpa@gmail.com

to all:
mr pickens will take over the management of the office effective immediately.
you will be contacted by sarah regarding an office meeting that will be scheduled asap.

danka k. michaels md
bluepoint medical group
las vegas nv

From: Danka Michaels <dankashen@icloud.com>
Date: August 26, 2014 at 1:23:27 PM PDT
To: Randhir S Tuli <rtuli@mdsynergy.com>
Cc: MDS Support <support@mdsynergy.com>, Christie Wanamaker <cwanamaker@bluepointmedicalgrouplv.com>, Nicole Omps <nomps@bluepointmedicalgrouplv.com>, Xoxo Pickens <tpickens@msn.com>
Subject: claims

dear mr tuli,
we encountered another problem.
during routine billing procedures my biller christie found claims sent out by ME! in july ... at weird hours of the day...7 am, 1 am.... all claims from 2011were billed in july 2014..... we printed the screen and faxed to your supoort team.
nobody knows my password. not even my husband!
we have no explanation, maybe you do!
dkm

From: danka michaels dankashen@icloud.com
Subject: Re: Corp Gty
Date: May 22, 2013 at 2:16 PM
To: Wallace, Christopher cwallace3@bankofamerica.com
Cc: Colleen Bevilacqua bevivegas@cox.net, Xoxo Pickens tpickens@msn.com

chris,
patience one is owned by both of us equally. i do not know which paperwork you could have that says otherwise. ALL of the required documents are with the BofA since last year!!!

danka k. michaels md
bluepoint medical group
las vegas nv

On May 22, 2013, at 10:13 AM, "Wallace, Christopher" <cwallace3@bankofamerica.com> wrote:

> Dr. Michaels,
>
> I need one more thing to close out the relocation loan. Per your loan agreement we need a corporate guarantee for the real estate holding company. It looks like the company is in Thomas Pickens name per the Articles of Corporation. Please have Tom sign the addendum and fill out the borrowers resolution for Patience One LLC to verify his ownership. Now if you have owner ship in this company too please let me know right away and I will have to create a new document for the both of you to sign.
>
> Thanks!
>
> **Chris Wallace**
>
> **Project Manager/Relationship Administrator II**
>
> **Bank of America Practice Solutions**
> 600 North Cleveland Ave. Ste 300
> Westerville, OH 43082
>
> Office: 1-800-360-0667 (Extension: 5647)
>
> Fax:404-965-7378
>
> Email: cwallace3@bankofamerica.com
>
> **"Tell a friend program. It's a pleasure to provide you our financing programs. Please send my contact information to colleagues, friends and others who also will benefit from the same great service and products you are receiving."**
>
> ---
>
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CASE
PROP

PENGAD 800-631-6989
PLAINTIFF'S EXHIBIT
148
2/4/20
D566737

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CASE
PROP
PENGAD 800-631-6989
PLAINTIFF'S EXHIBIT 149
DS600737
2/14/2

us by telephone at 702.948.8771 and e-mail the sender that you have received this communication in error. Thank you.

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From: D.K.Michaels [mailto:dankashen@pol.net]
Sent: Monday, July 09, 2012 6:38 PM
To: Andy Glendon
Cc: Roy Fritz; Cathy Jones; Tom Pickens
Subject: PSA - red draft

hi andy,
reviewed the contract.
re: 3.4.1.ii - wrong reference. the correct # is::
3.4.3 = we discussed just now with roy and he explained. all understood.

we need to include a contingency paragraph somewhere re obtaining financing ... we haven't been able to obtain a guarantee from the banks, only pre-approval. we have heard horror stories about financing - so we know that even with pre-approval the banks may take time or drag their feet or whatever.. we need to have it in writing that if unable to obtain financing, we inform the seller in writing and we can cancel the agreement with full return of deposit money.
please inform the seller that it is our full intention to buy this property (as they noticed by our patient waiting for the last 7 months!) and we will do our utmost to obtain financing from either bank - but we have no control over it.
thank you.
roy will get in touch with you - he knows the lingo better than we do.
d+t

----- Original Message -----
From: "Andy Glendon" <AGlendon@santoronevada.com>
To: "D.K.Michaels" <dankashen@pol.net>
Cc: "Roy Fritz" <RoyF@suncommercialre.com>, "Cathy Jones" <cathyj@suncommercialre.com>, "Tom Pickens" <tpickens@msn.com>
Sent: Monday, July 9, 2012 11:59:21 AM GMT -08:00 US/Canada Pacific
Subject: RE: from Danka : PSA

Danka and Tom. Thanks for your comments. I made some revisions shown on the attached to address same – namely, the broker section.

My objective was not to add confusion on the Pacific/Eastern time issues. For making the deposit, we need to do it by 5 Eastern. But I wanted to give us until 5 Pacific to perform due diligence and terminate if we have an issue (as this is a short due diligence period, I wanted to give us the full time). The rest of the time zone issues are for Seller, so I left those as Eastern.

In 3.6, the point is that if you don't want to do the deal, you need to affirmatively terminate prior to the end of the due diligence period, or you are deemed to have waived contingencies. So we all need to be on the same page as to this deadline (and, again, one of the reasons I made the time period 5 Pacific per the prior paragraph, was to make sure we had a few extra hours to terminate if we needed to). I did not revise the language, but call me if it is still confusing and we can try and fix it.

I did not understand your question regarding 3.4.1(ii). Please clarify and we can address same.

In 9.1, I am trying to give you more flexibility in deciding whether to do the deal or not if a portion of the premises are burned. The lower the figure, the more flexibility you have to terminate if needed. In 10.4, if Seller breaches (i.e., just flat refuses to sell the building to you), one remedy is for you to cover your expenses and move on – so I increased the cap on what amount of expenses Seller would pay – up top $20,000, to give you the ability to come close to being made "whole".

With your approval, I will send the revision to Seller's attorney. Thanks, Andy

ANDREW J. GLENDON, ESQ.
SANTORO WHITMIRE
10001 PARK RUN DRIVE
LAS VEGAS, NEVADA 89145
P: 702.948.8771 | F: 702.948.8773 | Direct: 702.749.5610
aglendon@santoronevada.com

Admitted in California and Nevada

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From: D.K.Michaels [mailto:dankashen@pol.net]
Sent: Sunday, July 08, 2012 8:13 PM
To: Andy Glendon
Cc: Fritz, Roy; Jones, Cathy; Pickens, Tom
Subject: Re: from Danka : PSA

hi andy,
just reviewed the contract.
thank you for your thorough work. let's hope they will accept all the changes.
i have few questions:

1. why do we have to use pacific AND eastern standard time within the same paragraph? ie: 2.2.; 3.5.1.
2. 3.4.1 ii - is this correct?
3. in 3.6. if agreement terminates, so does the 'due diligence period', right? shouldn't it be worded differently then?
4. in 5.3. and 7.1.6 - pls note that the seller is paying the "purchaser's broker" as well. as far as i know, they agreed on paying sun commercial 2%. - it may be that the other broker is sharing the commision?? ... we don't know the details about this == must be clarified!
5. pls explain why the $$ change in 9.1. and 10.4.
thank you.
d+t

----- Original Message -----
From: "Andy Glendon" <AGlendon@santoronevada.com>
To: "D.K.Michaels" <dankashen@pol.net>
Sent: Saturday, July 7, 2012 11:32:19 PM GMT -08:00 US/Canada Pacific
Subject: RE: from Danka : PSA

Danka and Tom. Attached is my proposed revision to the purchase agreement. I have incorporated just about all of the comments received from your broker. A few questions:

1) This is a very short due diligence period. Where are you in this process – environmental, building condition, zoning and any land use issues, etc.
2) Are you financing this acquisition – if so, where are you in the loan process.

Please review the attached revision and let me know if we can discuss same and the above. Once approved, I will send it to Seller's counsel for review.

ANDREW J. GLENDON, ESQ.
SANTORO WHITMIRE
10001 PARK RUN DRIVE
LAS VEGAS, NEVADA 89145
P: 702.948.8771 | F: 702.948.8773 | Direct: 702.749.5610
aglendon@santoronevada.com

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To comply with IRS regulations, we advise that any discussion of Federal tax issues in this E-mail was not intended or written to be used, and cannot be used by you i) to avoid any penalties imposed under the Internal Revenue Code or, ii) to promote, market or recommend to another party any transaction or matter addressed herein.

From: D.K.Michaels [mailto:dankashen@pol.net]
Sent: Thursday, July 05, 2012 3:03 PM

To: Andy Glendon
Subject: Re: from Danka : PSA

thank you andy.
may we ask you to include both of our names on future correspondence? my husband and i are partners in this deal together. His name is Tom Pickens, cell # 604-0038. (just in case i won't respond and you need one of us.)
thank you.
dkkm
ps do you need the name of the LLC? does it have to be listed anywhere on our correspondence?
----- Original Message -----
From: "Andy Glendon" <AGlendon@santoronevada.com>
To: "D.K.Michaels" <dankashen@pol.net>
Sent: Thursday, July 5, 2012 9:51:28 AM GMT -08:00 US/Canada Pacific
Subject: RE: from Danka : PSA

Danka. Attached is our firm's engagement letter and accompanying policies and procedures. Please review and let me know if you have any questions. Otherwise, please sign and return the copy of the engagement letter to me at your first convenience. Thanks, Andy

ANDREW J. GLENDON, ESQ.
SANTORO WHITMIRE
10001 PARK RUN DRIVE
LAS VEGAS, NEVADA 89145
P: 702.948.8771 | F: 702.948.8773 | Direct: 702.749.5610
aglendon@santoronevada.com

Admitted in California and Nevada

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From: D.K.Michaels [mailto:dankashen@pol.net]
Sent: Monday, July 02, 2012 8:15 PM
To: Andy Glendon
Subject: from Danka : PSA

Danka,

From: D.K.Michaels dankashen@pol.net
Subject: 3320 Buffalo
Date: May 9, 2012 at 2:34 PM
To: kimaz, joe joe.kimaz@madisonreg.com, Pickens, Tom tpickens@msn.com

mr kimaz,

we have a favor to ask: our bank = BofA is requesting a detailed estimate for the build-out of our space. otherwise they cannot proceed with the preparation for the loan. considering that we have only 45 days after the effective date to obtain loan from the bank, we'd rather not lose time.

would it be possible for the caretaker of the property to let my husband Tom Pickens into the buidling to properly measure the spaces, get idea about a/c, heating etc etc ... whatever he needs to make an educated guess about the money needed?

If at all possible, can we get the plans of the building - before we sign the agreement?

we really appreviate your help,

danka + tom

MARK N
CASE #
PROPO

From: **Danka Michaels** dankashen@pol.net
Subject: documents
Date: November 13, 2011 at 3:21 PM
To: info info@paxtour.sk
Cc: Tom Pickens tpickens@msn.com

dear miss k,
we are very happy with the flight and the timing is wonderful! thank you!!!

here are the passport # and full names:
Danka Katarina Michaels DOB Nov 26 1955 #214627017 exp Aug 2, 2015
Thomas Allen Pickens DOB Oct 5 1956 #455451538 exp June 2, 2019

my husband is not comfortable scanning passports and emailing you the documents.

we have not received the contract to sign yet.
hope, there is a reservation placed on the ama trip and the tickets...
once we have the contract signed, pls, charge the amex and let us know - the bank usually calls if it's a big amount of money and it's a new vendor on our account.

we are very excited about the trip - and looking forward to se you there as well...

D+T

MAR ION
CAS
PRO

Monday, December 5, 2016 9:27:24 AM Pacific Standard Time

Subject: Re: Family trust
Date: Monday, December 5, 2016 9:27:07 AM Pacific Standard Time
From: Shannon Evans
To: danka michaels

Of course! I will have my office prepare an amendment and you can stop in briefly to sign and notarize it.
Very easy and that is exactly why I was keeping everything revocable for you.

My fee for the amendment will be $100.
Thanks
Shannon

Shannon L. Evans
Evans & Associates
7251 W. Lake Mead Blvd. #530
Las Vegas, NV 89128
E-Mail: sle@evans-associates.com
Telephone: 702-699-7333
Facsimile: 702-699-7377

On 12/2/16 1:32 PM, "danka michaels" <dankashen@icloud.com> wrote:

> Hi shannon,
> I would like to delete the sentence from the family trust about " In the event of my death, tom will inherit 50% of the properties".
>
> Thanks.
>
> Danka K. Michaels MD
> BluePoint Medical Group
> 3320 N. Buffalo dr #106
> LV NV 89129
> 702.869.6190

#36

CONFORM COPY

Inst #: 20140630-0003398
Fees: $43.00
N/C Fee: $0.00
06/30/2014 03:08:03 PM
Receipt #: 2073044
CONFORM COPY
Requestor:
NEVADA TITLE LAS VEGAS
Recorded By: MJM Pgs: 27
DEBBIE CONWAY
CLARK COUNTY RECORDER

APN# 138-10-401-001
The undersigned hereby affirms that this document submitted for recording does not contain any personal information.

Michele Eaton T.O.

Assessor Parcel No(s): 138-10-401-001

Escrow No. 14-05-1043-JKH

~~RECORDATION REQUESTED BY:~~
Wells Fargo Bank, National Association; Fallon Business Banking; MAC # S4663-011; 2211 W. Williams; Fallon, NV 89406

WHEN RECORDED MAIL TO:
Wells Fargo Bank, National Association, BBSG - San Antonio Loan Ops LDI, P.O. Box 65119, San Antonio, TX 78265

SEND TAX NOTICES TO:
PATIENCE ONE LLC, 3320 N BUFFALO DR STE 208, LAS VEGAS, NV 89129

FOR RECORDER'S USE ONLY

PLAINTIFF'S EXHIBIT 153 02/11/2 D500737

200181819668500235

DEED OF TRUST

THIS DEED OF TRUST is dated June 25, 2014, among PATIENCE ONE LLC, who acquired title as Patience One, LLC, a Nevada limited liability company ("Grantor"); Wells Fargo Bank, National Association, whose address is Fallon Business Banking, MAC # S4663-011, 2211 W. Williams, Fallon, NV 89406 (referred to below sometimes as "Lender" and sometimes as "Beneficiary"); and Wells Fargo Financial National Bank, whose address is c/o BBSG-San Antonio Loan Ops LDI, PO Box 65119, San Antonio, TX 78265 (referred to below as "Trustee").

CONVEYANCE AND GRANT. For valuable consideration, Grantor irrevocably grants, bargains, sells and conveys to Trustee with power of sale for the benefit of Lender as Beneficiary all of Grantor's right, title, and interest in and to the following described real property, together with all existing or subsequently erected or affixed buildings, improvements and fixtures; all easements, rights of way, and appurtenances; all water, water rights and ditch rights (including stock in utilities with ditch or irrigation rights); and all other rights, royalties, and profits relating to the real property, including without limitation all minerals, oil, gas, geothermal and similar matters, **(the "Real Property") located in Clark County, State of Nevada:**

See Exhibit A attached hereto and made a part hereof.

The Real Property or its address is commonly known as 3320 N BUFFALO DR, LAS VEGAS, NV 89129. The Real Property tax identification number is 138-10-401-001.

Grantor presently, absolutely, and irrevocably assigns to Lender (also known as Beneficiary in this Deed of Trust) all of Grantor's right, title, and interest in and to all present and future leases of the Property and all Rents from the Property. In addition, Grantor grants to Lender a Uniform Commercial Code security interest in the Personal Property.

THIS DEED OF TRUST, INCLUDING THE ASSIGNMENT OF RENTS AND THE SECURITY INTEREST IN THE PERSONAL PROPERTY, IS GIVEN TO SECURE (A) PAYMENT OF THE INDEBTEDNESS INCLUDING FUTURE ADVANCES AND (B) PERFORMANCE OF ANY AND ALL OBLIGATIONS UNDER THE NOTE, THE RELATED DOCUMENTS, AND THIS DEED OF TRUST. THIS DEED OF TRUST IS GIVEN AND ACCEPTED ON THE FOLLOWING TERMS:

PAYMENT AND PERFORMANCE. Except as otherwise provided in this Deed of Trust, Grantor shall pay to Lender all amounts secured by this Deed of Trust as they become due, and shall strictly and in a timely manner perform all of Grantor's obligations under the Note, this Deed of Trust, and the Related Documents.

STATUTORY COVENANTS. The following Statutory Covenants are hereby adopted and made a part of this Deed of Trust: Covenants Nos. 1, 3, 4, 5, 6, 7 and 8 of N.R.S. 107.030. For Covenant 4, upon default, including failure to pay upon final maturity, the interest rate on the Note shall be increased by 4.000 percentage points However, in no event will the interest rate exceed the maximum interest rate limitations under applicable law. The percent of counsel fees under Covenant No. 7 shall be ten percent(10%). Except for Covenants Nos. 6, 7, and 8, to the extent any terms of this Deed of Trust are inconsistent with the Statutory Covenants the terms of this Deed of Trust shall control. Covenants 6, 7, and 8 shall control over the express terms of any inconsistent terms of this Deed of Trust.

POSSESSION AND MAINTENANCE OF THE PROPERTY. Grantor agrees that Grantor's possession and use of the Property shall be governed by the following provisions:

Possession and Use. Until the occurrence of an Event of Default, Grantor may (1) remain in possession and control of the Property; (2) use, operate or manage the Property; and (3) collect the Rents from the Property.

Duty to Maintain. Grantor shall maintain the Property in tenantable condition and promptly perform all repairs, replacements, and maintenance necessary to preserve its value.

Compliance With Environmental Laws. Grantor represents and warrants to Lender that: (1) During the period of Grantor's ownership of the Property, there has been no use, generation, manufacture, storage, treatment, disposal, release or threatened release of any Hazardous Substance by any person on, under, about or from the Property; (2) Grantor has no knowledge of, or reason to believe that there has been, except as previously disclosed to and acknowledged by Lender in writing, (a) any breach or violation of any Environmental Laws, (b) any use, generation, manufacture, storage, treatment, disposal, release or threatened release of any Hazardous Substance on, under, about or from the Property by any prior owners or occupants of the Property, or (c) any actual or threatened litigation or claims of any kind by any person relating to such matters; and (3) Except as previously disclosed to and acknowledged by Lender in writing, (a) neither Grantor nor any tenant, contractor, agent or other authorized user of the Property shall use, generate,

manufacture, store, treat, dispose of or release any Hazardous Substance on, under, about or from the Property; and (b) any such activity shall be conducted in compliance with all applicable federal, state, and local laws, regulations and ordinances, including without limitation all Environmental Laws. Grantor authorizes Lender and its agents to enter upon the Property to make such inspections and tests, at Grantor's expense, as Lender may deem appropriate to determine compliance of the Property with this section of the Deed of Trust. Any inspections or tests made by Lender shall be for Lender's purposes only and shall not be construed to create any responsibility or liability on the part of Lender to Grantor or to any other person. The representations and warranties contained herein are based on Grantor's due diligence in investigating the Property for Hazardous Substances. Grantor hereby (1) releases and waives any future claims against Lender for indemnity or contribution in the event Grantor becomes liable for cleanup or other costs under any such laws; and (2) agrees to indemnify, defend, and hold harmless Lender against any and all claims, losses, liabilities, damages, penalties, and expenses which Lender may directly or indirectly sustain or suffer resulting from a breach of this section of the Deed of Trust or as a consequence of any use, generation, manufacture, storage, disposal, release or threatened release occurring prior to Grantor's ownership or interest in the Property, whether or not the same was or should have been known to Grantor. The provisions of this section of the Deed of Trust, including the obligation to indemnify and defend, shall survive the payment of the Indebtedness and the satisfaction and reconveyance of the lien of this Deed of Trust and shall not be affected by Lender's acquisition of any interest in the Property, whether by foreclosure or otherwise.

Nuisance, Waste. Grantor shall not cause, conduct or permit any nuisance nor commit, permit, or suffer any stripping of or waste on or to the Property or any portion of the Property. Without limiting the generality of the foregoing, Grantor will not remove, or grant to any other party the right to remove, any timber, minerals (including oil and gas), coal, clay, scoria, soil, gravel or rock products without Lender's prior written consent.

Removal of Improvements. Grantor shall not demolish or remove any Improvements from the Real Property without Lender's prior written consent. As a condition to the removal of any Improvements, Lender may require Grantor to make arrangements satisfactory to Lender to replace such Improvements with Improvements of at least equal value.

Lender's Right to Enter. Lender and Lender's agents and representatives may enter upon the Real Property at all reasonable times to attend to Lender's interests and to inspect the Real Property for purposes of Grantor's compliance with the terms and conditions of this Deed of Trust.

Compliance with Governmental Requirements. Grantor shall promptly comply with all laws, ordinances, and regulations, now or hereafter in effect, of all governmental authorities applicable to the use or occupancy of the Property, including without limitation, the Americans With Disabilities Act. Grantor may contest in good faith any such law, ordinance, or regulation and withhold compliance during any proceeding, including appropriate appeals, so long as Grantor has notified Lender in writing prior to doing so and so long as, in Lender's sole opinion, Lender's interests in the Property are not jeopardized. Lender may require Grantor to post adequate security or a surety bond, reasonably satisfactory to Lender, to protect Lender's interest.

Duty to Protect. Grantor agrees neither to abandon or leave unattended the Property. Grantor shall do all other acts, in addition to those acts set forth above in this section, which from the character and use of the Property are reasonably necessary to protect and preserve the Property.

DUE ON SALE - CONSENT BY LENDER. Lender may, at Lender's option, declare immediately due and payable all sums secured by this Deed of Trust upon the sale or transfer, without Lender's prior written consent, of all or any part of the Real Property, or any interest in the Real Property or any mobile home or manufactured home located on the property whether or not it is legally a part of the real property. A "sale or transfer" means the conveyance of Real Property or any right, title or interest in the Real Property; whether legal, beneficial or equitable; whether voluntary or involuntary; whether by outright sale, deed, installment sale contract, land contract, contract for deed, leasehold interest with a term greater than three (3) years, lease-option contract, or by sale, assignment, or transfer of any beneficial interest in or to any land trust holding title to the Real Property, or by any other method of conveyance of an interest in the Real Property. If any Grantor is a corporation, partnership or limited liability company, transfer also includes any change in ownership of more than twenty-five percent (25%) of the voting stock, partnership interests or limited liability company interests, as the case may be, of such Grantor. However, this option shall not be exercised by Lender if such exercise is prohibited by federal law or by Nevada law.

TAXES AND LIENS. The following provisions relating to the taxes and liens on the Property are part of this Deed of Trust:

Payment. Grantor shall pay when due (and in all events prior to delinquency) all taxes, special taxes, assessments, charges (including water and sewer), fines and impositions levied against or on account of the Property, and shall pay when due all claims for work done on or for services rendered or material furnished to the Property. Grantor shall maintain the Property free of all liens having priority over or equal to the interest of Lender under this Deed of Trust, except for the lien of taxes and assessments not due and except as otherwise provided in this Deed of Trust.

Right to Contest. Grantor may withhold payment of any tax, assessment, or claim in connection with a good faith dispute over the obligation to pay, so long as Lender's interest in the Property is not jeopardized. If a lien arises or is filed as a result of nonpayment, Grantor shall within fifteen (15) days after the lien arises or, if a lien is filed, within fifteen (15) days after Grantor has notice of the filing, secure the discharge of the lien, or if requested by Lender, deposit with Lender cash or a sufficient corporate surety bond or other security satisfactory to Lender in an amount sufficient to discharge the lien plus any costs and attorneys' fees, or other charges that could accrue as a result of a foreclosure or sale under the lien. In any contest, Grantor shall defend itself and Lender and shall satisfy any adverse judgment before enforcement against the Property. Grantor shall name Lender as an additional obligee under any surety bond furnished in the contest proceedings.

Evidence of Payment. Grantor shall upon demand furnish to Lender satisfactory evidence of payment of the taxes or assessments and shall authorize the appropriate governmental official to deliver to Lender at any time a written statement of the taxes and assessments against the Property.

Notice of Construction. Grantor shall notify Lender at least fifteen (15) days before any

work is commenced, any services are furnished, or any materials are supplied to the Property, if any mechanic's lien, materialmen's lien, or other lien could be asserted on account of the work, services, or materials. Grantor will upon request of Lender furnish to Lender advance assurances satisfactory to Lender that Grantor can and will pay the cost of such improvements.

PROPERTY DAMAGE INSURANCE. The following provisions relating to insuring the Property are a part of this Deed of Trust.

Maintenance of Insurance. Grantor shall procure and maintain policies of fire insurance with standard extended coverage endorsements on a replacement basis for the full insurable value covering all Improvements on the Real Property in an amount sufficient to avoid application of any coinsurance clause, and with a standard mortgagee clause in favor of Lender. Grantor shall also procure and maintain comprehensive general liability insurance in such coverage amounts as Lender may request with Trustee and Lender being named as additional insureds in such liability insurance policies. Additionally, Grantor shall maintain such other insurance, including but not limited to hazard, business interruption, and boiler insurance, as Lender may reasonably require. Policies shall be written in form, amounts, coverages and basis reasonably acceptable to Lender and issued by a company or companies reasonably acceptable to Lender. Grantor, upon request of Lender, will deliver to Lender from time to time the policies or certificates of insurance in form satisfactory to Lender, including stipulations that coverages will not be cancelled or diminished without at least thirty (30) days prior written notice to Lender. Each insurance policy also shall include an endorsement providing that coverage in favor of Lender will not be impaired in any way by any act, omission or default of Grantor or any other person. Should the Real Property be located in an area designated by the Administrator of the Federal Emergency Management Agency as a special flood hazard area, Grantor agrees to obtain and maintain Federal Flood Insurance, if available, within 45 days after notice is given by Lender that the Property is located in a special flood hazard area, for the full unpaid principal balance of the loan and any prior liens on the property securing the loan, up to the maximum policy limits set under the National Flood Insurance Program, or as otherwise required by Lender, and to maintain such insurance for the term of the loan.

Application of Proceeds. Grantor shall promptly notify Lender of any loss or damage to the Property. Lender may make proof of loss if Grantor fails to do so within fifteen (15) days of the casualty. Whether or not Lender's security is impaired, Lender may, at Lender's election, receive and retain the proceeds of any insurance and apply the proceeds to the reduction of the Indebtedness, payment of any lien affecting the Property, or the restoration and repair of the Property. If Lender elects to apply the proceeds to restoration and repair, Grantor shall repair or replace the damaged or destroyed Improvements in a manner satisfactory to Lender. Lender shall, upon satisfactory proof of such expenditure, pay or reimburse Grantor from the proceeds for the reasonable cost of repair or restoration if Grantor is not in default under this Deed of Trust. Any proceeds which have not been disbursed within 180 days after their receipt and which Lender has not committed to the repair or restoration of the Property shall be used first to pay any amount owing to Lender under this Deed of Trust, then to pay accrued interest, and the remainder, if any, shall be applied to the principal balance of the Indebtedness. If Lender holds any proceeds after payment in full of the Indebtedness, such proceeds shall be paid to Grantor as Grantor's

interests may appear.

Grantor's Report on Insurance. Upon request of Lender, however not more than once a year, Grantor shall furnish to Lender a report on each existing policy of insurance showing: (1) the name of the insurer; (2) the risks insured; (3) the amount of the policy; (4) the property insured, the then current replacement value of such property, and the manner of determining that value; and (5) the expiration date of the policy. Grantor shall, upon request of Lender, have an independent appraiser satisfactory to Lender determine the cash value replacement cost of the Property.

LENDER'S EXPENDITURES. If any action or proceeding is commenced that would materially affect Lender's interest in the Property or if Grantor fails to comply with any provision of this Deed of Trust or any Related Documents, including but not limited to Grantor's failure to discharge or pay when due any amounts Grantor is required to discharge or pay under this Deed of Trust or any Related Documents, Lender on Grantor's behalf may (but shall not be obligated to) take any action that Lender deems appropriate, including but not limited to discharging or paying all taxes, liens, security interests, encumbrances and other claims, at any time levied or placed on the Property and paying all costs for insuring, maintaining and preserving the Property. All such expenditures incurred or paid by Lender for such purposes will then bear interest at the rate charged under the Note from the date incurred or paid by Lender to the date of repayment by Grantor. All such expenses will become a part of the Indebtedness and, at Lender's option, will (A) be payable on demand; (B) be added to the balance of the Note and be apportioned among and be payable with any installment payments to become due during either (1) the term of any applicable insurance policy; or (2) the remaining term of the Note; or (C) be treated as a balloon payment which will be due and payable at the Note's maturity. The Deed of Trust also will secure payment of these amounts. Such right shall be in addition to all other rights and remedies to which Lender may be entitled upon Default.

WARRANTY; DEFENSE OF TITLE. The following provisions relating to ownership of the Property are a part of this Deed of Trust:

Title. Grantor warrants that: (a) Grantor holds good and marketable title of record to the Property in fee simple, free and clear of all liens and encumbrances other than those set forth in the Real Property description or in any title insurance policy, title report, or final title opinion issued in favor of, and accepted by, Lender in connection with this Deed of Trust, and (b) Grantor has the full right, power, and authority to execute and deliver this Deed of Trust to Lender.

Defense of Title. Subject to the exception in the paragraph above, Grantor warrants and will forever defend the title to the Property against the lawful claims of all persons. In the event any action or proceeding is commenced that questions Grantor's title or the interest of Trustee or Lender under this Deed of Trust, Grantor shall defend the action at Grantor's expense. Grantor may be the nominal party in such proceeding, but Lender shall be entitled to participate in the proceeding and to be represented in the proceeding by counsel of Lender's own choice, and Grantor will deliver, or cause to be delivered, to Lender such instruments as Lender may request from time to time to permit such participation.

Compliance With Laws. Grantor warrants that the Property and Grantor's use of the Property complies with all existing applicable laws, ordinances, and regulations of governmental authorities.

Survival of Representations and Warranties. All representations, warranties, and agreements made by Grantor in this Deed of Trust shall survive the execution and delivery of this Deed of Trust, shall be continuing in nature, and shall remain in full force and effect until such time as Grantor's Indebtedness shall be paid in full.

CONDEMNATION. The following provisions relating to condemnation proceedings are a part of this Deed of Trust:

Proceedings. If any proceeding in condemnation is filed, Grantor shall promptly notify Lender in writing, and Grantor shall promptly take such steps as may be necessary to defend the action and obtain the award. Grantor may be the nominal party in such proceeding, but Lender shall be entitled to participate in the proceeding and to be represented in the proceeding by counsel of its own choice, and Grantor will deliver or cause to be delivered to Lender such instruments and documentation as may be requested by Lender from time to time to permit such participation.

Application of Net Proceeds. If all or any part of the Property is condemned by eminent domain proceedings or by any proceeding or purchase in lieu of condemnation, Lender may at its election require that all or any portion of the net proceeds of the award be applied to the Indebtedness or the repair or restoration of the Property. The net proceeds of the award shall mean the award after payment of all reasonable costs, expenses, and attorneys' fees incurred by Trustee or Lender in connection with the condemnation. Grantor waives any legal or equitable interest in the net proceeds and any right to require any apportionment of the net proceeds of the award. Grantor agrees that Lender is entitled to apply the award in accordance with this paragraph without demonstrating that its security has been impaired.

IMPOSITION OF TAXES, FEES AND CHARGES BY GOVERNMENTAL AUTHORITIES. The following provisions relating to governmental taxes, fees and charges are a part of this Deed of Trust:

Current Taxes, Fees and Charges. Upon request by Lender, Grantor shall execute such documents in addition to this Deed of Trust and take whatever other action is requested by Lender to perfect and continue Lender's lien on the Real Property. Grantor shall reimburse Lender for all taxes, as described below, together with all expenses incurred in recording, perfecting or continuing this Deed of Trust, including without limitation all taxes, fees, documentary stamps, and other charges for recording or registering this Deed of Trust.

Taxes. The following shall constitute taxes to which this section applies: (1) a specific tax upon this type of Deed of Trust or upon all or any part of the Indebtedness secured by this Deed of Trust; (2) a specific tax on Grantor which Grantor is authorized or required to deduct from payments on the Indebtedness secured by this type of Deed of Trust; (3) a tax on this type of Deed of Trust chargeable against the Lender or the holder of the Note; and (4) a specific tax on all or any portion of the Indebtedness or on payments of principal and interest made by Grantor.

Subsequent Taxes. If any tax to which this section applies is enacted subsequent to the date of this Deed of Trust, this event shall have the same effect as an Event of Default, and Lender may exercise any or all of its available remedies for an Event of Default as provided below unless Grantor either (1) pays the tax before it becomes delinquent, or (2)

contests the tax as provided above in the Taxes and Liens section and deposits with Lender cash or a sufficient corporate surety bond or other security satisfactory to Lender.

SECURITY AGREEMENT; FINANCING STATEMENTS. The following provisions relating to this Deed of Trust as a security agreement are a part of this Deed of Trust:

Security Agreement. This instrument shall constitute a Security Agreement to the extent any of the Property constitutes fixtures, and Lender shall have all of the rights of a secured party under the Uniform Commercial Code as amended from time to time.

Security Interest. Upon request by Lender, Grantor shall take whatever action is requested by Lender to perfect and continue Lender's security interest in the Rents and Personal Property. In addition to recording this Deed of Trust in the real property records, Lender may, at any time and without further authorization from Grantor, file executed counterparts, copies or reproductions of this Deed of Trust as a financing statement. Grantor shall reimburse Lender for all expenses incurred in perfecting or continuing this security interest. Upon default, Grantor shall not remove, sever or detach the Personal Property from the Property. Upon default, Grantor shall assemble any Personal Property not affixed to the Property in a manner and at a place reasonably convenient to Grantor and Lender and make it available to Lender within three (3) days after receipt of written demand from Lender to the extent permitted by applicable law.

Addresses. The mailing addresses of Grantor (debtor) and Lender (secured party) from which information concerning the security interest granted by this Deed of Trust may be obtained (each as required by the Uniform Commercial Code) are as stated on the first page of this Deed of Trust.

FURTHER ASSURANCES; ATTORNEY-IN-FACT. The following provisions relating to further assurances and attorney-in-fact are a part of this Deed of Trust:

Further Assurances. At any time, and from time to time, upon request of Lender, Grantor will make, execute and deliver, or will cause to be made, executed or delivered, to Lender or to Lender's designee, and when requested by Lender, cause to be filed, recorded, refiled, or rerecorded, as the case may be, at such times and in such offices and places as Lender may deem appropriate, any and all such mortgages, deeds of trust, security deeds, security agreements, financing statements, continuation statements, instruments of further assurance, certificates, and other documents as may, in the sole opinion of Lender, be necessary or desirable in order to effectuate, complete, perfect, continue, or preserve (1) Grantor's obligations under the Note, this Deed of Trust, and the Related Documents, and (2) the liens and security interests created by this Deed of Trust as first and prior liens on the Property, whether now owned or hereafter acquired by Grantor. Unless prohibited by law or Lender agrees to the contrary in writing, Grantor shall reimburse Lender for all costs and expenses incurred in connection with the matters referred to in this paragraph.

Attorney-in-Fact. If Grantor fails to do any of the things referred to in the preceding paragraph, Lender may do so for and in the name of Grantor and at Grantor's expense. For such purposes, Grantor hereby irrevocably appoints Lender as Grantor's attorney-in-fact for the purpose of making, executing, delivering, filing, recording, and doing all other things as may be necessary or desirable, in Lender's sole opinion, to accomplish the matters referred to in the preceding paragraph.

EVENTS OF DEFAULT. Each of the following, at Lender's option, shall constitute an Event of Default under this Deed of Trust:

Payment Default. Grantor fails to make any payment when due under the Indebtedness.

Other Defaults. Grantor fails to comply with or to perform any other term, obligation, covenant or condition contained in this Deed of Trust or in any of the Related Documents or to comply with or to perform any term, obligation, covenant or condition contained in any other agreement between Lender and Grantor.

Compliance Default. Failure to comply with any other term, obligation, covenant or condition contained in this Deed of Trust, the Note or in any of the Related Documents.

Default on Other Payments. Failure of Grantor within the time required by this Deed of Trust to make any payment for taxes or insurance, or any other payment necessary to prevent filing of or to effect discharge of any lien.

Default in Favor of Third Parties. Should Grantor default under any loan, extension of credit, security agreement, purchase or sales agreement, or any other agreement, in favor of any other creditor or person that may materially affect any of Grantor's property or Grantor's ability to repay the Indebtedness or Grantor's ability to perform Grantor's obligations under this Deed of Trust or any of the Related Documents.

Default on Subordinate Indebtedness. Default by Grantor under any subordinate obligation or instrument securing any subordinate obligation or commencement of any suit or other action to foreclose any subordinate lien on the Property.

False Statements. Any warranty, representation or statement made or furnished to Lender by Grantor or on Grantor's behalf under this Deed of Trust or the Related Documents is false or misleading in any material respect, either now or at the time made or furnished or becomes false or misleading at any time thereafter.

Defective Collateralization. This Deed of Trust or any of the Related Documents ceases to be in full force and effect (including failure of any collateral document to create a valid and perfected security interest or lien) at any time and for any reason.

Death or Insolvency. The dissolution of Grantor's (regardless of whether election to continue is made), any member withdraws from the limited liability company, or any other termination of Grantor's existence as a going business or the death of any member, the insolvency of Grantor, the appointment of a receiver for any part of Grantor's property, any assignment for the benefit of creditors, any type of creditor workout, or the commencement of any proceeding under any bankruptcy or insolvency laws by or against Grantor.

Creditor or Forfeiture Proceedings. Commencement of foreclosure or forfeiture proceedings, whether by judicial proceeding, self-help, repossession or any other method, by any creditor of Grantor or by any governmental agency against any property securing the Indebtedness. This includes a garnishment of any of Grantor's accounts, including deposit accounts, with Lender. However, this Event of Default shall not apply if there is a good faith dispute by Grantor as to the validity or reasonableness of the claim which is the basis of the creditor or forfeiture proceeding and if Grantor gives Lender written notice of the creditor or forfeiture proceeding and deposits with Lender monies or a surety bond for the creditor or forfeiture proceeding, in an amount determined by Lender, in its sole discretion, as being an adequate

reserve or bond for the dispute.

Events Affecting Guarantor. Any of the preceding events occurs with respect to any Guarantor of any of the Indebtedness or any Guarantor dies or becomes incompetent, or revokes or disputes the validity of, or liability under, any Guaranty of the Indebtedness.

Adverse Change. A material adverse change occurs in Grantor's financial condition, or Lender believes the prospect of payment or performance of the Indebtedness is impaired.

Insecurity. Lender in good faith believes itself insecure.

RIGHTS AND REMEDIES ON DEFAULT. If an Event of Default occurs under this Deed of Trust, at any time thereafter, Trustee or Lender may exercise any one or more of the following rights and remedies:

Election of Remedies. Election by Lender to pursue any remedy shall not exclude pursuit of any other remedy, and an election to make expenditures or to take action to perform an obligation of Grantor under this Deed of Trust, after Grantor's failure to perform, shall not affect Lender's right to declare a default and exercise its remedies.

Accelerate Indebtedness. Lender shall have the right at its option without notice to Grantor to declare the entire Indebtedness immediately due and payable, including any prepayment penalty which Grantor would be required to pay.

Foreclosure. With respect to all or any part of the Real Property, the Trustee shall have the right to foreclose by notice and sale, and Lender shall have the right to foreclose by judicial foreclosure, in either case in accordance with and to the full extent provided by applicable law.

UCC Remedies. With respect to all or any part of the Personal Property, Lender shall have all the rights and remedies of a secured party under the Uniform Commercial Code.

Collect Rents. Lender shall have the right, without notice to Grantor to take possession of and manage the Property, and, whether or not Lender takes possession, collect the Rents, including amounts past due and unpaid, and apply the net proceeds, over and above Lender's costs, against the Indebtedness. In furtherance of this right, Lender may require any tenant or other user of the Property to make payments of rent or use fees directly to Lender. If the Rents are collected by Lender, then Grantor irrevocably designates Lender as Grantor's attorney-in-fact to endorse instruments received in payment thereof in the name of Grantor and to negotiate the same and collect the proceeds. Payments by tenants or other users to Lender in response to Lender's demand shall satisfy the obligations for which the payments are made, whether or not any proper grounds for the demand existed. Lender may exercise its rights under this subparagraph either in person, by agent, or through a receiver.

Appoint Receiver. Lender shall have the right to have a receiver appointed to take possession of all or any part of the Property, with the power to protect and preserve the Property, to operate the Property preceding foreclosure or sale, and to collect the Rents from the Property and apply the proceeds, over and above the cost of the receivership, against the Indebtedness. The receiver may serve without bond if permitted by law. Lender's right to the appointment of a receiver shall exist whether or not the apparent value of the Property exceeds the Indebtedness by a substantial amount. Employment by Lender

shall not disqualify a person from serving as a receiver.

Tenancy at Sufferance. If Grantor remains in possession of the Property after the Property is sold as provided above or Lender otherwise becomes entitled to possession of the Property upon default of Grantor, Grantor shall become a tenant at sufferance of Lender or the purchaser of the Property and shall, at Lender's option, either (1) pay a reasonable rental for the use of the Property, or (2) vacate the Property immediately upon the demand of Lender.

Other Remedies. Trustee or Lender shall have any other right or remedy provided in this Deed of Trust or the Note or available at law or in equity.

Notice of Sale. Lender shall give Grantor reasonable notice of the time and place of any public sale of the Personal Property or of the time after which any private sale or other intended disposition of the Personal Property is to be made. Reasonable notice shall mean notice given at least ten (10) days before the time of the sale or disposition. Notices given by Lender or Trustee under the real property foreclosure proceedings shall be deemed reasonable. Any sale of the Personal Property may be made in conjunction with any sale of the Real Property.

Sale of the Property. To the extent permitted by applicable law, Grantor hereby waives any and all rights to have the Property marshalled. In exercising its rights and remedies, the Trustee or Lender shall be free to sell all or any part of the Property together or separately, in one sale or by separate sales. Lender shall be entitled to bid at any public sale on all or any portion of the Property. The power of sale under this Deed of Trust shall not be exhausted by any one or more sales (or attempts to sell) as to all or any portion of the Real Property remaining unsold, but shall continue unimpaired until all of the Real Property has been sold by exercise of the power of sale and all Indebtedness has been paid in full.

Attorneys' Fees; Expenses. If Lender institutes any suit or action to enforce any of the terms of this Deed of Trust, Lender shall be entitled to recover such sum as the court may adjudge reasonable as attorneys' fees at trial and upon any appeal. Whether or not any court action is involved, and to the extent not prohibited by law, all reasonable expenses Lender incurs that in Lender's opinion are necessary at any time for the protection of its interest or the enforcement of its rights shall become a part of the Indebtedness payable on demand and shall bear interest at the Note rate from the date of the expenditure until repaid. Expenses covered by this paragraph include, without limitation, however subject to any limits under applicable law, Lender's attorneys' fees and Lender's legal expenses, whether or not there is a lawsuit, including attorneys' fees and expenses for bankruptcy proceedings (including efforts to modify or vacate any automatic stay or injunction), appeals, and any anticipated post-judgment collection services, the cost of searching records, obtaining title reports (including foreclosure reports), surveyors' reports, and appraisal fees, title insurance, and fees for the Trustee, to the extent permitted by applicable law. Grantor also will pay any court costs, in addition to all other sums provided by law. Fees and expenses shall include attorneys' fees that Lender, Trustee, or both incur, if either or both are made parties to any action to enjoin foreclosure or to any legal proceeding that Grantor institutes. The fees and expenses are secured by this Deed of Trust and are recoverable from the Property.

Rights of Trustee. Trustee shall have all of the rights and duties of Lender as set forth in

this section.

POWERS AND OBLIGATIONS OF TRUSTEE. The following provisions relating to the powers and obligations of Trustee are part of this Deed of Trust:

Powers of Trustee. In addition to all powers of Trustee arising as a matter of law, Trustee shall have the power to take the following actions with respect to the Property upon the written request of Lender and Grantor: (a) join in preparing and filing a map or plat of the Real Property, including the dedication of streets or other rights to the public; (b) join in granting any easement or creating any restriction on the Real Property; and (c) join in any subordination or other agreement affecting this Deed of Trust or the interest of Lender under this Deed of Trust.

Obligations to Notify. Trustee shall not be obligated to notify any other party of a pending sale under any other trust deed or lien, or of any action or proceeding in which Grantor, Lender, or Trustee shall be a party, unless the action or proceeding is brought by Trustee.

Trustee. Trustee shall meet all qualifications required for Trustee under applicable law. In addition to the rights and remedies set forth above, with respect to all or any part of the Property, the Trustee shall have the right to foreclose by notice and sale, and Lender shall have the right to foreclose by judicial foreclosure, in either case in accordance with and to the full extent provided by applicable law.

Successor Trustee. Lender, at Lender's option, may from time to time appoint a successor Trustee or Trustees to any Trustee under this Deed of Trust by an instrument executed and acknowledged by Lender, which shall be conclusive proof of the proper appointment of such substituted Trustee or Trustees. Upon the recording of such executed and acknowledged instrument in the office of the recorder of the county where the Real Property is located, the successor trustee or trustees, without conveyance of the Property, shall succeed to, and be vested with, all the title, powers, interests, duties and trusts vested in or conferred upon the Trustee in this Deed of Trust and by applicable law. If there be more than one Trustee, either may act alone and execute the trusts upon the request of Lender, and all of the Trustee's acts thereunder shall be deemed to be the acts of all Trustees, and the recital in any conveyance executed by such sole Trustee of such request shall be conclusive evidence thereof, and of the authority of such sole Trustee to act. This procedure for substitution of Trustee shall govern to the exclusion of all other provisions for substitution.

CONSENT TO SELL LOAN. The parties hereto agree: (a) Lender may sell or transfer all or part of this loan to one or more purchasers, whether related or unrelated to Lender, without notice and without the consent of the parties; (b) Lender may provide to any purchaser, or potential purchaser, any information or knowledge Lender may have about the parties or about any other matter relating to this loan obligation, without notice, and the parties waive any rights to privacy it may have with respect to such matters; (c) the purchaser of a loan will be considered its absolute owner and will have all the rights granted under the loan documents or agreements governing the sale of the loan; (d) the purchaser of a loan may enforce its interests irrespective of any claims or defenses that the parties may have against Lender; and (e) to waive all notices of sale of the loan, as well as all notices of any repurchase, and all rights of offset or counterclaim that the parties have now or later against Lender or against any purchaser of the loan.

FACSIMILE AND COUNTERPART. This document may be signed in any number of separate copies, each of which shall be effective as an original, but all of which taken together shall constitute a single document. An electronic transmission or other facsimile of this document or any related document shall be deemed an original and shall be admissible as evidence of the document and the signer's execution.

COMMUNITY AND OTHER PROPERTY. In addition to the rights of Lender under any applicable community property laws, Borrower, Guarantor or Grantor who is a Married Person and who has an interest in marital or community property under applicable law acknowledges and agrees that his/her obligation as a Borrower, Guarantor or Grantor is incurred in the interest of and to benefit the marital community (or domestic partnership, if applicable), and expressly agrees that recourse may be had against his or her separate property and his or her rights in community property and community assets for all of his or her obligations to Lender, in addition to any other property that may be subject to rights of Lender. Borrower and Guarantor also agree not to, without Lender's prior written consent, enter into any community property agreement which alters the separate or community property character of any of such party's property. For the purpose of this provision, "Married Person" means a person in a spousal relationship and shall include parties to a duly registered and/or legally recognized same-sex civil union, domestic partnership, and other terms, whether or not gender-specific in a spousal relationship, that denote spousal relationship, as those terms are used throughout the laws, codes and regulations of states and/or jurisdictions that recognize legally married same-sex couples, civil unions and/or domestic partnerships, and any references herein to a married person or marital status shall be deemed to also include the applicable corresponding term, or other reference relating to a party to a civil union or domestic partnership. To the extent this provision may conflict with another provision of this Guaranty that other provision shall control.

EXECUTION OF DOCUMENTS, CONSULTATION WITH COUNSEL. Each party hereto acknowledges and agrees that he/she/it has had an opportunity to review and consider the terms and provisions of this agreement and each related loan document, to consult with counsel of his/her/its choice, if desired, and to suggest changes to the structure and terms of the agreements. Each party hereto warrants and agrees that his/her/its execution of this agreement and any related loan documents is made voluntarily and with full knowledge of the significance and effect of such agreements.

DEFINITION OF INDEBTEDNESS. The definition of "Indebtedness" herein includes, without limitation, all liability of Borrower or other party having its obligations to Lender secured by this Deed of Trust, whether liquidated or unliquidated, defined, contingent, conditional or of any other nature whatsoever, and performance of all other obligations, arising under any swap, derivative, foreign exchange or hedge transaction or arrangement (or other similar transaction or arrangement howsoever described or defined) at any time entered into with Lender in connection with the Note.

ENCUMBRANCES. Grantor/Mortgagor/Trustor shall not, without Lender's consent, mortgage, assign, grant a lien upon or security interest in, or otherwise encumber the Property or any interest in the Property, or allow such a lien or security interest to exist or arise, whether voluntarily, involuntarily or by operation of law, except for liens and security interests in favor of Lender, or property taxes attributable to the Property which are not past due.

APPRAISALS, FEES AND EXPENSES. Grantor/Trustor agrees that Lender may obtain appraisals

and reappraisals and perform property evaluations and appraisal reviews of the Real Property when required by the regulations of the Federal Reserve Board or the Office of the Comptroller of the Currency, or any other regulatory agency, or at such other times as Lender may reasonably require. Appraisals shall be performed by an independent third party appraiser selected by Lender; property evaluations and appraisal reviews may be performed by third party appraisers or appraisers and staff of Lender. The fees, expenses and other cost of such appraisals, reappraisals, property evaluations and appraisal reviews shall be paid by Grantor/Trustor. In addition, Grantor/Trustor shall be responsible for payment of all fees and expenses of Lender and third parties relating to inspecting the Real Property, environmental review, title policies and endorsements (or title searches, abstracts of title or legal opinions of title where applicable), and monitoring the payment of property taxes, and any governmental taxes, fees and recording costs relating to this deed.

LEASES AND RENTS. Grantor/Trustor/Mortgagor presently assigns to Lender all of Grantor/Trustor/Mortgagor's right, title and interest in and to all present and future leases of the Property and all rents from the Property. **This Assignment of Rents is given to secure (A) Payment of the Indebtedness and (B) Performance of any and all obligations under the Note and Mortgage/Deed of Trust.** Grantor/Trustor/Mortgagor's present assignment to Lender hereunder is of all present and future leases includes all leases, licenses, rental agreements and other agreements of any kind relating to the use or occupancy of any of the Property, together with all guarantees of and security for any tenant's performance, and all extensions, renewals and modifications thereto (as used in this paragraph, each, a "Lease" and collectively, the "Leases"), together with any and all Rents from the Property. This assignment shall not impose upon Lender any duty to produce Rents, nor cause Lender to be a "mortgagee in possession," or responsible for performing any of the obligations of the lessor under any Lease. Lender confers upon Grantor/Trustor/Mortgagor a license to collect and retain the Rents as they come due, until the occurrence of any Event of Default, at which time the license shall be automatically revoked, and Lender, or its designated agent may, at its option and without notice, make, cancel, enforce or modify any Lease or Rents, collect Rents and do any acts which Lender deems proper to protect the security hereof or exercise any other right or remedy hereunder. Grantor/Trustor/Mortgagor represents and warrants that there exists no material default under present Leases and that those Leases are in full force and effect. Lender, at its option and without notice, may notify any tenant of this assignment of the Leases and Rents. Grantor/Trustor/Mortgagor agrees, at its expense, (i) to comply with and enforce all the terms and conditions under each Lease, and defend in any action in connection with any Lease; (ii) not to modify any Lease in any material respect, nor accept surrender under or terminate the term of any Lease, nor waive or release any tenant under any Lease; (iii) not to anticipate the Rents under any Lease; and (iv) to give prompt notice to Lender of any default by any tenant under any Lease, and of any notice of default on the part of Grantor/Trustor/Mortgagor under any Lease received from a tenant. Should Grantor/Trustor/Mortgagor fail to do any act required to be done by Grantor/Trustor/Mortgagor hereunder, then Lender, at its option and without notice, may make or do the same in such manner and to such extent as Lender deems necessary to protect the security hereof. Grantor/Trustor/Mortgagor agrees to pay to Lender immediately upon demand all sums expended under the authority hereof, including reasonable attorneys' fees, together with interest thereon at the highest rate per annum payable under any Indebtedness, and the same, at Lender's option, may be added to the Indebtedness and secured hereby.

ASSOCIATION OF UNIT OWNERS. The following provisions apply if the Real Property has been submitted to unit ownership law or similar law for the establishment of condominiums or cooperative ownership of the Real Property:

A. Power of Attorney. Trustor/Grantor grants an irrevocable power of attorney to Lender to vote in Lender's discretion on any matter that may come before the association of unit owners. Lender shall have the right to exercise this power of attorney only after Trustor's/Grantor's default; however, Lender may decline to exercise this power as Lender sees fit.

B. Insurance. The insurance as required herein may be carried by the association of unit owners on Trustor's/Grantor's behalf, and the proceeds of such insurance may be paid to the association of unit owners for the purpose of repairing or reconstructing the Property. If not so used by the association, such proceeds shall be paid to Lender.

C. Default. Trustor's/Grantor's failure to perform any of the obligations imposed on Trustor/Grantor by the declaration submitting the Real Property to unit ownership, by the bylaws of the association of unit owners, or by any rules or regulations thereunder, shall be an event of default under this Deed of Trust. If Trustor's/Grantor's interest in the Real Property is a leasehold interest and such property has been submitted to unit ownership, any failure by Trustor/Grantor to perform any of the obligations imposed on Trustor/Grantor by the lease of the Real Property from its owner, any default under such lease which might result in termination of the lease as it pertains to the Real Property, or any failure of Trustor/Grantor as a member of an association of unit owners to take any reasonable action within Trustor's/Grantor's power to prevent a default under such lease by the association of unit owners or by any member of the association shall be an Event of Default under this Deed of Trust.

FAILURE TO PROVIDE INSURANCE. Grantor/Trustor/Mortgagor ("Owner") acknowledges and agrees that if Owner fails to provide any required insurance on the terms set forth herein or in any Related Documents, or fails to continue such insurance in force in compliance with the requirements of this agreement or any Related Documents, Lender may purchase insurance at Owner's expense as provided therein. Such insurance may protect Lender's interests, and may otherwise protect none of, or less than all of, Owner's interests. The cost of any such insurance shall become a part of the Indebtedness and shall be payable on demand or added to the Note as provided herein, at Lender's option. OWNER ACKNOWLEDGES THAT IF LENDER SO PURCHASES ANY SUCH INSURANCE, THE INSURANCE MAY PROVIDE LIMITED PROTECTION AGAINST PHYSICAL DAMAGE TO THE COLLATERAL, UP TO THE BALANCE OF THE LOAN; HOWEVER, OWNER'S EQUITY IN THE COLLATERAL MAY NOT BE INSURED. IN ADDITION, THE INSURANCE MAY NOT PROVIDE ANY PUBLIC LIABILITY OR PROPERTY DAMAGE INDEMNIFICATION AND MAY NOT MEET THE REQUIREMENTS OF ANY FINANCIAL RESPONSIBILITY LAWS.

LENDER TO BE NAMED LOSS PAYEE. All required policies and certificates of insurance shall name Mortgagee/Beneficiary as loss payee, and shall provide that the insurance cannot be terminated as to Mortgagee/Beneficiary except upon a minimum of ten (10) days' prior written notice to Mortgagee/Beneficiary. Immediately upon any request by Lender/Mortgagee/Beneficiary, Grantor/Trustor/Mortgagor shall deliver to Lender/Mortgagee/Beneficiary the original of all such policies or certificates, with receipts evidencing annual prepayment of the premiums.

ARBITRATION AGREEMENT. **Arbitration - Binding Arbitration.** Lender and each party to this

agreement hereby agree, upon demand by any party, to submit any Dispute to binding arbitration in accordance with the terms of this Arbitration Program. Arbitration may be demanded before the institution of a judicial proceeding, or during a judicial proceeding, but not more than 60 days after service of a complaint, third party complaint, cross-claim, or any answer thereto, or any amendment to any of such pleadings. A "Dispute" shall include any dispute, claim or controversy of any kind, whether in contract or in tort, legal or equitable, now existing or hereafter arising, relating in any way to any aspect of this agreement, or any related note, instrument or agreement incorporating this Arbitration Program (the "Documents"), or any renewal, extension, modification or refinancing of any indebtedness or obligation relating thereto, including without limitation, their negotiation, execution, collateralization, administration, repayment, modification, extension, substitution, formation, inducement, enforcement, default or termination, or any request for additional credit. This provision is a material inducement for the parties entering into the transactions relating to this Agreement. In the event of a court ordered arbitration, the party requesting arbitration shall be responsible for timely filing the demand for arbitration and paying the appropriate filing fee within 30 days of the abatement order or the time specified by the court; the party's failure to do so shall result in that party's right to demand arbitration being automatically terminated with respect to such Dispute. DISPUTES SUBMITTED TO ARBITRATION ARE NOT RESOLVED IN COURT BY A JUDGE OR JURY. TO THE EXTENT ALLOWED BY APPLICABLE LAW, THE PARTIES IRREVOCABLY AND VOLUNTARILY WAIVE ANY RIGHT THEY MAY HAVE TO A TRIAL BY JURY WITH RESPECT TO ANY DISPUTE ARBITRATED PURSUANT TO THIS ARBITRATION PROGRAM.

A. Governing Rules. Any arbitration proceeding will (i) be governed by the Federal Arbitration Act (Title 9 of the United States Code), notwithstanding any conflicting choice of law provision in any of the documents between the parties; and (ii) be conducted by the American Arbitration Association ("AAA"), or such other administrator as the parties shall mutually agree upon, in accordance with the AAA's commercial dispute resolution procedures, unless the claim or counterclaim is at least $1,000,000.00 exclusive of claimed interest, arbitration fees and costs, in which case the arbitration shall be conducted in accordance with the AAA's optional procedures for large, complex commercial disputes (the commercial dispute resolution procedures or the optional procedures for large, complex commercial disputes are referred to herein, as applicable, as the "Rules"). If there is any inconsistency between the terms hereof and the Rules, the terms and procedures set forth herein shall control. Arbitration proceedings hereunder shall be conducted at a location mutually agreeable to the parties, or if they cannot agree, then at a location selected by the AAA in the state of the applicable substantive law primarily governing the Note. Any party who fails or refuses to submit to arbitration following a demand by any other party shall bear all costs and expenses incurred by such other party in compelling arbitration of any Dispute. The arbitrator shall award all costs and expenses of the arbitration proceeding.

B. No Waiver of Provisional Remedies, Self-Help and Foreclosure. The arbitration requirement does not limit the right of any party to (i) foreclose against real or personal property collateral; (ii) exercise self-help remedies relating to collateral or proceeds of collateral such as setoff or repossession; or (iii) obtain provisional or ancillary remedies such as replevin, injunctive relief, attachment or the appointment of a receiver, before during or after the pendency of any arbitration proceeding. This exclusion does not constitute a waiver of the right or obligation of any party to submit any Dispute to arbitration or reference hereunder, including those arising

from the exercise of the actions detailed in sections (i), (ii) and (iii) of this paragraph.

C. Arbitrator Qualifications and Powers. Any arbitration proceeding in which the amount in controversy is $5,000,000.00 or less will be decided by a single arbitrator selected according to the Rules, and who shall not render an award of greater than $5,000,000.00. Any Dispute in which the amount in controversy exceeds $5,000,000.00 shall be decided by majority vote of a panel of three arbitrators; provided however, that all three arbitrators must actively participate in all hearings and deliberations. Every arbitrator shall be a neutral practicing attorney or a retired member of the state or federal judiciary, in either case with a minimum of ten years experience in the substantive law applicable to the subject matter of the Dispute. The arbitrator will determine whether or not an issue is arbitratable and will give effect to the statutes of limitation in determining any claim. In any arbitration proceeding the arbitrator will decide (by documents only or with a hearing at the arbitrator's discretion) any pre-hearing motions which are similar to motions to dismiss for failure to state a claim or motions for summary adjudication. The arbitrator shall resolve all Disputes in accordance with the applicable substantive law and may grant any remedy or relief that a court of such state could order or grant within the scope hereof and such ancillary relief as is necessary to make effective any award. The arbitrator shall also have the power to award recovery of all costs and fees, to impose sanctions and to take such other action as the arbitrator deems necessary to the same extent a judge could pursuant to the Federal Rules of Civil Procedure, the applicable state rules of civil procedure, or other applicable law. Judgment upon the award rendered by the arbitrator may be entered in any court having jurisdiction. The institution and maintenance of an action for judicial relief or pursuit of a provisional or ancillary remedy shall not constitute a waiver of the right of any party, including the plaintiff, to submit the controversy or claim to arbitration if any other party contests such action for judicial relief.

D. Discovery. In any arbitration proceeding discovery will be permitted in accordance with the Rules. All discovery shall be expressly limited to matters directly relevant to the Dispute being arbitrated and must be completed no later than 20 days before the hearing date. Any requests for an extension of the discovery periods, or any discovery disputes, will be subject to final determination by the arbitrator upon a showing that the request for discovery is essential for the party's presentation and that no alternative means for obtaining information is available.

E. Class Proceedings and Consolidations. No party hereto shall be entitled to join or consolidate disputes by or against others in any arbitration, except parties to this agreement, or any contract, instrument or document relating to this agreement, or to include in any arbitration any dispute as a representative or member of a class, or to act in any arbitration in the interest of the general public or in a private attorney general capacity.

F. Small Claims Court. Any party may require that a Dispute be resolved in Small Claims Court if the Dispute and related claims are fully within that court's jurisdiction.

G. State Specific Provisions:

If Delaware, Pennsylvania or Virginia law governs the Dispute, **the following provision is applicable if there is a Confession of Judgment in the Note, any Guaranty, or Related Documents: Confession of Judgment.** Notwithstanding anything herein to the contrary, the arbitration requirement does not limit or preclude the right of Lender to confess judgment pursuant to a warrant of attorney provision set forth in the Note, any Guaranty, or Related

Documents. No party shall have the right to demand binding arbitration of any claim, dispute or controversy seeking to (i) strike-off or open a judgment obtained by confession pursuant to a warrant of attorney contained in the Note, any Guaranty, or Related Documents, or (ii) challenge the waiver of a right to prior notice and a hearing before judgment is entered, or after judgment is entered, but before execution upon the judgment. Any claims, disputes or controversies challenging the confession of judgment shall be commenced and prosecuted in accordance with the procedures set forth, and in the forum specified by the applicable state rules of civil procedure or other applicable law.

If Maryland law governs the Dispute, the following provision is applicable if there is a Confession of Judgment in the Note, any Guaranty, or Related Documents: Confession of Judgment. Notwithstanding anything herein to the contrary, the arbitration requirement does not limit or preclude the right of Lender to confess judgment, and no party shall have the right to demand binding arbitration of any claim, dispute or controversy seeking to open a judgment obtained by confession. Nothing herein, including the arbitration requirement, shall limit the right of any party to foreclose judicially or non-judicially against any real or personal property collateral, or exercise judicial or non-judicial power of sale rights. No provision regarding submission to a jurisdiction and/or venue in any court or the waiver of any right to trial by jury is intended or shall be construed to be in derogation of the provisions for arbitration of any dispute. Any claim or counterclaim or defense raised in connection with Lender's exercise of any rights set forth in the Note, any Guaranty, or Related Documents shall be subject to the arbitration requirement.

If South Carolina law governs the Dispute, the following provision is included: WAIVER OF JURY TRIAL. NOTWITHSTANDING ANYTHING HEREIN TO THE CONTRARY, WITHOUT INTENDING IN ANY WAY TO LIMIT THE PARTIES' AGREEMENT TO ARBITRATE ANY DISPUTE AS SET FORTH IN THIS MORTGAGE, TO THE EXTENT ANY DISPUTE IS NOT SUBMITTED TO ARBITRATION OR IS DEEMED BY THE ARBITRATOR OR BY ANY COURT WITH JURISDICTION TO BE NOT ARBITRABLE OR NOT REQUIRED TO BE ARBITRATED, LENDER AND MORTGAGOR WAIVE TRIAL BY JURY IN RESPECT OF ANY SUCH DISPUTE AND ANY ACTION ON SUCH DISPUTE. THIS WAIVER IS KNOWINGLY, WILLINGLY AND VOLUNTARILY MADE BY LENDER AND MORTGAGOR, AND THEY HEREBY REPRESENT THAT NO REPRESENTATIONS OF FACT OR OPINION HAVE BEEN MADE BY ANY PERSON OR ENTITY TO INDUCE THIS WAIVER OF TRIAL BY JURY OR TO IN ANY WAY MODIFY OR NULLIFY ITS EFFECT. THIS PROVISION IS A MATERIAL INDUCEMENT FOR THE PARTIES ENTERING INTO THE LOAN DOCUMENTS. LENDER AND MORTGAGOR ARE EACH HEREBY AUTHORIZED TO FILE A COPY OF THIS SECTION IN ANY PROCEEDING AS CONCLUSIVE EVIDENCE OF THIS WAIVER OF JURY TRIAL. MORTGAGOR FURTHER REPRESENTS AND WARRANTS THAT IT HAS BEEN REPRESENTED IN THE SIGNING OF THIS MORTGAGE AND IN THE MAKING OF THIS WAIVER BY INDEPENDENT LEGAL COUNSEL, OR HAS HAD THE OPPORTUNITY TO BE REPRESENTED BY INDEPENDENT LEGAL COUNSEL SELECTED OF ITS OWN FREE WILL, AND THAT IT HAS HAD THE OPPORTUNITY TO DISCUSS THIS WAIVER WITH COUNSEL.

H. Real Property Collateral:

If California law governs the Dispute, the following provisions are included: Real Property Collateral; Judicial Reference. Notwithstanding anything herein to the contrary, no Dispute shall be submitted to arbitration if the Dispute concerns indebtedness secured directly or indirectly, in whole or in part, by any real property unless (i) the holder of the mortgage, lien or security

interest specifically elects in writing to proceed with the arbitration, or (ii) all parties to the arbitration waive any rights or benefits that might accrue to them by virtue of the single action rule statute of California, thereby agreeing that all indebtedness and obligations of the parties, and all mortgages, liens and security interests securing such indebtedness and obligations, shall remain fully valid and enforceable. If any such Dispute is not submitted to arbitration, the Dispute shall be referred to a referee in accordance with California Code of Civil Procedure Section 638 et seq., and this general reference agreement is intended to be specifically enforceable in accordance with said Section 638, as amended or replaced from time to time. A referee with the qualifications required herein for arbitrators shall be selected pursuant to the AAA's selection procedures. Judgment upon the decision rendered by a referee shall be entered in the court in which such proceeding was commenced in accordance with California Code of Civil Procedure Sections 644 and 645, as amended or replaced from time to time.

If Connecticut law governs the Dispute, the following provision is included: Real Property Collateral. Notwithstanding anything herein to the contrary, no dispute shall be submitted to arbitration if the dispute concerns indebtedness secured directly or indirectly, in whole or in part, by any real property located in Connecticut unless (i) the holder of the mortgage, lien or security interest specifically elects in writing to proceed with the arbitration, or (ii) all parties to the arbitration waive any rights or benefits that might accrue to them by virtue of Sections 49-1 and 49-14 et seq. of the Connecticut General Statutes, as amended or replaced from time to time, thereby agreeing that all indebtedness and obligations of the parties, and all mortgages, liens and security interests securing such indebtedness and obligations, shall remain fully valid and enforceable.

If Idaho, Kansas, Montana, Nevada, South Dakota or Virginia law governs the Dispute, the following provision is included:

Real Property Collateral. Notwithstanding anything herein to the contrary, no Dispute shall be submitted to arbitration if the Dispute concerns indebtedness secured directly or indirectly, in whole or in part, by any real property unless (i) the holder of the mortgage, lien or security interest specifically elects in writing to proceed with the arbitration, or (ii) all parties to the arbitration waive any rights or benefits that might accrue to them by virtue of the single action rule statute of Idaho, Kansas, Montana, Nevada, South Dakota or Virginia, thereby agreeing that all indebtedness and obligations of the parties, and all mortgages, liens and security interests securing such indebtedness and obligations, shall remain fully valid and enforceable.

If Utah law governs the Dispute, the following provision is included: Real Property Collateral; Judicial Reference. Notwithstanding anything herein to the contrary, no Dispute shall be submitted to arbitration if the Dispute concerns indebtedness secured directly or indirectly, in whole or in part, by any real property unless (i) the holder of the mortgage, lien or security interest specifically elects in writing to proceed with the arbitration, or (ii) all parties to the arbitration waive any rights or benefits that might accrue to them by virtue of the single action rule statute of Utah, thereby agreeing that all indebtedness and obligations of the parties, and all mortgages, liens and security interests securing such indebtedness and obligations, shall remain fully valid and enforceable. If any such Dispute is not submitted to arbitration, the Dispute shall be referred to a master in accordance with Utah Rule of Civil Procedure 53, as amended or replaced from time to time, and this general reference agreement is intended to be specifically enforceable. A master with the qualifications required herein for arbitrators shall be selected pursuant to the AAA's selection procedures. Judgment upon the decision rendered by

a master shall be entered in the court in which such proceeding was commenced in accordance with Utah Rule of Civil Procedure 53(e), as amended or replaced from time to time.

I. Miscellaneous. To the maximum extent practicable, the AAA, the arbitrators and the parties shall take all action required to conclude any arbitration proceeding within 180 days of the filing of the Dispute with the AAA. No arbitrator or other party to an arbitration proceeding may disclose the existence, content or results thereof, except for disclosures of information by a party required in the ordinary course of its business or by applicable law or regulation. If more than one agreement for arbitration by or between the parties potentially applies to a Dispute, the arbitration provision most directly related to the documents between the parties or the subject matter of the Dispute shall control. This arbitration provision shall survive the repayment of the Note and the termination, amendment or expiration of any of the Documents or any relationship between the parties.

MISCELLANEOUS PROVISIONS. The following miscellaneous provisions are a part of this Deed of Trust:

Amendments. This Deed of Trust, together with any Related Documents, constitutes the entire understanding and agreement of the parties as to the matters set forth in this Deed of Trust. No alteration of or amendment to this Deed of Trust shall be effective unless given in writing and signed by the party or parties sought to be charged or bound by the alteration or amendment.

Annual Reports. If the Property is used for purposes other than Grantor's residence, Grantor shall furnish to Lender, upon request, a certified statement of net operating income received from the Property during Grantor's previous fiscal year in such form and detail as Lender shall require. "Net operating income" shall mean all cash receipts from the Property less all cash expenditures made in connection with the operation of the Property.

Caption Headings. Caption headings in this Deed of Trust are for convenience purposes only and are not to be used to interpret or define the provisions of this Deed of Trust.

Merger. There shall be no merger of the interest or estate created by this Deed of Trust with any other interest or estate in the Property at any time held by or for the benefit of Lender in any capacity, without the written consent of Lender.

Governing Law. This Deed of Trust will be governed by federal law applicable to Lender and, to the extent not preempted by federal law, the laws of the State of Nevada without regard to its conflicts of law provisions. This Deed of Trust has been accepted by Lender in the State of Nevada.

No Waiver by Lender. Lender shall not be deemed to have waived any rights under this Deed of Trust unless such waiver is given in writing and signed by Lender. No delay or omission on the part of Lender in exercising any right shall operate as a waiver of such right or any other right. A waiver by Lender of a provision of this Deed of Trust shall not prejudice or constitute a waiver of Lender's right otherwise to demand strict compliance with that provision or any other provision of this Deed of Trust. No prior waiver by Lender, nor any course of dealing between Lender and Grantor, shall constitute a waiver of any of Lender's rights or of any of Grantor's obligations as to any future transactions. Whenever the consent of Lender is required under this Deed of Trust, the granting of such consent by Lender in any instance shall not constitute continuing consent to subsequent instances

where such consent is required and in all cases such consent may be granted or withheld in the sole discretion of Lender.

Severability. If a court of competent jurisdiction finds any provision of this Deed of Trust to be illegal, invalid, or unenforceable as to any circumstance, that finding shall not make the offending provision illegal, invalid, or unenforceable as to any other circumstance. If feasible, the offending provision shall be considered modified so that it becomes legal, valid and enforceable. If the offending provision cannot be so modified, it shall be considered deleted from this Deed of Trust. Unless otherwise required by law, the illegality, invalidity, or unenforceability of any provision of this Deed of Trust shall not affect the legality, validity or enforceability of any other provision of this Deed of Trust.

Successors and Assigns. Subject to any limitations stated in this Deed of Trust on transfer of Grantor's interest, this Deed of Trust shall be binding upon and inure to the benefit of the parties, their successors and assigns. If ownership of the Property becomes vested in a person other than Grantor, Lender, without notice to Grantor, may deal with Grantor's successors with reference to this Deed of Trust and the Indebtedness by way of forbearance or extension without releasing Grantor from the obligations of this Deed of Trust or liability under the Indebtedness.

Time is of the Essence. Time is of the essence in the performance of this Deed of Trust.

Waiver of Homestead Exemption. Grantor hereby releases and waives all rights and benefits of the homestead exemption laws of the State of Nevada as to all Indebtedness secured by this Deed of Trust.

DEFINITIONS. The following capitalized words and terms shall have the following meanings when used in this Deed of Trust. Unless specifically stated to the contrary, all references to dollar amounts shall mean amounts in lawful money of the United States of America. Words and terms used in the singular shall include the plural, and the plural shall include the singular, as the context may require. Words and terms not otherwise defined in this Deed of Trust shall have the meanings attributed to such terms in the Uniform Commercial Code:

Beneficiary. The word "Beneficiary" means Wells Fargo Bank, National Association, and its successors and assigns.

Borrower. The word "Borrower" means PATIENCE ONE LLC and includes all co-signers and co-makers signing the Note and all their successors and assigns.

Deed of Trust. The words "Deed of Trust" mean this Deed of Trust among Grantor, Lender, and Trustee.

Default. The word "Default" means the Default set forth in this Deed of Trust in the section titled "Default".

Environmental Laws. The words "Environmental Laws" mean any and all state, federal and local statutes, regulations and ordinances relating to the protection of human health or the environment, including without limitation the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended, 42 U.S.C. Section 9601, et seq. ("CERCLA"), the Superfund Amendments and Reauthorization Act of 1986, Pub. L. No. 99-499 ("SARA"), the Hazardous Materials Transportation Act, 49 U.S.C. Section 1801, et seq., the Resource Conservation and Recovery Act, 42 U.S.C. Section 6901, et seq., or

other applicable state or federal laws, rules, or regulations adopted pursuant thereto.

Event of Default. The words "Event of Default" mean any of the events of default set forth in this Deed of Trust in the events of default section of this Deed of Trust.

Grantor. The word "Grantor" means PATIENCE ONE LLC.

Guarantor. The word "Guarantor" means any guarantor, surety, or accommodation party of any or all of the Indebtedness.

Guaranty. The word "Guaranty" means the guaranty from Guarantor to Lender, including without limitation a guaranty of all or part of the Note.

Hazardous Substances. The words "Hazardous Substances" mean materials that, because of their quantity, concentration or physical, chemical or infectious characteristics, may cause or pose a present or potential hazard to human health or the environment when improperly used, treated, stored, disposed of, generated, manufactured, transported or otherwise handled. The words "Hazardous Substances" are used in their very broadest sense and include without limitation any and all hazardous or toxic substances, materials or waste as defined by or listed under the Environmental Laws. The term "Hazardous Substances" also includes, without limitation, petroleum and petroleum by-products or any fraction thereof and asbestos.

Improvements. The word "Improvements" means all existing and future improvements, buildings, structures, mobile homes affixed on the Real Property, facilities, additions, replacements and other construction on the Real Property.

Indebtedness. The word "Indebtedness" means all principal, interest, and other amounts, costs and expenses payable under the Note or Related Documents, together with all renewals of, extensions of, modifications of, consolidations of and substitutions for the Note or Related Documents and any amounts expended or advanced by Lender to discharge Grantor's obligations or expenses incurred by Trustee or Lender to enforce Grantor's obligations under this Deed of Trust, together with interest on such amounts as provided in this Deed of Trust.

Lender. The word "Lender" means Wells Fargo Bank, National Association, its successors and assigns.

Note. The word "Note" means the promissory note dated June 25, 2014, **in the original principal amount of $1,500,000.00** from Grantor to Lender, together with all renewals of, extensions of, modifications of, refinancings of, consolidations of, and substitutions for the promissory note or agreement.

Personal Property. The words "Personal Property" mean all equipment, fixtures, mobile homes, manufactured homes or modular homes which have not been legally acceded to the real property in accordance with Nevada law, and other articles of personal property now or hereafter owned by Grantor, and now or hereafter attached or affixed to or used in the operation of the Real Property; together with all accessions, parts, and additions to, all replacements of, and all substitutions for, any of such property; and together with all proceeds (including without limitation all insurance proceeds and refunds of premiums) from any sale or other disposition of the Property.

Property. The word "Property" means collectively the Real Property and the Personal Property.

Real Property. The words "Real Property" mean the real property, interests and rights, as further described in this Deed of Trust.

Related Documents. The words "Related Documents" mean all promissory notes, credit agreements, loan agreements, environmental agreements, security agreements, mortgages, deeds of trust, security deeds, collateral mortgages, and all other instruments, agreements and documents, whether now or hereafter existing, executed in connection with the Indebtedness; except that the words do not mean any guaranty whether now or hereafter existing, executed in connection with the Indebtedness.

Rents. The word "Rents" means all present and future rents, revenues, income, issues, royalties, profits, and other benefits derived from the Property.

Trustee. The word "Trustee" means Wells Fargo Financial National Bank, whose address is c/o BBSG-San Antonio Loan Ops LDI, PO Box 65119, San Antonio, TX 78265 and any substitute or successor trustees.

GRANTOR ACKNOWLEDGES HAVING READ ALL THE PROVISIONS OF THIS DEED OF TRUST, AND GRANTOR AGREES TO ITS TERMS.

GRANTOR:

PATIENCE ONE LLC

By: _____
Thomas A Pickens, Manager of PATIENCE ONE LLC

By: _____
Danka K Michaels, Manager of PATIENCE ONE LLC

Thomas A Pickens, Manager of PATIENCE ONE LLC

Danka K Michaels, Manager of PATIENCE ONE LLC

LIMITED LIABILITY COMPANY ACKNOWLEDGMENT

STATE OF Nevada)
) SS
COUNTY OF Clark)

This instrument was acknowledged before me on June 30, 2014 by Thomas A Pickens, Manager of PATIENCE ONE LLC, as designated agent of PATIENCE ONE LLC.

SANDRA L CLARK
Notary Public-State of Nevada
APPT. NO. 88-1652-1
My App. Expires Februdry 06, 2017

Sandra L Clark
(Signature of notarial officer)

Notary Public in and for State of NV

(Seal, if any)

Sandra L. Clark/#88-1652-1/Exp: 2-6-17

LIMITED LIABILITY COMPANY ACKNOWLEDGMENT

STATE OF Nevada)
) SS
COUNTY OF Clark)

This instrument was acknowledged before me on June 30, 2014 by Danka K Michaels, Manager of PATIENCE ONE LLC, as designated agent of PATIENCE ONE LLC.

SANDRA L CLARK
Notary Public-State of Nevada
APPT. NO. 88-1652-1
My App. Expires February 06, 2017

Sandra L Clark
(Signature of notarial officer)

Notary Public in and for State of NV

(Seal, if any)

Sandra L. Clark/#88-1652-1/Exp: 2-6-17

REQUEST FOR FULL RECONVEYANCE

(To be used only when obligations have been paid in full)

To: _____, Trustee

The undersigned is the legal owner and holder of all Indebtedness secured by this Deed of Trust. All sums secured by this Deed of Trust have been fully paid and satisfied. You are hereby directed, upon payment to you of any sums owing to you under the terms of this Deed of Trust or pursuant to any applicable statute, to cancel the Note secured by this Deed of Trust (which is delivered to you together with this Deed of Trust), and to reconvey, without warranty, to the parties designated by the terms of this Deed of Trust, the estate now held by you under this Deed of Trust. Please mail the reconveyance and Related Documents to:

_____.

Date: _____ Beneficiary: _____

By: _____

Its: _____

LASER PRO Lending, Ver. 14.2.0.021 Copr. D+H USA Corporation 1997, 2014. All Rights Reserved. - NV X:\LPROD\CFI\LPL\G01.FC TR-192495 PR-689

Escrow No.: 14-05-1043-JKH

EXHIBIT "A"

LEGAL DESCRIPTION

THE NORTHWEST QUARTER (NW ¼) OF THE NORTHWEST QUARTER (NW ¼) OF THE SOUTHWEST QUARTER (SW ¼) OF THE SOUTHWEST QUARTER (SW ¼) OF SECTION 19, TOWNSHIP 20 SOUTH, RANGE 60 EAST, M.D.M.

EXCEPTING THE INTEREST IN AND TO THE WEST AND NORTH THIRTY (30) FEET AS CONVEYED BY DEED RECORDED JANUARY 10, 1963, IN BOOK 411, AS DOCUMENT NO. 331992 OF OFFICIAL RECORDS, CLARK COUNTY, NEVADA.

FURTHER EXCEPTING THE EASTERLY TWENTY (20) FEET FO THE WESTERLY FIFTY (50) FEET OF SAID LAND AS CONVEYED TO CLARK COUNTY BY DEED RECORDED JULY 8, 1965 IN BOOK 640 AS DOCUMENT NO. 515041, OF OFFICIAL RECORDS, CLARK COUNTY, NEVADA.

FURTHER EXCEPTING THAT PORTION CONVEYED TO THE CITY OF LAS VEGAS BY DEED RECORDED FEBRUARY 16, 1996 IN BOOK 960216 AS DOCUMENT NO. 01486, OF OFFICIAL RECORDS, CLARK COUNTY, NEVADA.

GENERAL PROVISIONS

I. **CLOSE OF ESCROW, TIME OF THE ESSENCE:** Time is of the essence. Escrow Agent is authorized to take any administrative steps necessary to effect the closing of this escrow subsequent to the date set forth in the Escrow Instructions. Deposit of final funds and executed documents to Escrow by Borrower shall signify that all of the terms and/or conditions in the AGREEMENT have been complied with, or waived, to the satisfaction of the respective depositing party. When the conditions of this Escrow have been so complied with, you are authorized to close Escrow. The term "Close of Escrow" shall mean "Settlement Date: the date all conditions precedent to closing, and/or delivery of deed, have been satisfied". The settlement by Escrow shall include delivery of the instruments and funds to the parties entitled.

II. **DEMAND STATEMENTS:** Escrow Agent is authorized to pay any encumbrance, which a title search reveals against the subject property based on the lienholder's demand, except as set forth herein.

III. **UTILITIES:** Escrow Agent shall have no responsibility for investigating or guaranteeing the status of any trash fee, power, water, telephone, gas and or other utility or use bill, except as otherwise specifically required herein.

REPUBLIC SERVICES: In the event that the purchase agreement requires that Escrow Agent prorate the trash fees represented by Republic Services, it is understood that the period which the seller has paid in advance which would be charged to the buyer and credited to the seller in the prorations, may also be charged to the buyer again by Republic Services upon arranging for new trash services.

CITY OF LAS VEGAS SEWER: In the event the subject property is located within the City of Las Vegas and is subject to City of Las Vegas sewer fees, prorations will be made based solely on the information provided by the City of Las Vegas website. When no specific figure is provided, Escrow Agent will use the general billing information given by the City and prorate accordingly. Escrow Agent will not be responsible for adjustments or corrections of prorations due to lack of information provided by the City. Further, if the subject property has a pool, Escrow Agent will always presume that said pool is less than 30,000 gallons unless instructed in writing to the contrary.

CITY OF NORTH LAS VEGAS, CITY OF HENDERSON AND BOULDER CITY: In the event the subject property is located within the City of North Las Vegas, City of Henderson or Boulder City, there can be NO PRORATIONS of the utility bills. These entities bill all utilities together in a monthly billing and do not provide information other than delinquencies. Escrow Agent's only responsibility when the property is located in said cities shall be to pay any delinquencies or any amounts due relative to an EXISTING lien.

IV. **PERSONAL PROPERTY:** Escrow Agent assumes no liability in connection with any PERSONAL PROPERTY which may be a part of this escrow.

V. **CLEAR FUNDS:** Any check presented for deposit into this escrow by either party shall be subject to clearance thereof and Escrow Agent shall not be obligated to act upon nor disburse against any such funds until notified by the bank that said check has cleared. Any fees imposed by the clearing bank will be the responsibility of the drawer of the instrument. **EFFECTIVE 10/1/2009, NEVADA REVISED STATUTES REQUIRE THAT THE FUNDS USED FOR CLOSING MUST BE ONE OF THE FOLLOWING FORMS:**

1. **CASH (will not be accepted by Nevada Title Company)**
2. **INTERBANK ELECTRONIC TRANSFER (WIRED FUNDS)**
3. **CASHIER'S CHECK OR CERTIFIED CHECK DRAWN ON A NEVADA BANKING INSTITUTION WILL CREATE A 24 HOUR DELAY FROM DATE OF DEPOSIT. A CASHIER'S CHECK DRAWN ON A NON-NEVADA BANK IS NOT ACCEPTABLE FOR IMMEDIATE CLOSING AND COULD CREATE A DELAY OF SEVERAL DAYS AFTER THE DATE OF DEPOSIT.**

VI. **CANCELLATION:** Either party requesting cancellation of this escrow shall notify Escrow Agent in writing. Escrow Agent shall notify the other party by depositing a copy of said notice in the United States Mail, to the last address filed with Escrow Agent or by facsimile or email. Should no address, facsimile number or email address be filed, Escrow Agent shall deposit such notice in the United States Mail c/o General Delivery. The notice shall be deemed to have been given upon deposit of said notice in the United States Mail, addressed as specified

herein, with proper postage affixed thereto and no further notice or evidence of receipt shall be required. Unless written objection to any cancellation notice is received by Escrow Agent within ten (10) business days following Escrow Agent's notification of said cancellation, Escrow Agent is authorized at their discretion to comply with such cancellation notice upon payment of its cancellation charges and expenditures. In the event that such written objection is received, Escrow Agent, acting in its sole discretion, may hold all or part of any money or instruments in this escrow pending mutual written instructions by the parties hereto, or an order by a court of competent jurisdiction.

VII. **INTERPLEADER:** Notwithstanding anything to the contrary herein all parties agree that Escrow Agent shall have the right, at its sole discretion, to file a suit or counter claim in interpleader and to obtain an order from the court directing disbursement of the funds. In the event such suit or claim is brought, the parties hereto jointly and severally agree to pay Escrow Agent all costs, expenses and reasonable attorney fees which it may expend or incur in such interpleader action, the amount thereof to be fixed and judgment therefore to be rendered by the court in such suit. Upon the filing of such suit or counterclaim said Escrow Agent shall thereupon be fully released and discharged from all obligation to further perform any duties or obligations otherwise imposed by the terms of this escrow. Escrow Agent shall have the right at any time to resign its duties as Escrow Agent and/or to refrain from taking any act hereunder.

VIII. **COUNTERPART SIGNATURES:** These instructions may be executed in counterparts.

IX. **PRIVACY NOTICE (15 U.S.C. 6801 and 16 CRF Part 313):** Nonpublic personal information about you is provided to us from information you submit on forms and documents and from others who are involved in your transaction. We do not disclose any nonpublic personal information about our customers or former customers to anyone, except as permitted by law. We restrict access to nonpublic personal information about you to those employees who need to know that information in order to provide products or services to you. We maintain physical, electronic and procedural safeguards that comply with federal regulations to guard your nonpublic personal information.

X. **DELIVERY OF DOCUMENTS TO THIRD PARTIES:** Escrow shall cause recordation and/or filing of original conveyance/security documents with the appropriate State/County Public Official Records Office. Escrow Agent may furnish copies of closing statements and escrow instructions to the Lender and/or Broker involved herein.

XI. **SERVICE FEES:** Upon the close of escrow, or a request for cancellation, NEVADA TITLE COMPANY is hereby authorized to retain out of any funds deposited in said escrow, a reasonable service charge of not less than twenty-five ($25.00) dollars per month for the administration of said funds. In addition, should this escrow be cancelled, Escrow Agent may impose a reasonable cancellation fee for services performed.

XII. **DORMANT/ABANDONED OR UNCLAIMED PROPERTY:** In the event that fun from this transaction remain in an account held by Escrow Agent for such a period of time that they are deemed "abandoned" under the provisions of Chapter 120A of the Nevada Revised Statutes, Escrow Agent is hereby authorized to impose a charge upon the dormant escrow account. Said charge shall be no less than $5.00 per month and may not exceed the highest rate of charge permitted by statute or regulation. Escrow Agent is further authorized and directed to deduct the charge from the dormant escrow account for as long as the funds are held by the Escrow Agent.

XIII. **RIGHT TO RESIGN:** It is expressly understood and agreed that the Escrow Agent, without any obligation to exercise such right, retains the right to resign Escrow Agent and/or to refrain from taking any act which at the sole discretion of Escrow Agent, is deemed inadvisable. No liability shall accrue to Escrow Agent for any such act or forbearance.

XIV. **FACSIMILE/ELECTRONIC TRANSMISSIONS:** Borrower hereby authorize Escrow Agent to rely upon "facsimile" and/or electronically ("email") transmitted signed documents as if they bore original signatures whenever acceptable in compliance with 3rd party requirements.

XV. **CLERICAL ERRORS:** In the event there are any clerical, typographical or scrivener errors to be corrected after the close of escrow, Escrow Agent is authorized to make such corrections as are necessary to make the documents conform to the escrow instructions and other agreements upon which the transaction is based.

XVI. **COMPLIANCE AGREEMENT:** In the event a post-closing or post-disbursement adjustment is necessary, the undersigned authorize Nevada Title Company to advance funds on their behalf to effect an accurate closing settlement. The undersigned agree to fully cooperate and pay to Nevada Title Company any and all funds so advanced on their behalf.

XVII. **1099 FILING REGULATIONS:** Seller is hereby made aware that there is a regulation which became effective January 1, 1987 that requires all Escrow Agents to complete a modified 1099 form, based upon specific information known only between parties in this transaction and the Escrow Agent. You are hereby authorized and instructed to provide this information to the Internal Revenue Service after the close of escrow in the manner prescribed. It is understood that without this information, this transaction will not close with Nevada Title Company as the Escrow Agent.

BORROWER(S), BY THEIR SIGNATURES BELOW, HEREBY EVIDENCE THEIR ACCEPTANCE AND APPROVAL OF THE TERMS SET FORTH ON THIS PAGE

BORROWERS:

Patience One LLC

By: Thomas A. Pickens, Manager

Order No.: 14-05-1043-JKH

GAP INDEMNITY

WHEREAS **Nevada Title Company, its Underwriters and/or Reinsurers (The Company)** is about to issue its title insurance policy upon the real estate described in the order number above.

WHEREAS, **The Company** is unable to access records of all documents recorded effective to the date of closing. This gives rise to the potential for the following:

> Liens, encumbrances, adverse claims or other matters, if any, created by the undersigned first appearing in public records or attaching subsequent to the effective date of the commitment or preliminary report issued in the above referenced order number, but prior to the date proposed insured acquires for value of record the estate or interest or mortgage therein.

WHEREAS, **The Company** has been requested to issue such policies without taking exception to the potential for such matters that may be the responsibility of the undersigned or that the undersigned may have knowledge of.

NOW THEREFORE, in consideration of the issuance of said title insurance policy, the undersigned covenants and agrees with **The Company** (1) to indemnify the Company from and against the above mentioned matters; (2) to defend and save harmless the Company from all loss, costs, damages, attorney's fees and expenses it may suffer, expend or incur under or by reason of them, or which at any time may be claimed to exist under or by reason, or in consequence of or growing out of said matters or of any of them; (3) that each and every provision hereof shall extend to and be in force concerning any and every other title insurance policy or policies which the Company may at anytime or times hereafter issue, insuring against loss by reason of such matters in the manner described above; (4) to reimburse the Company for reasonable attorney's fees and other costs of enforcing this agreement.

The Company shall have the right at any time hereafter, when it shall deem it necessary or expedient, in its reasonable discretion and upon prior written notice to the undersigned to pay, discharge, satisfy or remove from the title to said real estate the said matters or any of them and the undersigned covenants and agree to pay the Company all amounts reasonably expended on demand.

In case such matters are removed from the title to said real estate (other than by the Company) to the reasonable satisfaction of the Company, then the above obligation to be void, otherwise to remain in full force and virtue.

THE UNDERSIGNED EXECUTES THIS AGREEMENT BECAUSE OF THE BENEFITS DIRECTLY AND INDIRECTLY ACCRUING TO IT BY REASON OF THE ISSUANCE OF SAID POLICIES.

Date: June 19, 2014

Patience One LLC

By: Thomas A. Pickens, Manager

SANDRA L CLARK
Notary Public-State of Nevada
APPT. NO. 88-1652-1
My App. Expires February 06, 2017

State of NEVADA }
} ss:
County of Clark }

This instrument was acknowledged before me on June 30, 2014

by Thomas A. Pickens, Manager of Patience One LLC

Sandra L Clark
NOTARY PUBLIC
My Commission
Expires: 02-06-2017

Electronically Filed
2/20/2020 4:25 PM
Steven D. Grierson
CLERK OF THE COURT

NOTC

Jennifer V. Abrams, Esq.
Nevada State Bar Number: 7575
The Abrams & Mayo Law Firm
6252 South Rainbow Blvd., Suite 100
Las Vegas, Nevada 89118
Tel: (702) 222-4021
Fax: (702) 248-9750
Email: jvagroup@theabramslawfirm.com
Attorney for Defendant

Eighth Judicial District Court
Family Division
Clark County, Nevada

THOMAS A. PICKENS, individually, and as trustee of the LV Blue Trust, Plaintiff, vs. DANKA K. MICHAELS, individually, and as trustee of the Mich-Mich Trust, Defendant.	Case No.: D-17-560737-D Department: J

NOTICE OF INTENT TO APPEAR BY COMMUNICATION EQUIPMENT

Defendant, Danka K. Michaels, by and through her attorney of record, Jennifer V. Abrams, Esq., of The Abrams & Mayo Law Firm, hereby submits this Notice of Intent to Appear by Communication Equipment relating to the witness, Rich Wolf, for the Trial currently

scheduled for February 21, 2020, at 9:00 a.m. For the purpose of this appearance, Rich Wolf can be reached at the following telephone number: (408) 306-7412. Defendant wishes to call Mr. Wolf around 4:00 p.m. on February 21, 2020 via Skype. Mr. Wolf has been informed that it is his responsibility to ensure that he can be reached at this telephone number on the date and time of the Trial. He has also been informed that due to the unpredictable nature of court proceedings, the Trial may be called at a time other than the scheduled time. Further, Mr. Wolf has been informed that his failure to be available at the above telephone number will constitute a nonappearance.

DATED Thursday, February 20, 2020.

Respectfully Submitted,

THE ABRAMS & MAYO LAW FIRM

_/s/ *Jennifer V. Abrams, Esq.*_____
Jennifer V. Abrams, Esq.
Nevada State Bar Number: 7575
6252 South Rainbow Blvd., Suite 100
Las Vegas, Nevada 89118
Attorney for Defendant

CERTIFICATE OF SERVICE

I hereby certify that the foregoing NOTICE OF INTENT TO APPEAR BY COMMUNICATION EQUIPMENT was filed electronically with the Eighth Judicial District Court in the above-entitled matter on Thursday, February 20, 2020. Electronic service of the foregoing document shall be made in accordance with the Master Service List, pursuant to NEFCR 9, as follows:

Michele T. LoBello, Esq.
Attorney for Plaintiff

_/s/ *Chantel Wade*_____
An Employee of The Abrams & Mayo Law Firm

Electronically Filed
2/20/2020 11:14 AM
Steven D. Grierson
CLERK OF THE COURT

REQT
BLACK & LOBELLO
Michele Touby LoBello, Esq.
Nevada Bar No. 5527
John D. Jones, Esq.
Nevada Bar No. 6699
10777 West Twain Avenue, Suite 300
Las Vegas, Nevada 89135
Telephone No.: 702-869-8801
Facsimile No.: 702-869-2669
Email: mlobello@blacklobello.law
Attorneys for Plaintiff,
THOMAS A. PICKENS

DISTRICT COURT
FAMILY DIVISION
CLARK COUNTY, NEVADA

THOMAS A. PICKENS, Individually and as Trustee of the LV Blue Trust, Plaintiff/Counterdefendant. vs. DANKA K. MICHAELS, Individually and as Trustee of the Mich-Mich Trust, Defendant/Counterclaimant; and related Counterclaims.	CASE NO.: D-17-560737-D DEPT. J **Dates of Trial: February 14, 2020 & February 21, 2020** **Time of Trial: 9:00 a.m.**

PLAINTIFF'S REQUEST FOR THE COURT TO TAKE JUDICIAL NOTICE PURSUANT TO NRS 47.130

Plaintiff, Thomas A. Pickens ("Tom"), by and through his attorneys of record, Michele Touby LoBello, John D. Jones and the law firm of Black & LoBello hereby requests this Court take judicial notice of the following documents:

BLACK & LOBELLO
10777 W. Twain Avenue, 3rd Floor
Las Vegas, Nevada 89135
(702) 869-8801 FAX: (702) 869-2669

Case Number: D-17-560737-D

1. Physician's Desk Reference Drug Summary for Percocet.

2. Physician's Desk Reference Drug Summary for Tramadol.

3. Physician's Desk Reference Drug Summary for Xanax.

Pursuant to NRS 47.130, this Court may take judicial notice of facts generally known within the territorial jurisdiction of the trial court or capable of accurate and ready determination by resort to sources whose accuracy cannot reasonably be questioned, so that the fact is not subject to reasonable dispute.

The Defendant has already recognized the Physician's Desk Reference (PDR) as the authority on drugs, their side effects and their interactions with one another. Neither party can dispute the accuracy of the contents of the PDR drug summaries. Of particular note for the Court are the following pages of each drug summary which deal with side effects and drug interactions:

1. Percocet pages and 8 and 41 regarding interaction with Xanax (Alprazolam) and Tramadol.

2. Tramadol pages 9 and 22 for interaction with Xanax (Alprazolam) and Percocet (Hydrocodone).

3. Xanax pages 16 and 23 for interaction with Percocet (Hydrocodone) and Tramadol.

Also relevant are the lengthy list of counterindications and warnings for each drug which are found starting on pages 3 and 4 of each drug summary.

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NRS 47.150 provides that a judge or court may take judicial notice, whether requested or not, and a judge or court shall take judicial notice if requested by a party and supplied with the necessary information. NRS 47.160 provides, "A party is entitled upon timely request to an opportunity to be heard as to the propriety of taking judicial notice and the tenor of the matter to be noticed." As to timing, NRS 47.170 provides: "Judicial notice may be taken at any stage of the proceeding prior to submission to the court or jury."

RESPECTFULLY SUBMITTED this 20 day of February, 2020.

BLACK & LOBELLO

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CERTIFICATE OF SERVICE

Pursuant to NRCP 5(b), I certify that I am an employee of BLACK & LOBELLO and that on the 20th day of February, 2020, I caused the above and foregoing document entitled foregoing PLAINTIFF'S REQUEST FOR THE COURT TO TAKE JUDICIAL NOTICE PURSUANT TO NRS 47.130 to be served as follows:

☐ by placing same to be deposited for mailing in the United States Mail, in a sealed envelope upon which first class postage was prepaid in Las Vegas, Nevada; and

☒ pursuant to N.E.F.C.R. 9, to be sent via electronic service;

☐ pursuant to EDCR 7.26, to be sent via facsimile;

☒ by email to JVAGroup@TheAbramsLawFirm.com

☐ hand delivered

to the party or their attorney(s) listed below at the address and/or facsimile number indicated below:

Jennifer V. Abrams, Esq.
The Abrams & Mayo Law Firm
6252 South Rainbow Blvd., #100
Las Vegas, NV 89118
Email: JVAGroup@TheAbramsLawFirm.com
Attorney for Defendant

and that there is regular communication by mail between the place of mailing and the place(s) so addressed.

Cheryl Berdahl
An Employee of Black & LoBello

Exhibit 1

Exhibit 1

PDR.net

CLASSES

Opioid Agonists and Other Drug Combinations

BOXED WARNING

Accidental exposure, asthma, chronic obstructive pulmonary disease (COPD), coadministration with other CNS depressants, cor pulmonale, hypoxemia, obesity, pulmonary disease, respiratory depression, respiratory insufficiency, scoliosis, sleep apnea, status asthmaticus

As with other opiate agonists, products containing oxycodone should be avoided in patients with severe pulmonary disease. Additionally, avoid coadministration with other CNS depressants unless no other alternatives are available, as this significantly increases the risk for respiratory depression, low blood pressure, and death. Acetaminophen; oxycodone use is contraindicated in patients with significant respiratory depression, and in patients with acute or severe asthma (e.g., status asthmaticus) or hypercarbia in unmonitored care settings or in the absence of resuscitative equipment. Receipt of moderate oxycodone doses in these patients may significantly decrease pulmonary ventilation. In patients with chronic obstructive pulmonary disease (COPD), cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, respiratory insufficiency, upper airway obstruction, or preexisting respiratory depression, it is recommended that non-opioid analgesics be considered as alternatives to acetaminophen; oxycodone, as even usual therapeutic doses of oxycodone may decrease respiratory drive and cause apnea in these patient populations. Extreme caution should also be used in patients with chronic asthma, kyphoscoliosis (a type of scoliosis), hypoxemia, or paralysis of the phrenic nerve. Patients with advanced age, debilitation, or sleep apnea are at an increased risk for the development of respiratory depression associated with oxycodone. Use with caution in patients with obesity as this is a risk factor for obstructive sleep apnea syndrome and/or decreased respiratory reserve. Respiratory depression, if left untreated, may cause respiratory arrest and death. Carbon dioxide retention from respiratory depression may also worsen opioid sedating effects. Due to the risk of serious respiratory depression, the extended-release tablets should be reserved for patients in whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. Do not use extended-release tablets on an as needed basis. Proper dosing and titration are essential; patients should be monitored for respiratory depression, particularly during the first 24—72 hours after therapy initiation or after a dose increase. Patients must be instructed to keep acetaminophen; oxycodone away from pediatric patients and others for whom the drug was not prescribed, as accidental exposure or improper use may lead to fatal respiratory depression. Management of respiratory depression should include observation, necessary supportive measures, and opioid antagonist use when indicated.

Substance abuse

Oxycodone is a strong opiate agonist; therefore, acetaminophen; oxycodone is subject to substance abuse and psychologic dependence. Addiction may occur in patients appropriately prescribed oxycodone. Patients with a previous history of substance abuse may be at increased risk of relapse if treated with acetaminophen; oxycodone. Also, patients with mental illness (e.g., major depression) or a family history of substance abuse or alcoholism may be at greater risk. Monitor patients for signs of misuse, abuse, or addiction. Abuse or misuse of the extended-release tablets by crushing, chewing, snorting, or injecting the dissolved product will lead to uncontrolled drug delivery that may be fatal. Health care professionals should not let concerns over psychologic dependence deter them from using adequate amounts of opiate agonists in the management of severe pain.

Labor, neonatal opioid withdrawal syndrome, obstetric delivery, pregnancy

Acetaminophen; oxycodone is classified as FDA pregnancy risk category C. No well-controlled studies in pregnant women have been performed. Some experts suggest increased risk of oxycodone if used for prolonged periods or at high doses near term. Chronic maternal use of opioids during pregnancy may result in neonatal opioid withdrawal syndrome. This syndrome can be life-threatening and includes symptoms such as poor feeding, irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, rigidity, and seizures. Neonates whose mothers have been taking oxycodone chronically may show some respiratory depression and/or withdrawal symptoms at birth or within a few days. Neonatal opioid withdrawal syndrome may be life-threatening and should be treated according to protocols developed by neonatology experts. Acetaminophen; oxycodone should not be used immediately prior to or during labor or obstetric delivery due to the potential for respiratory depression in the newborn. No overall increase in fetal mortality, as determined by pregnancy outcomes of mothers that overdosed on various amounts of acetaminophen, was apparent amongst 300 women. Treatment with acetylcysteine or methionine did not appear to affect fetal or neonatal toxicity. Of 235 babies exposed to an overdose of only acetaminophen, 168 were normal, 8 had malformations, 16 were spontaneously aborted, and 43 were electively terminated. Of 67 babies exposed to an overdose of a combination acetaminophen product, 51 were normal, 3 had malformations, 2 were spontaneously aborted (late fetal deaths), and 11 were electively terminated. None of the babies with malformations were exposed during the first trimester, but all of the spontaneous abortions and one of the late fetal deaths were subsequent to first trimester exposure.

Alcoholism, hepatic disease, hepatitis, hepatotoxicity, potential for overdose or poisoning

Acetaminophen has the potential for overdose or poisoning that can cause acute hepatic failure, at times resulting in liver transplantation or death. Most cases of hepatotoxicity are a result of exceeding maximum daily dosage limits and often involve the use of more than one acetaminophen-containing product. Acetaminophen; oxycodone should be used with caution in patients with alcoholism, chronic malnutrition, active hepatitis, or severe hypovolemia, as these patients may be at increased risk for acetaminophen-induced hepatotoxicity. In patients with chronic hepatic disease, acetaminophen can be used safely and is often preferred to nonsteroidal anti-inflammatory drugs (NSAIDs) due to the absence of platelet impairment, gastrointestinal toxicity, and nephrotoxicity. Though the half-life of acetaminophen may be prolonged, repeated dosing does not result in drug or metabolite accumulation. In addition, cytochrome P450 activity is not increased and glutathione stores are not depleted in hepatically impaired patients taking therapeutic doses, therefore toxic metabolite formation and accumulation is not altered. Although it is always prudent to use the smallest dose of acetaminophen for the shortest duration necessary, courses less than 2 weeks in length have been administered safely to adult patients with stable chronic liver disease. In patients without pre-existing hepatic impairment, hepatotoxicity may occur if the total daily dose exceeds 4,000 mg/day or more than 3 alcoholic beverages per day are consumed while taking acetaminophen. Patients and caregivers should be appropriately counseled on acetaminophen intake and reminded that all acetaminophen-containing prescription and over-the-counter products, both single-entity and combination, must be considered in the total daily dosage. Oxycodone may accumulate leading to a prolonged duration of action in patients with decreased liver function. Close monitoring is warranted to avoid respiratory depression. Guidelines for use of the extended-release tablets in patients with hepatic impairment recommend initiating treatment at 50% of the normal starting dosage.

DEA CLASS

Rx, schedule II

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DESCRIPTION

Combination product to treat moderate to severe pain. Acetaminophen is a non-salicylate analgesic; oxycodone is an oral semisynthetic opiate agonist. The combination produces additive analgesia as compared to either agent alone.

COMMON BRAND NAMES

Endocet, Nalocet, Percocet, Primlev, Roxicet

HOW SUPPLIED

Endocet/Nalocet/Oxycodone Hydrochloride, Acetaminophen/Oxycodone, Acetaminophen/Percocet/Primlev/Roxicet Oral Tab: 10-300mg, 10-325mg, 2.5-300mg, 2.5-325mg, 5-300mg, 5-325mg, 7.5-300mg, 7.5-325mg
Oxycodone Hydrochloride, Acetaminophen/Oxycodone, Acetaminophen/Roxicet Oral Sol: 5mL, 5-325mg

DOSAGE & INDICATIONS

For the treatment of moderate pain to moderately-severe pain.

For the treatment of acute pain severe enough to require opioid treatment and for which alternative treatment options (e.g., non-opioid analgesics) are inadequate.

Oral dosage (extended-release tablets, Xartemis XR)

Adults

2 tablets PO every 12 hours administered with or without food. A second dose of 2 tablets may be given as early as 8 hours after the initial dose if needed for analgesia at that time. Subsequent doses are to be administered every 12 hours. Individualize the dosage regimen, considering prior analgesic exposure and risk for abuse. Monitor patients closely for excessive sedation and respiratory depression, particularly in the first 24—72 hours of treatment. To discontinue, use a gradual downward titration of 50% every 2—4 days to prevent withdrawal in the physically dependent patient. Extended-release tablets are NOT interchangeable with other acetaminophen; oxycodone products.

Oral dosage (immediate-release tablets or capsules)

Adults

1—2 tablets or capsules (2.5—10 mg of oxycodone) PO every 6 hours as needed. It may be necessary to exceed the usual dosage recommendation (i.e., give every 4 hours) in cases of severe pain or in those patients who have become tolerant to the analgesic effect of opiate agonists. Maximum acetaminophen dose is 4 g/day.

Oral dosage (liquid)

Adults

5—10 ml (5—10 mg of oxycodone) PO every 6 hours as needed. It may be necessary to exceed the usual dosage recommendation (i.e., give every 4 hours) in cases of severe pain or in those patients who have become tolerant to the analgesic effect of opiate agonists. Maximum acetaminophen dose is 4 g/day.

Children†

0.05—0.15 mg oxycodone/kg PO every 6 hours as needed. May titrate up to 5 mg oxycodone PO every 4—6 hours. The maximum acetaminophen dose is 75 mg/kg/day.

MAXIMUM DOSAGE

Adults

Immediate-release formulations: Acetaminophen 4 g/day PO; the maximum dose of the acetaminophen; oxycodone combination is limited by the total daily limit of acetaminophen.
Extended-release tablets: 4 tablets/day PO. Total daily dose of acetaminophen from all products should not exceed 4 g/day PO.

Geriatric

Immediate-release formulations: Acetaminophen 4 g/day PO; the maximum dose of the acetaminophen; oxycodone combination is limited by the total daily limit of acetaminophen.
Extended-release tablets: 4 tablets/day PO. Total daily dose of acetaminophen from all products should not exceed 4 g/day PO.

Adolescents

Immediate-release formulations: Safety and efficacy have not been established. Doses containing up to acetaminophen 4 g/day PO have been used. The maximum dose of the acetaminophen; oxycodone combination is limited by the total daily limit of acetaminophen.
Extended-release tablets: Safety and efficacy have not been established.

Children

Immediate-release formulations: Safety and efficacy have not been established. Doses up to acetaminophen 75 mg/kg/day PO or 4 g/day PO, whichever is less, have been used. The maximum dose of the acetaminophen; oxycodone combination is limited by the total daily limit of acetaminophen.
Extended-release tablets: Safety and efficacy have not been established.

Infants

Safety and efficacy have not been established.

Neonates

Safety and efficacy have not been established.

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DOSING CONSIDERATIONS

Hepatic Impairment

Dosage should be modified depending upon the clinical response and degree of hepatic impairment. For initiation of the extended-release tablets, give 1 tablet and adjust dosage as needed.

Renal Impairment

Dosage should be modified depending upon the clinical response and degree of renal impairment. For initiation of the extended-release tablets, give 1 tablet and adjust dosage as needed.

ADMINISTRATION

Oral Administration

Immediate-release formulations:
Administer with a full glass of water. May be taken food or milk to minimize GI irritation.
Extended-release tablets:
Swallow whole, 1 tablet at a time, with enough water to ensure complete swallowing immediately after placing in mouth.
May be given with or without food.
Do not break, chew, crush, cut, dissolve, or split the tablets due to the risk of uncontrolled drug delivery.

STORAGE

Endocet:
- Store at controlled room temperature (between 68 and 77 degrees F)
Magnacet:
- Store at controlled room temperature (between 68 and 77 degrees F)
Nalocet:
- Protect from moisture
- Store between 68 to 77 degrees F
Narvox:
- Store at controlled room temperature (between 68 and 77 degrees F)
Percocet:
- Store at controlled room temperature (between 68 and 77 degrees F)
Perloxx:
- Protect from light
- Store at controlled room temperature (between 68 and 77 degrees F)
Primalev:
- Store at controlled room temperature (between 68 and 77 degrees F)
Primlev:
- Store at controlled room temperature (between 68 and 77 degrees F)
Roxicet:
- Store at controlled room temperature (between 68 and 77 degrees F)
Tylox:
- Protect from moisture
- Store at room temperature (between 59 to 86 degrees F)
XARTEMIS XR:
- Store at 77 degrees F; excursions permitted to 59-86 degrees F
Xolox:
- Store at controlled room temperature (between 68 and 77 degrees F)

CONTRAINDICATIONS / PRECAUTIONS

General Information

NOTE: This monograph discusses the contraindications/precautions of acetaminophen; oxycodone combination products. Clinicians may wish to consult the individual monographs for more information about each agent.

Acetaminophen hypersensitivity, opiate agonist hypersensitivity, sulfite hypersensitivity

Acetaminophen; oxycodone combinations are contraindicated in patients with known acetaminophen hypersensitivity, oxycodone hypersensitivity, or opiate agonist hypersensitivity. Acetaminophen hypersensitivity reactions are rare, but severe sensitivity reactions are possible. Although true opiate agonist hypersensitivity is rare, patients who have demonstrated a prior hypersensitivity reaction to oxycodone should not receive other opioid agonists of the phenanthrene subclass including morphine, codeine, and hydromorphone. Use with caution in patients with sulfite hypersensitivity, as some acetaminophen; oxycodone capsules contain sodium metabisulfite and some tablet dosage formulations may as well. Sulfite may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Acute abdomen, constipation, dysphagia, esophageal stricture, GI disease, GI obstruction, ileus, inflammatory bowel disease, ulcerative colitis

Oxycodone is contraindicated in patients who have or are suspected of having paralytic ileus. Due to the effects of opiate agonists on the gastrointestinal tract, all forms of acetaminophen; oxycodone should be used cautiously in patients with GI disease including GI obstruction, ulcerative colitis, or pre-existing constipation. Patients with ulcerative colitis or other inflammatory bowel disease may be more sensitive to constipation caused by opiate agonists. Opiate agonists may obscure the diagnosis or clinical course in patients with an acute abdomen. The extended-release tablets may swell and become sticky when exposed to liquids such as saliva; consider the use of an alternative analgesic in patients with pre-existing esophageal stricture or dysphagia. Do not pre-soak, lick, or wet the extended-release tablet prior to ingestion, or give via feeding tubes as it may cause obstruction.

Accidental exposure, asthma, chronic obstructive pulmonary disease (COPD), coadministration with other CNS depressants, cor pulmonale, hypoxemia, obesity, pulmonary disease, respiratory depression, respiratory insufficiency,

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scoliosis, sleep apnea, status asthmaticus

As with other opiate agonists, products containing oxycodone should be avoided in patients with severe pulmonary disease. Additionally, avoid coadministration with other CNS depressants unless no other alternatives are available, as this significantly increases the risk for respiratory depression, low blood pressure, and death. Acetaminophen; oxycodone use is contraindicated in patients with significant respiratory depression, and in patients with acute or severe asthma (e.g., status asthmaticus) or hypercarbia in unmonitored care settings or in the absence of resuscitative equipment. Receipt of moderate oxycodone doses in these patients may significantly decrease pulmonary ventilation. In patients with chronic obstructive pulmonary disease (COPD), cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, respiratory insufficiency, upper airway obstruction, or preexisting respiratory depression, it is recommended that non-opioid analgesics be considered as alternatives to acetaminophen; oxycodone, as even usual therapeutic doses of oxycodone may decrease respiratory drive and cause apnea in these patient populations. Extreme caution should also be used in patients with chronic asthma, kyphoscoliosis (a type of scoliosis), hypoxemia, or paralysis of the phrenic nerve. Patients with advanced age, debilitation, or sleep apnea are at an increased risk for the development of respiratory depression associated with oxycodone. Use with caution in patients with obesity as this is a risk factor for obstructive sleep apnea syndrome and/or decreased respiratory reserve. Respiratory depression, if left untreated, may cause respiratory arrest and death. Carbon dioxide retention from respiratory depression may also worsen opioid sedating effects. Due to the risk of serious respiratory depression, the extended-release tablets should be reserved for patients in whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. Do not use extended-release tablets on an as needed basis. Proper dosing and titration are essential; patients should be monitored for respiratory depression, particularly during the first 24—72 hours after therapy initiation or after a dose increase. Patients must be instructed to keep acetaminophen; oxycodone away from pediatric patients and others for whom the drug was not prescribed, as accidental exposure or improper use may lead to fatal respiratory depression. Management of respiratory depression should include observation, necessary supportive measures, and opioid antagonist use when indicated.

Abrupt discontinuation

Abrupt discontinuation of prolonged oxycodone therapy can result in withdrawal symptoms. Patients who have been taking acetaminophen; oxycodone regularly and may be physically dependent should be gradually tapered off the medication to avoid a withdrawal reaction. A downward titration of 50% of the dose every 2—4 days may be used in patients taking the extended-release tablets.

Substance abuse

Oxycodone is a strong opiate agonist; therefore, acetaminophen; oxycodone is subject to substance abuse and psychologic dependence. Addiction may occur in patients appropriately prescribed oxycodone. Patients with a previous history of substance abuse may be at increased risk of relapse if treated with acetaminophen; oxycodone. Also, patients with mental illness (e.g., major depression) or a family history of substance abuse or alcoholism may be at greater risk. Monitor patients for signs of misuse, abuse, or addiction. Abuse or misuse of the extended-release tablets by crushing, chewing, snorting, or injecting the dissolved product will lead to uncontrolled drug delivery that may be fatal. Health care professionals should not let concerns over psychologic dependence deter them from using adequate amounts of opiate agonists in the management of severe pain.

CNS depression, head trauma, increased intracranial pressure, intracranial mass, psychosis

Use acetaminophen; oxycodone with caution in patients with CNS depression, toxic psychosis, head trauma, intracranial mass, or increased intracranial pressure. Opioids may aggravate these conditions and alter neurologic parameters (e.g., level of consciousness, pupillary responses). Oxycodone-induced hypoventilation can produce cerebral hypoxia, carbon dioxide retention, and raise cerebrospinal fluid pressure. Monitor for signs of drowsiness or depressed respirations.

Cardiac arrhythmias, cardiac disease, hypotension, hypovolemia, orthostatic hypotension

Use acetaminophen; oxycodone with caution in patients with cardiac disease, cardiac arrhythmias, hypotension, orthostatic hypotension, or hypovolemia. Opiate agonists, such as oxycodone, induce histamine release and produce cholinergic side effects like bradycardia, peripheral vasodilation, and hypotension. These effects may produce severe hypotension in patients whose ability to maintain blood pressure has been compromised by a depleted blood volume. Orthostatic hypotension may occur.

Labor, neonatal opioid withdrawal syndrome, obstetric delivery, pregnancy

Acetaminophen; oxycodone is classified as FDA pregnancy risk category C. No well-controlled studies in pregnant women have been performed. Some experts suggest increased risk of oxycodone if used for prolonged periods or at high doses near term. Chronic maternal use of opioids during pregnancy may result in neonatal opioid withdrawal syndrome. This syndrome can be life-threatening and includes symptoms such as poor feeding, irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, rigidity, and seizures. Neonates whose mothers have been taking oxycodone chronically may show some respiratory depression and/or withdrawal symptoms at birth or within a few days. Neonatal opioid withdrawal syndrome may be life-threatening and should be treated according to protocols developed by neonatology experts. Acetaminophen; oxycodone should not be used immediately prior to or during labor or obstetric delivery due to the potential for respiratory depression in the newborn. No overall increase in fetal mortality, as determined by pregnancy outcomes of mothers that overdosed on various amounts of acetaminophen, was apparent amongst 300 women. Treatment with acetylcysteine or methionine did not appear to affect fetal or neonatal toxicity. Of 235 babies exposed to an overdose of only acetaminophen, 168 were normal, 8 had malformations, 16 were spontaneously aborted, and 43 were electively terminated. Of 67 babies exposed to an overdose of a combination acetaminophen product, 51 were normal, 3 had malformations, 2 were spontaneously aborted (late fetal deaths), and 11 were electively terminated. None of the babies with malformations were exposed during the first trimester, but all of the spontaneous abortions and one of the late fetal deaths were subsequent to first trimester exposure.

Breast-feeding

Use caution when prescribing acetaminophen; oxycodone for mothers of breast-feeding infants. According to the manufacturer, oxycodone and acetaminophen are both distributed into breast milk, and acetaminophen; oxycodone generally should not be used by breast-feeding mothers because of the possibility of sedation and/or respiratory depression in the baby. A retrospective study compared central nervous system (CNS) depression in breast-feeing infants of mothers receiving oxycodone (n = 139), codeine (n = 210), or acetaminophen (n = 184). Symptoms of CNS depression were determined through questionnaires to the mothers. CNS depression was significantly higher in breast-fed infants exposed to oxycodone compared to acetaminophen (20.1% vs 0.5%, $p < 0.0001$) and was not significantly different compared to infants exposed to codeine (16.7%, $p > 0.05$). The doses of both oxycodone and codeine in the mothers with infants that experienced symptoms were significantly higher compared to those that did not (oxycodone median 0.4 mg/kg/day vs 0.15 mg/kg/day, $p = 0.0005$; codeine median 1.4 mg/kg/day vs 0.9 mg/kg/day, $p < 0.001$). As with all opioid-containing products, if acetaminophen; oxycodone is used by a breast-feeding mother, the infant should be monitored for sedation, respiratory depression, and changes in feeding patterns. According to the American Academy of Pediatrics (AAP), acetaminophen as maternal monotherapy has not been associated with any observable changes in nursing infants. The AAP regards acetaminophen as a maternal medicine that is usually compatible with breast feeding. Other alternative analgesics considered to be usually compatible with breast-feeding by the AAP include ibuprofen and morphine; the AAP has not evaluated the use of oxycodone in breast-feeding women. Acetaminophen; oxycodone should not be used chronically during breast-feeding as withdrawal symptoms may occur in the infant when the mother stops chronic oxycodone therapy.

Bladder obstruction, oliguria, prostatic hypertrophy, renal disease, renal impairment, urethral stricture, urinary retention

Acetaminophen; oxycodone should be used cautiously in patients with renal impairment or renal failure; dosage adjustments may be required. Oxycodone can cause urinary retention and oliguria, due to increasing the tension of the detrusor muscle. Patients more prone to these effects

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include those with prostatic hypertrophy, urethral stricture, bladder obstruction or pelvic tumors. In addition, oxycodone may accumulate in these patients leading to a prolonged duration of action and potential increase in side effects. Chronic acetaminophen administration should be avoided in patients with underlying renal disease; however it may be used for episodic pain.

Alcoholism, hepatic disease, hepatitis, hepatotoxicity, potential for overdose or poisoning

Acetaminophen has the potential for overdose or poisoning that can cause acute hepatic failure, at times resulting in liver transplantation or death. Most cases of hepatotoxicity are a result of exceeding maximum daily dosage limits and often involve the use of more than one acetaminophen-containing product. Acetaminophen; oxycodone should be used with caution in patients with alcoholism, chronic malnutrition, active hepatitis, or severe hypovolemia, as these patients may be at increased risk for acetaminophen-induced hepatotoxicity. In patients with chronic hepatic disease, acetaminophen can be used safely and is often preferred to nonsteroidal anti-inflammatory drugs (NSAIDs) due to the absence of platelet impairment, gastrointestinal toxicity, and nephrotoxicity. Though the half-life of acetaminophen may be prolonged, repeated dosing does not result in drug or metabolite accumulation. In addition, cytochrome P450 activity is not increased and glutathione stores are not depleted in hepatically impaired patients taking therapeutic doses, therefore toxic metabolite formation and accumulation is not altered. Although it is always prudent to use the smallest dose of acetaminophen for the shortest duration necessary, courses less than 2 weeks in length have been administered safely to adult patients with stable chronic liver disease. In patients without pre-existing hepatic impairment, hepatotoxicity may occur if the total daily dose exceeds 4,000 mg/day or more than 3 alcoholic beverages per day are consumed while taking acetaminophen. Patients and caregivers should be appropriately counseled on acetaminophen intake and reminded that all acetaminophen-containing prescription and over-the-counter products, both single-entity and combination, must be considered in the total daily dosage. Oxycodone may accumulate leading to a prolonged duration of action in patients with decreased liver function. Close monitoring is warranted to avoid respiratory depression. Guidelines for use of the extended-release tablets in patients with hepatic impairment recommend initiating treatment at 50% of the normal starting dosage.

Geriatric

Geriatric and debilitated patients are at particular risk for respiratory depression when given large initial doses of oxycodone or when oxycodone is given in conjunction with other agents that depress respiration. Special precaution should be given when determining the dosing and frequency of dosing for geriatric patients, since clearance of oxycodone may be slightly reduced in this patient population vs. younger adults. Initial doses may need to be reduced, and doses should be carefully titrated, taking into account analgesic effects, adverse reactions, and concomitant conditions and drugs that may increase CNS depression and depress respiration. According to the Beers Criteria, opiate agonists are considered potentially inappropriate medications (PIMs) in geriatric patients with a history of falls or fractures and should be avoided in these patient populations, except in the setting of severe acute pain, since opiates can produce ataxia, impaired psychomotor function, syncope, and additional falls. If an opiate must be used, consider reducing the use of other CNS-active medications that increase the risk of falls and fractures and implement strategies to reduce fall risk. In patients receiving palliative care or hospice, the balance of benefits and harms of medication management may differ from those of the general population of older adults.[63923] The federal Omnibus Budget Reconciliation Act (OBRA) regulates medication use in residents of long-term care facilities (LTCFs). OBRA cautions that opioids may cause constipation, nausea, vomiting, sedation, lethargy, weakness, confusion, dysphoria, physical and psychological dependency, hallucinations, and unintended respiratory depression, especially in individuals with compromised pulmonary function. These adverse effects can lead to other consequences such as falls. The initiation of longer-acting opioids is not recommended unless shorter-acting opioids have been unsuccessful, or titration of shorter-acting doses has established a clear daily dose of opioid analgesic that can be provided by using a long-acting form.[60742]

Children, infants, neonates

Acetaminophen; oxycodone is used in pediatric patients with moderate to severe pain in clinical practice; however, safety and efficacy have not been established in neonates, infants, children, or adolescents. Consider pediatric-specific precautions before use. Neonates and infants < 6 months of age have highly variable clearance of opiate agonists. Therefore, infants younger than 6 months of age may be given opiate agonists but must be closely monitored for apnea until 24 hours after their last dose. Clinical practice guidelines suggest close monitoring of children up to 1 year of age.

G6PD deficiency

Patients with G6PD deficiency who overdose with acetaminophen may be at increased risk for drug-induced hemolysis. Practitioners should be aware of this potential complication and monitor at-risk patients for signs and symptoms of hemolysis while taking acetaminophen; oxycodone. Conflicting data exists on whether therapeutic doses of acetaminophen can cause hemolysis in G6PD deficient patients. However, a direct cause and effect relationship has not been well established, and therefore, therapeutic doses are generally considered safe in this population.

Bone marrow suppression, immunosuppression, infection

Symptoms of acute infection (e.g., fever, pain) can be masked during treatment with acetaminophen; oxycodone in patients who have bone marrow suppression or immunosuppression.

Driving or operating machinery

Any patient receiving acetaminophen; oxycodone should be warned about the possibility of sedation and to use caution when driving or operating machinery.

Biliary tract disease, pancreatitis

Oxycodone can increase the tone of the biliary tract causing spasms, especially in the sphincter of Oddi. Acetaminophen; oxycodone should be used cautiously in patients with biliary tract disease or acute pancreatitis. Biliary effects of opioids may result in elevations of plasma amylase concentration.

Adrenal insufficiency, hypothyroidism, myxedema

Use acetaminophen; oxycodone with caution in patients with adrenal insufficiency (i.e., Addison's disease), hypothyroidism, or myxedema. Such patients may be at increased risk of adverse events. Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH); however, the thyroid stimulating hormone may be either stimulated or inhibited by opioids. Rarely, adrenal insufficiency has been reported in association with opioid use. Patients should seek immediate medical attention if they experience symptoms such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or hypotension. If adrenocortical insufficiency is suspected, confirm with diagnostic testing as soon as possible. If diagnosed, the patient should be treated with physiologic replacement doses of corticosteroids, and if appropriate, weaned off of opioid therapy. If the opioid can be discontinued, a follow-up assessment of adrenal function should be performed to determine if corticosteroid treatment can be discontinued. Other opioids may be tried; some cases reported use of a different opioid with no recurrence of adrenocortical insufficiency. It is unclear which, if any, opioids are more likely to cause adrenocortical insufficiency. In addition, chronic opioid use may lead to symptoms of hypogonadism, resulting from changes in the hypothalamic-pituitary-gonadal axis. Monitor patients for symptoms of opioid-induced endocrinopathy, particularly those receiving a daily dose equivalent to 100 mg or more of morphine. Patients presenting with signs or symptoms of androgen deficiency should undergo laboratory evaluation.

ADVERSE REACTIONS

Severe

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oliguria / Early / 0-1.0
neonatal opioid withdrawal syndrome / Delayed / Incidence not known
cerebral edema / Early / Incidence not known
seizures / Delayed / Incidence not known
suicidal ideation / Delayed / Incidence not known
respiratory arrest / Rapid / Incidence not known
pulmonary edema / Early / Incidence not known
apnea / Delayed / Incidence not known
GI obstruction / Delayed / Incidence not known
ileus / Delayed / Incidence not known
pancreatitis / Delayed / Incidence not known
hepatic necrosis / Delayed / Incidence not known
hepatotoxicity / Delayed / Incidence not known
hepatic failure / Delayed / Incidence not known
proteinuria / Delayed / Incidence not known
interstitial nephritis / Delayed / Incidence not known
renal papillary necrosis / Delayed / Incidence not known
renal tubular necrosis / Delayed / Incidence not known
renal failure (unspecified) / Delayed / Incidence not known
agranulocytosis / Delayed / Incidence not known
hemolytic anemia / Delayed / Incidence not known
pancytopenia / Delayed / Incidence not known
angioedema / Rapid / Incidence not known
anaphylactoid reactions / Rapid / Incidence not known
Stevens-Johnson syndrome / Delayed / Incidence not known
acute generalized exanthematous pustulosis (AGEP) / Delayed / Incidence not known
laryngeal edema / Rapid / Incidence not known
toxic epidermal necrolysis / Delayed / Incidence not known
anaphylactic shock / Rapid / Incidence not known
cardiac arrest / Early / Incidence not known
bradycardia / Rapid / Incidence not known
visual impairment / Early / Incidence not known
hyperkalemia / Delayed / Incidence not known
rhabdomyolysis / Delayed / Incidence not known
hearing loss / Delayed / Incidence not known
serotonin syndrome / Delayed / Incidence not known

Moderate

constipation / Delayed / 4.0-4.0
withdrawal / Early / 0-1.0
euphoria / Early / 0-1.0
myoclonia / Delayed / 0-1.0
memory impairment / Delayed / 0-1.0
confusion / Early / 0-1.0
dyspnea / Early / 0-1.0
dysuria / Early / 1.0-1.0
migraine / Early / 0-1.0
erythema / Early / 1.0-1.0
palpitations / Early / 0-1.0
hypertension / Early / 0-1.0
blurred vision / Early / 0-1.0
peripheral edema / Delayed / 1.0-1.0
elevated hepatic enzymes / Delayed / 1.0
psychological dependence / Delayed / Incidence not known
physiological dependence / Delayed / Incidence not known
tolerance / Delayed / Incidence not known
depression / Delayed / Incidence not known
dysphoria / Early / Incidence not known
hallucinations / Early / Incidence not known
hypoventilation / Rapid / Incidence not known
tachypnea / Early / Incidence not known
respiratory depression / Rapid / Incidence not known
hyperbilirubinemia / Delayed / Incidence not known
hepatitis / Delayed / Incidence not known
jaundice / Delayed / Incidence not known
hypoprothrombinemia / Delayed / Incidence not known
encephalopathy / Delayed / Incidence not known
urinary retention / Early / Incidence not known
neutropenia / Delayed / Incidence not known
thrombocytopenia / Delayed / Incidence not known
edema / Delayed / Incidence not known
contact dermatitis / Delayed / Incidence not known
chest pain (unspecified) / Early / Incidence not known
orthostatic hypotension / Delayed / Incidence not known
sinus tachycardia / Rapid / Incidence not known
hypotension / Rapid / Incidence not known
hyperemia / Delayed / Incidence not known
dehydration / Delayed / Incidence not known
hypoglycemia / Early / Incidence not known
hyperglycemia / Delayed / Incidence not known
metabolic acidosis / Delayed / Incidence not known
infertility / Delayed / Incidence not known
impotence (erectile dysfunction) / Delayed / Incidence not known
adrenocortical insufficiency / Delayed / Incidence not known

Mild

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nausea / Early / 4.1-31.0
dizziness / Early / 13.0-13.0
headache / Early / 10.0-10.0
vomiting / Early / 4.8-9.0
drowsiness / Early / 4.0-4.0
rash / Early / 2.0-2.0
paresthesias / Delayed / 0-1.0
tremor / Early / 0-1.0
anxiety / Delayed / 0-1.0
throat irritation / Early / 0-1.0
hiccups / Early / 0-1.0
abdominal pain / Early / 0-1.0
anorexia / Delayed / 0-1.0
ecchymosis / Delayed / 0-1.0
urticaria / Rapid / 0-1.0
hyperhidrosis / Delayed / 0-1.0
pruritus / Rapid / 1.0-1.0
flushing / Rapid / 0-1.0
chills / Rapid / 0-1.0
malaise / Early / 0-1.0
polydipsia / Early / 0-1.0
asthenia / Delayed / 0-1.0
arthralgia / Delayed / 0-1.0
tinnitus / Delayed / 0-1.0
insomnia / Early / 1.0
cough / Delayed / 1.0
xerostomia / Early / 1.0
diarrhea / Early / 1.0
dyspepsia / Early / 1.0
fatigue / Early / 1.0
agitation / Early / Incidence not known
hypoesthesia / Delayed / Incidence not known
lethargy / Early / Incidence not known
flatulence / Early / Incidence not known
dysgeusia / Early / Incidence not known
purpura / Delayed / Incidence not known
syncope / Early / Incidence not known
miosis / Early / Incidence not known
diaphoresis / Early / Incidence not known
hypothermia / Delayed / Incidence not known
myalgia / Early / Incidence not known
amenorrhea / Delayed / Incidence not known
gonadal suppression / Delayed / Incidence not known
libido decrease / Delayed / Incidence not known

DRUG INTERACTIONS

Abacavir; Lamivudine, 3TC; Zidovudine, ZDV: (Minor) Both acetaminophen and zidovudine, ZDV undergo glucuronidation. Competition for the metabolic pathway is thought to have caused a case of acetaminophen-related hepatotoxicity. This interaction may be more clinically significant in patients with depleted glutathione stores, such as patients with acquired immunodeficiency syndrome, poor nutrition, or alcoholism.
Acetaminophen; Aspirin, ASA; Caffeine: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.
Acetaminophen; Butalbital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.
Acetaminophen; Butalbital; Caffeine: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.
Acetaminophen; Butalbital; Caffeine; Codeine: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.
Acetaminophen; Caffeine; Dihydrocodeine: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.
Acetaminophen; Caffeine; Magnesium Salicylate; Phenyltoloxamine: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. Although salicylates are rarely associated with nephrotoxicity, high-dose, chronic administration of salicylates combined other analgesics, including acetaminophen, significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Additive hepatic toxicity may occur, especially in combined overdose situations. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations

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needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Acetaminophen; Codeine: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.
Acetaminophen; Dextromethorphan; Doxylamine: (Moderate) Concomitant use of opioid agonists with doxylamine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with doxylamine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Acetaminophen; Diphenhydramine: (Moderate) Concomitant use of opioid agonists with diphenhydramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with diphenhydramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Acetaminophen; Hydrocodone: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression.
Acetaminophen; Pentazocine: (Major) Avoid the concomitant use of pentazocine and opiate agonists, such as oxycodone. Pentazocine is a mixed opiate agonist/antagonist that may block the effects of opiate agonists and reduce analgesic effects of oxycodone. Pentazocine may cause withdrawal symptoms in patients receiving chronic opiate agonists. Concurrent use of pentazocine with other opiate agonists can cause additive CNS, respiratory, and hypotensive effects. The additive or antagonistic effects are dependent upon the dose of the opiate agonist used; antagonistic effects are more common at low to moderate doses of the opiate agonist.
Acetaminophen; Propoxyphene: (Major) Propoxyphene is a weak mu-opiate receptor agonist. As other opiate agonists bind to mu-opiate receptors, concurrent use of an opiate agonist with propoxyphene is not desirable. Also, propoxyphene will only partially suppress the withdrawal syndrome in patients physically dependent on morphine or other narcotics. The choice of one mu-opiate receptor agonist needs to be made to avoid duplicate therapy and possible adverse effects. For example, concomitant use of propoxyphene with other CNS depressants (e.g., other opiate agonists) can potentiate the effects of respiratory depression and/or sedation. Propoxyphene in combination with other CNS depressants is a major cause of drug-related death. Fatalities within the first hour of overdosage are not uncommon. Extreme caution is needed during concomitant use of any CNS-depressant drug and propoxyphene. Assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.
Acetaminophen; Tramadol: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Acrivastine; Pseudoephedrine: (Moderate) Concomitant use of opioid agonists with acrivastine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with acrivastine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Aldesleukin, IL-2: (Moderate) Aldesleukin, IL-2 may affect CNS function significantly. Therefore, psychotropic pharmacodynamic interactions could occur following concomitant administration of drugs with significant CNS or psychotropic activity such as opiate agonists. In addition, aldesleukin, IL-2, is a CYP3A4 inhibitor and may increase oxycodone plasma concentrations and related toxicities including potentially fatal respiratory depression. If therapy with both agents is necessary, monitor patients for an extended period and adjust oxycodone dosage as necessary.
Alfentanil: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.
Aliskiren; Amlodipine: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of amlodipine is necessary. If amlodipine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like amlodipine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If amlodipine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Aliskiren; Amlodipine; Hydrochlorothiazide, HCTZ: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of amlodipine is necessary. If amlodipine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like amlodipine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If amlodipine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone. (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Aliskiren; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Almotriptan: (Moderate) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as serotonin-receptor agonists. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.
Alosetron: (Major) Patients taking medications that decrease GI motility may be at greater risk for serious complications from alosetron, like constipation, via a pharmacodynamic interaction. Constipation is the most frequently reported adverse effect with alosetron. Alosetron, if used with drugs such as opiate agonists, may seriously worsen constipation, leading to events such as GI obstruction/impaction or paralytic ileus.
Alprazolam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at one-third to one-half the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Alvimopan: (Moderate) Patients should not take alvimopan if they have received therapeutic doses of opiate agonists for more than seven

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consecutive days immediately before initiation of alvimopan therapy. Patients recently exposed to opioids are expected to be more sensitive to the effects of mu-opioid receptor antagonists and may experience adverse effects localized to the gastrointestinal tract such as abdominal pain, nausea, vomiting, and diarrhea.

Amide local anesthetics: (Moderate) The use of these drugs together must be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Amifampridine: (Moderate) Carefully consider the need for concomitant treatment with opioid agonists and amifampridine, as coadministration may increase the risk of seizures. If coadministration occurs, closely monitor patients for seizure activity. Seizures have been observed in patients without a history of seizures taking amifampridine at recommended doses. Opioid agonists may increase the risk of seizures.

Amiloride: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when amiloride is administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Amiloride; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when amiloride is administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone. (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Amiodarone: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of amiodarone is necessary. If amiodarone is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like amiodarone can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If amiodarone is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Amitriptyline: (Major) Concomitant use of opioid agonists with tricyclic antidepressants may cause excessive sedation, somnolence, and increased risk of serotonin syndrome. The anticholinergic properties of tricyclic antidepressants may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Limit the use of opioid pain medications with tricyclic antidepressants to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and serotonin syndrome. Monitor for signs of urinary retention and reduced gastric motility.

Amitriptyline; Chlordiazepoxide: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. (Major) Concomitant use of opioid agonists with tricyclic antidepressants may cause excessive sedation, somnolence, and increased risk of serotonin syndrome. The anticholinergic properties of tricyclic antidepressants may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Limit the use of opioid pain medications with tricyclic antidepressants to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and serotonin syndrome. Monitor for signs of urinary retention and reduced gastric motility.

Amlodipine: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of amlodipine is necessary. If amlodipine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like amlodipine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If amlodipine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Amlodipine; Atorvastatin: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of amlodipine is necessary. If amlodipine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like amlodipine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If amlodipine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Amlodipine; Benazepril: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of amlodipine is necessary. If amlodipine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like amlodipine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If amlodipine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Amlodipine; Celecoxib: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of amlodipine is necessary. If amlodipine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like amlodipine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If amlodipine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Amlodipine; Hydrochlorothiazide, HCTZ; Olmesartan: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of amlodipine is necessary. If amlodipine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like amlodipine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If amlodipine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone. (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Amlodipine; Hydrochlorothiazide, HCTZ; Valsartan: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of amlodipine is necessary. If amlodipine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like amlodipine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If amlodipine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone. (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

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Amlodipine; Olmesartan: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of amlodipine is necessary. If amlodipine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like amlodipine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If amlodipine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Amlodipine; Telmisartan: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of amlodipine is necessary. If amlodipine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like amlodipine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If amlodipine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Amlodipine; Valsartan: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of amlodipine is necessary. If amlodipine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like amlodipine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If amlodipine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Amobarbital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.
Amoxapine: (Major) Concomitant use of opioid agonists with amoxapine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with amoxapine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Amoxicillin; Clarithromycin; Lansoprazole: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of clarithromycin is necessary. If clarithromycin is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like clarithromycin can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If clarithromycin is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Amoxicillin; Clarithromycin; Omeprazole: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of clarithromycin is necessary. If clarithromycin is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like clarithromycin can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If clarithromycin is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Antacids: (Minor) Antacids can delay the oral absorption of acetaminophen, but the interactions are not likely to be clinically significant as the extent of acetaminophen absorption is not appreciably affected.
Anticholinergics: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when oxycodone is used concomitantly with an anticholinergic drug. The concomitant use of oxycodone and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Apalutamide: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with apalutamide is necessary; consider increasing the dose of oxycodone as needed. If apalutamide is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and apalutamide is a strong CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Apomorphine: (Major) Concomitant use of opioid agonists with apomorphine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with apomorphine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. Dopaminergic agents like apomorphine have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment.
Apraclonidine: (Minor) Theoretically, apraclonidine might potentiate the effects of CNS depressant drugs such as opiate agonists. Although no specific drug interactions were identified with systemic agents and apraclonidine during clinical trials, apraclonidine can cause dizziness and somnolence.
Aprepitant, Fosaprepitant: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of aprepitant/fosaprepitant is necessary. If aprepitant/fosaprepitant is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like aprepitant/fosaprepitant can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If aprepitant/fosaprepitant is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone. Aprepitant, when administered as a 3-day oral regimen (125 mg/80 mg/80 mg), is a moderate CYP3A4 inhibitor. When administered as a single oral or single intravenous dose, the inhibitory effect of aprepitant on CYP3A4 is weak and did not result in a clinically significant increase in the AUC of a sensitive substrate. (Minor) Use caution if acetaminophen and aprepitant are used concurrently and monitor for an increase in acetaminophen-related adverse effects for several days after administration of a multi-day aprepitant regimen. Acetaminophen is a minor (10 to 15%) substrate of CYP3A4. Aprepitant, when administered as a 3-day oral regimen (125 mg/80 mg/80 mg), is a moderate CYP3A4 inhibitor and inducer and may increase plasma concentrations of acetaminophen. For example, a 5-day oral aprepitant regimen increased the AUC of another CYP3A4 substrate, midazolam (single dose), by 2.3-fold on day 1 and by 3.3-fold on day 5. After a 3-day oral aprepitant regimen, the AUC of midazolam (given on days 1, 4, 8, and 15) increased by 25% on day 4, and then decreased by 19% and 4% on days 8 and 15, respectively. As a single 125 mg or 40 mg oral dose, the inhibitory effect of aprepitant on CYP3A4 is weak, with the AUC of midazolam increased by 1.5-fold and 1.2-fold, respectively. After administration, fosaprepitant is rapidly converted to aprepitant and shares many of the same drug interactions. However, as a single 150 mg intravenous dose, fosaprepitant only weakly inhibits CYP3A4 for a duration of 2 days; there is no evidence of CYP3A4 induction. Fosaprepitant 150 mg IV as a single dose increased the AUC of midazolam (given on days 1 and 4) by approximately 1.8-fold on day 1; there was no effect on day 4. Less than a 2-fold increase in the midazolam AUC is not considered clinically important.
Aripiprazole: (Moderate) Concomitant use of opioid agonists with aripiprazole may cause excessive sedation and somnolence. Limit the use of opioid pain medications with aripiprazole to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Armodafinil: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with armodafinil is necessary; consider increasing the dose of oxycodone as needed. If armodafinil is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and armodafinil is a weak CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Articaine; Epinephrine: (Moderate) Coadministration of articaine with oxidizing agents, such as acetaminophen, may increase the risk of

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developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue articaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. (Moderate) The use of these drugs together must be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Asenapine: (Moderate) Concomitant use of opioid agonists with asenapine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with asenapine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Aspirin, ASA: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.

Aspirin, ASA; Butalbital; Caffeine: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.

Aspirin, ASA; Butalbital; Caffeine; Codeine: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.

Aspirin, ASA; Caffeine; Dihydrocodeine: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.

Aspirin, ASA; Caffeine; Orphenadrine: (Major) Concomitant use of oxycodone with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.

Aspirin, ASA; Carisoprodol: (Major) Concomitant use of oxycodone with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.

Aspirin, ASA; Carisoprodol; Codeine: (Major) Concomitant use of oxycodone with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.

Aspirin, ASA; Citric Acid; Sodium Bicarbonate: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy. (Minor) Antacids can delay the oral absorption of acetaminophen, but the interactions are not likely to be clinically significant as the extent of acetaminophen absorption is not appreciably affected.

Aspirin, ASA; Dipyridamole: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.

Aspirin, ASA; Omeprazole: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.

Aspirin, ASA; Oxycodone: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.

Aspirin, ASA; Pravastatin: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.

Atazanavir: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of atazanavir is necessary. If atazanavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like atazanavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If atazanavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy

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of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Atazanavir; Cobicistat: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of atazanavir is necessary. If atazanavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like atazanavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If atazanavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone. (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of cobicistat is necessary. If cobicistat is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like cobicistat can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If cobicistat is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Atenolol; Chlorthalidone: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Atomoxetine: (Major) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as serotonin norepinephrine reuptake inhibitors (SNRIs). Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. If concomitant treatment is clinically warranted, careful observation of the patient is advised, especially during initiation of the second therapy and after dosage increases of either agent. Instruct patients to immediately report symptoms of agitation, hallucinations, tachycardia, fever, excessive sweating, shivering or shaking, muscle twitching or stiffness, trouble with coordination, nausea, vomiting, or diarrhea.
Atracurium: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of alfentanil on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.
Atropine; Benzoic Acid; Hyoscyamine; Methenamine; Methylene Blue; Phenyl Salicylate: (Major) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as methylene blue. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. If concomitant treatment is clinically warranted, careful observation of the patient is advised, especially during initiation of the second therapy and after dosage increases of either agent. Instruct patients to immediately report symptoms of agitation, hallucinations, tachycardia, fever, excessive sweating, shivering or shaking, muscle twitching or stiffness, trouble with coordination, nausea, vomiting, or diarrhea.
Atropine; Difenoxin: (Moderate) Concurrent administration of diphenoxylate/difenoxin with other opiate agonists can potentiate the CNS-depressant effects of diphenoxylate/difenoxin. Use caution during coadministration. In addition, diphenoxylate/difenoxin use may cause constipation; cases of severe GI reactions including toxic megacolon and adynamic ileus have been reported. Reduced GI motility when combined with opiate agonists may increase the risk of serious GI related adverse events.
Atropine; Diphenoxylate: (Moderate) Concurrent administration of diphenoxylate/difenoxin with other opiate agonists can potentiate the CNS-depressant effects of diphenoxylate/difenoxin. Use caution during coadministration. In addition, diphenoxylate/difenoxin use may cause constipation; cases of severe GI reactions including toxic megacolon and adynamic ileus have been reported. Reduced GI motility when combined with opiate agonists may increase the risk of serious GI related adverse events.
Atropine; Hyoscyamine; Phenobarbital; Scopolamine: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.
Azelastine: (Major) Concomitant use of opioid agonists with azelastine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with azelastine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Azelastine; Fluticasone: (Major) Concomitant use of opioid agonists with azelastine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with azelastine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Azilsartan; Chlorthalidone: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Baclofen: (Major) Concomitant use of oxycodone with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.
Barbiturates: (Major) Concomitant use of oxycodone with a barbiturate may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a barbiturate to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concurrent use of oxycodone with a barbiturate may decrease oxycodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to opioid agonists. Monitor for signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of increased opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; oxycodone is a CYP3A4 substrate. (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.
Belladonna Alkaloids; Ergotamine; Phenobarbital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.
Belladonna; Opium: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.
Benazepril; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Bendroflumethiazide; Nadolol: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Benzhydrocodone; Acetaminophen: (Major) Concomitant use of opioid agonists with benzhydrocodone may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of benzhydrocodone with opioid agonists to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If benzhydrocodone is initiated in a patient taking oxycodone, reduce initial dosage and titrate to clinical response. If oxycodone is prescribed in a patient taking benzhydrocodone, use a lower initial dose of oxycodone and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Careful monitoring, particularly during treatment initiation and dose adjustment, is recommended during coadministration of benzhydrocodone and oxycodone because of the potential risk of serotonin syndrome. Discontinue benzhydrocodone if serotonin syndrome is suspected. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome.

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Benzoic Acid; Hyoscyamine; Methenamine; Methylene Blue; Phenyl Salicylate: (Major) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as methylene blue. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. If concomitant treatment is clinically warranted, careful observation of the patient is advised, especially during initiation of the second therapy and after dosage increases of either agent. Instruct patients to immediately report symptoms of agitation, hallucinations, tachycardia, fever, excessive sweating, shivering or shaking, muscle twitching or stiffness, trouble with coordination, nausea, vomiting, or diarrhea.
Benzonatate: (Moderate) Coadministration of oxycodone and benzonatate may result in additive CNS depression.
Bethanechol: (Moderate) Bethanechol facilitates intestinal and bladder function via parasympathomimetic actions. Opiate agonists impair the peristaltic activity of the intestine. Thus, these drugs can antagonize the beneficial actions of bethanechol on GI motility.
Bexarotene: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with bexarotene is necessary; consider increasing the dose of oxycodone as needed. If bexarotene is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and bexarotene is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Bicalutamide: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of bicalutamide is necessary. If bicalutamide is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like bicalutamide can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If bicalutamide is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Bismuth Subcitrate Potassium; Metronidazole; Tetracycline: (Moderate) Additive constipation may be seen with concurrent use of opiate agonists and antidiarrheals. Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Bismuth Subsalicylate: (Moderate) Additive constipation may be seen with concurrent use of opiate agonists and antidiarrheals. Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect. (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. Although salicylates are rarely associated with nephrotoxicity, high-dose, chronic administration of salicylates combined other analgesics, including acetaminophen, significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Additive hepatic toxicity may occur, especially in combined overdose situations. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.
Bismuth Subsalicylate; Metronidazole; Tetracycline: (Moderate) Additive constipation may be seen with concurrent use of opiate agonists and antidiarrheals. Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect. (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. Although salicylates are rarely associated with nephrotoxicity, high-dose, chronic administration of salicylates combined other analgesics, including acetaminophen, significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Additive hepatic toxicity may occur, especially in combined overdose situations. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.
Bisoprolol; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Boceprevir: (Moderate) Close clinical monitoring is advised when administering acetaminophen with boceprevir due to an increased potential for acetaminophen-related adverse events. If acetaminophen dose adjustments are made, re-adjust the dose upon completion of boceprevir treatment. Although this interaction has not been studied, predictions about the interaction can be made based on the metabolic pathway of acetaminophen. Acetaminophen is partially metabolized by the hepatic isoenzyme CYP3A4; boceprevir inhibits this isoenzyme. Coadministration may result in elevated acetaminophen plasma concentrations. (Moderate) Close clinical monitoring is advised when administering oxycodone with boceprevir due to an increased potential for oxycodone-related adverse events. If oxycodone dose adjustments are made, re-adjust the dose upon completion of boceprevir treatment. Although this interaction has not been studied, predictions about the interaction can be made based on the metabolic pathway of oxycodone. Oxycodone is partially metabolized by the hepatic isoenzyme CYP3A4; boceprevir inhibits this isoenzyme. Coadministration may result in elevated oxycodone plasma concentrations.
Bosentan: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with bosentan is necessary; consider increasing the dose of oxycodone as needed. If bosentan is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and bosentan is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Brexpiprazole: (Major) Concomitant use of opioid agonists with brexpiprazole may cause excessive sedation and somnolence. Limit the use of opioid pain medications with brexpiprazole to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Brigatinib: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with brigatinib is necessary; consider increasing the dose of oxycodone as needed. If brigatinib is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate. At clinically relevant concentrations, brigatinib induced CYP3A via activation of the pregnane X receptor (PXR); this may decrease concentrations of sensitive CYP3A substrates. Concomitant use with CYP3A4 inducers can decrease oxycodone levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Brimonidine: (Moderate) Based on the sedative effects of brimonidine in individual patients, brimonidine administration has potential to enhance the CNS depressants effects of opiate agonists.
Brimonidine; Brinzolamide: (Moderate) Based on the sedative effects of brimonidine in individual patients, brimonidine administration has potential to enhance the CNS depressants effects of opiate agonists.
Brimonidine; Timolol: (Moderate) Based on the sedative effects of brimonidine in individual patients, brimonidine administration has potential to enhance the CNS depressants effects of opiate agonists.
Brompheniramine: (Moderate) Concomitant use of opioid agonists with brompheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with brompheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Brompheniramine; Carbetapentane; Phenylephrine: (Moderate) Concomitant use of opioid agonists with brompheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with brompheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including morphine.
Brompheniramine; Dextromethorphan; Guaifenesin: (Moderate) Concomitant use of opioid agonists with brompheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with brompheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Brompheniramine; Guaifenesin; Hydrocodone: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate

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hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression. (Moderate) Concomitant use of opioid agonists with brompheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with brompheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Brompheniramine; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression. (Moderate) Concomitant use of opioid agonists with brompheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with brompheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Brompheniramine; Pseudoephedrine: (Moderate) Concomitant use of opioid agonists with brompheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with brompheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Bumetanide: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when loop diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Bupivacaine Liposomal: (Moderate) Coadministration of bupivacaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue bupivacaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. (Moderate) The use of these drugs together must be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Bupivacaine: (Moderate) Coadministration of bupivacaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue bupivacaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. (Moderate) The use of these drugs together must be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Bupivacaine; Lidocaine: (Moderate) Coadministration of bupivacaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue bupivacaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. (Moderate) Coadministration of lidocaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue lidocaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. (Moderate) The use of these drugs together must be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Buprenorphine: (Major) Buprenorphine is a mixed opiate agonist/antagonist with strong affinity for the mu-receptor that may partially block the effects of full mu-receptor opiate agonists and reduce analgesic effects. In some cases of acute pain, trauma, or during surgical management, opiate-dependent patients receiving buprenorphine maintenance therapy may require concurrent treatment with opiate agonists, such as oxycodone. In these cases, health care professionals must exercise caution in opiate agonist dose selection, as higher doses of an opiate agonist may be required to compete with buprenorphine at the mu-receptor. Management strategies may include adding a short-acting opiate agonist to achieve analgesia in the presence of buprenorphine, discontinuation of buprenorphine and use of an opiate agonist to avoid withdrawal and achieve analgesia, or conversion of buprenorphine to methadone while using additional opiate agonists if needed. Closely monitor patients for CNS or respiratory depression. When buprenorphine is used for analgesia, avoid co-use with opiate agonists. Buprenorphine may cause withdrawal symptoms in patients receiving chronic opiate agonists as well as possibly potentiate CNS, respiratory, and hypotensive effects. The additive or antagonistic effects are dependent upon the dose of the opiate agonist used; antagonistic effects are more common at low to moderate doses of the opiate agonist.

Buprenorphine; Naloxone: (Major) Buprenorphine is a mixed opiate agonist/antagonist with strong affinity for the mu-receptor that may partially block the effects of full mu-receptor opiate agonists and reduce analgesic effects. In some cases of acute pain, trauma, or during surgical management, opiate-dependent patients receiving buprenorphine maintenance therapy may require concurrent treatment with opiate agonists, such as oxycodone. In these cases, health care professionals must exercise caution in opiate agonist dose selection, as higher doses of an opiate agonist may be required to compete with buprenorphine at the mu-receptor. Management strategies may include adding a short-acting opiate agonist to achieve analgesia in the presence of buprenorphine, discontinuation of buprenorphine and use of an opiate agonist to avoid withdrawal and achieve analgesia, or conversion of buprenorphine to methadone while using additional opiate agonists if needed. Closely monitor patients for CNS or respiratory depression. When buprenorphine is used for analgesia, avoid co-use with opiate agonists. Buprenorphine may cause withdrawal symptoms in patients receiving chronic opiate agonists as well as possibly potentiate CNS, respiratory, and hypotensive effects. The additive or antagonistic effects are dependent upon the dose of the opiate agonist used; antagonistic effects are more common at low to moderate doses of the opiate agonist. (Major) Naloxone can antagonize the therapeutic efficacy of oxycodone in addition to precipitating withdrawal symptoms in patients who are physically dependent on opiate drugs including oxycodone.

Bupropion: (Moderate) Bupropion is an inhibitor of the CYP2D6 isoenzyme. Plasma concentrations of opiate agents metabolized by CYP2D6 such as oxycodone may be increased if bupropion is added. Dosage reductions in these agents may be needed. Conversely, if bupropion therapy is discontinued, dosages of these agents may need to be adjusted upward in some patients. Excessive use of opioid agonists (e.g., opiate addiction) is associated with an increased seizure risk; seizures may be more likely to occur during concurrent use of bupropion in these patients since bupropion is associated with a dose-related risk of seizures.

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Bupropion; Naltrexone: (Major) When naltrexone is used as adjuvant treatment of opiate or alcohol dependence, use is contraindicated in patients currently receiving opiate agonists. Naltrexone will antagonize the therapeutic benefits of opiate agonists and will induce a withdrawal reaction in patients with physical dependence to opioids. Also, patients should be opiate-free for at least 7-10 days prior to initiating naltrexone therapy. If there is any question of opioid use in the past 7-10 days and the patient is not experiencing opioid withdrawal symptoms and/or the urine is negative for opioids, a naloxone challenge test needs to be performed. If a patient receives naltrexone, and an opiate agonist is needed for an emergency situation, large doses of opiate agonists may ultimately overwhelm naltrexone antagonism of opiate receptors. Immediately following administration of exogenous opiate agonists, the opiate plasma concentration may be sufficient to overcome naltrexone competitive blockade, but the patient may experience deeper and more prolonged respiratory depression and thus, may be in danger of respiratory arrest and circulatory collapse. Non-receptor mediated actions like facial swelling, itching, generalized erythema, or bronchoconstriction may occur presumably due to histamine release. A rapidly acting opiate agonist is preferred as the duration of respiratory depression will be shorter. Patients receiving naltrexone may also experience opiate side effects with low doses of opiate agonists. If the opiate agonist is taken in such a way that high concentrations remain in the body beyond the time naltrexone exerts its therapeutic effects, serious side effects may occur. (Moderate) Bupropion is an inhibitor of the CYP2D6 isoenzyme. Plasma concentrations of opiate agents metabolized by CYP2D6 such as oxycodone may be increased if bupropion is added. Dosage reductions in these agents may be needed. Conversely, if bupropion therapy is discontinued, dosages of these agents may need to be adjusted upward in some patients. Excessive use of opioid agonists (e.g., opiate addiction) is associated with an increased seizure risk; seizures may be more likely to occur during concurrent use of bupropion in these patients since bupropion is associated with a dose-related risk of seizures.
Buspirone: (Moderate) Concomitant use of CNS depressants, such as buspirone, can potentiate the effects of oxycodone, which may potentially lead to respiratory depression, CNS depression, sedation, or hypotensive responses. If concurrent use of codeine and buspirone is imperative, reduce the dose of one or both drugs.
Busulfan: (Moderate) Use busulfan and acetaminophen together with caution; concomitant use may result in increased busulfan levels and increased busulfan toxicity. Separating the administration of these drugs may mitigate this interaction; avoid giving acetaminophen within 72 hours prior to or concurrently with busulfan. Busulfan is metabolized in the liver through conjugation with glutathione; acetaminophen decreases glutathione levels in the blood and tissues and may reduce the clearance of busulfan.
Butabarbital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.
Butorphanol: (Major) Avoid the concomitant use of butorphanol and opiate agonists, such as oxycodone. Butorphanol is a mixed opiate agonist/antagonist that may block the effects of opiate agonists and reduce analgesic effects. Butorphanol may cause withdrawal symptoms in patients receiving chronic opiate agonists. Concurrent use of butorphanol with other opiate agonists can cause additive CNS, respiratory, and hypotensive effects. The additive or antagonistic effects are dependent upon the dose of the opiate agonist used; antagonistic effects are more common at low to moderate doses of the opiate agonist.
Candesartan; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Cannabidiol: (Moderate) Concomitant use of opioid agonists with cannabidiol may cause excessive sedation and somnolence. Limit the use of opioid pain medications with cannabidiol to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Capsaicin; Metaxalone: (Major) Concomitant use of oxycodone with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.
Captopril; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Carbamazepine: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with carbamazepine is necessary; consider increasing the dose of oxycodone as needed. If carbamazepine is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and carbamazepine is a strong CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. (Minor) Carbamazepine may potentially accelerate the hepatic metabolism of acetaminophen. In addition, due to enzyme induction, carbamazepine may increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolite, NAPQI. Clinicians should be alert to decreased effect of acetaminophen. Dosage adjustments may be necessary, and closer monitoring of clinical and/or adverse effects is warranted.
Carbetapentane; Chlorpheniramine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including morphine.
Carbetapentane; Chlorpheniramine; Phenylephrine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including morphine.
Carbetapentane; Diphenhydramine; Phenylephrine: (Moderate) Concomitant use of opioid agonists with diphenhydramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with diphenhydramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including morphine.
Carbetapentane; Guaifenesin: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including morphine.
Carbetapentane; Guaifenesin; Phenylephrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including morphine.
Carbetapentane; Phenylephrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including morphine.
Carbetapentane; Phenylephrine; Pyrilamine: (Moderate) Concomitant use of opioid agonists with pyrilamine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with pyrilamine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including morphine.
Carbetapentane; Pseudoephedrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including morphine.
Carbetapentane; Pyrilamine: (Moderate) Concomitant use of opioid agonists with pyrilamine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with pyrilamine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about

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the risks and symptoms of excessive CNS depression. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including morphine.
Carbinoxamine: (Moderate) Concomitant use of opioid agonists with carbinoxamine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with carbinoxamine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Carbinoxamine; Dextromethorphan; Pseudoephedrine: (Moderate) Concomitant use of opioid agonists with carbinoxamine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with carbinoxamine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Carbinoxamine; Hydrocodone; Phenylephrine: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression. (Moderate) Concomitant use of opioid agonists with carbinoxamine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with carbinoxamine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Carbinoxamine; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression. (Moderate) Concomitant use of opioid agonists with carbinoxamine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with carbinoxamine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Carbinoxamine; Phenylephrine: (Moderate) Concomitant use of opioid agonists with carbinoxamine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with carbinoxamine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Carbinoxamine; Pseudoephedrine: (Moderate) Concomitant use of opioid agonists with carbinoxamine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with carbinoxamine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Cariprazine: (Moderate) Due to the CNS effects of cariprazine, caution is advisable when cariprazine is given in combination with other centrally-acting medications including opiate agonists.
Carisoprodol: (Major) Concomitant use of oxycodone with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.
Ceritinib: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ceritinib is necessary. If ceritinib is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with strong CYP3A4 inhibitors like ceritinib can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ceritinib is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Cetirizine: (Moderate) Concomitant use of opioid agonists with cetirizine/levocetirizine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with cetirizine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Cetirizine; Pseudoephedrine: (Moderate) Concomitant use of opioid agonists with cetirizine/levocetirizine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with cetirizine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Charcoal: (Minor) Activated charcoal binds many drugs within the gut. Administering charcoal dietary supplements at the same time as a routine acetaminophen dosage would be expected to interfere with the analgesic and antipyretic efficacy of acetaminophen. Charcoal is mostly used in the setting of acetaminophen overdose; however, patients should never try to treat an acetaminophen overdose with charcoal dietary supplements. Advise patients to get immediate medical attention for an acetaminophen overdose.
Chlophedianol; Dexbrompheniramine: (Moderate) Concomitant use of opioid agonists with dexbrompheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with dexbrompheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Chlophedianol; Dexchlorpheniramine; Pseudoephedrine: (Moderate) Concomitant use of opioid agonists with dexchlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with dexchlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Chloral Hydrate: (Major) Concomitant use of opioid agonists with chloral hydrate may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chloral hydrate to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Chloramphenicol: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of chloramphenicol is necessary. If chloramphenicol is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like chloramphenicol can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If chloramphenicol is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Chlorcyclizine: (Moderate) Concomitant use of opioid agonists with chlorcyclizine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorcyclizine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Chlordiazepoxide: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical

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effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Chlordiazepoxide; Clidinium: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Chloroprocaine: (Moderate) Coadministration of chloroprocaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue chloroprocaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. (Minor) Due to the CNS depression potential of all local anesthetics, they should be used with caution with other agents that can cause respiratory depression, such as opiate agonists.

Chlorothiazide: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Chlorpheniramine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpheniramine; Codeine: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpheniramine; Dextromethorphan: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpheniramine; Dihydrocodeine; Phenylephrine: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpheniramine; Dihydrocodeine; Pseudoephedrine: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpheniramine; Guaifenesin; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression. (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpheniramine; Hydrocodone: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression. (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpheniramine; Hydrocodone; Phenylephrine: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression. (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and

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somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpheniramine; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression. (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpheniramine; Phenylephrine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpheniramine; Pseudoephedrine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpromazine: (Moderate) Concomitant use of oxycodone with phenothiazines may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. Furthermore, oxycodone is metabolized in part by 2D6 to oxymorphone, which represents < 15% of the total administered dose. Concurrent use of some agents that inhibit CYP2D6 (e.g., quinidine) has not been shown to result in clinically significant interactions. However, many phenothiazines are inhibitors of CYP2D6 (e.g., chlorpromazine, perphenazine, thioridazine) and may potentially increase the effects of oxycodone. Also, severe hypotension may be potentiated with concurrent phenothiazine usage or other drug that compromises vasomotor tone.

Chlorthalidone: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Chlorthalidone; Clonidine: (Moderate) Clonidine has CNS depressive effects and can potentiate the actions of other CNS depressants including opiate agonists. (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Chlorzoxazone: (Major) Concomitant use of oxycodone with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.

Cholestyramine: (Moderate) Cholestyramine has been shown to decrease the absorption of acetaminophen by roughly 60%. Experts have recommended that cholestyramine not be given within 1 hour of acetaminophen if analgesic or antipyretic effect is to be achieved.

Choline Salicylate; Magnesium Salicylate: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. Although salicylates are rarely associated with nephrotoxicity, high-dose, chronic administration of salicylates combined other analgesics, including acetaminophen, significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Additive hepatic toxicity may occur, especially in combined overdose situations. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.

Cimetidine: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of cimetidine is necessary. If cimetidine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like cimetidine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If cimetidine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Ciprofloxacin: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ciprofloxacin is necessary. If ciprofloxacin is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like ciprofloxacin can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ciprofloxacin is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Cisatracurium: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of alfentanil on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.

Citalopram: (Moderate) The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue the suspected drugs if serotonin syndrome is suspected and manage clinically. There has been a case report of possible serotonin syndrome caused by the combination of oxycodone and selective serotonin reuptake inhbitors (SSRIs).

Clarithromycin: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of clarithromycin is necessary. If clarithromycin is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like clarithromycin can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If clarithromycin is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Clemastine: (Moderate) Concomitant use of opioid agonists with clemastine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with clemastine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Clobazam: (Major) Concomitant use of oxycodone with clobazam may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with clobazam to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concurrent use of oxycodone with clobazam may decrease oxycodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to opioid agonists. Monitor for signs of opioid withdrawal. Discontinuation of clobazam may increase the risk of opioid-related adverse reactions, such as fatal respiratory depression. clobazam induces CYP3A4; oxycodone is a CYP3A4 substrate.

Clomipramine: (Major) Concomitant use of opioid agonists with tricyclic antidepressants may cause excessive sedation, somnolence, and increased risk of serotonin syndrome. The anticholinergic properties of tricyclic antidepressants may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Limit the use of opioid pain medications with tricyclic antidepressants to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment

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durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and serotonin syndrome. Monitor for signs of urinary retention and reduced gastric motility.

Clonazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Clonidine: (Moderate) Clonidine has CNS depressive effects and can potentiate the actions of other CNS depressants including opiate agonists.

Clopidogrel: (Moderate) Coadministration of opioid agonists, such as oxycodone, delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Clorazepate: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Clozapine: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as clozapine, can lead to additive respiratory depression, hypotension, profound sedation, or coma. In addition, this drug combination may result in additive effects on intestinal motility or bladder function. Prior to concurrent use of oxycodone in patients taking clozapine, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Oxycodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate oxycodone at one-third to one-half the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider using a lower clozapine dose. Monitor patients for sedation and respiratory depression.

Cobicistat: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of cobicistat is necessary. If cobicistat is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like cobicistat can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If cobicistat is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Codeine: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.

Codeine; Guaifenesin: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.

Codeine; Phenylephrine; Promethazine: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. (Moderate) Concomitant use of oxycodone with phenothiazines may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. Furthermore, oxycodone is metabolized in part by 2D6 to oxymorphone, which represents < 15% of the total administered dose. Concurrent use of some agents that inhibit CYP2D6 (e.g., quinidine) has not been shown to result in clinically significant interactions. However, many phenothiazines are inhibitors of CYP2D6 (e.g., chlorpromazine, perphenazine, thioridazine) and may potentially increase the effects of oxycodone. Also, severe hypotension may be potentiated with concurrent phenothiazine usage or other drug that compromises vasomotor tone.

Codeine; Promethazine: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. (Moderate) Concomitant use of oxycodone with phenothiazines may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. Furthermore, oxycodone is metabolized in part by 2D6 to oxymorphone, which represents < 15% of the total administered dose. Concurrent use of some agents that inhibit CYP2D6 (e.g., quinidine) has not been shown to result in clinically significant interactions. However, many phenothiazines are inhibitors of CYP2D6 (e.g., chlorpromazine, perphenazine, thioridazine) and may potentially increase the effects of oxycodone. Also, severe hypotension may be potentiated with concurrent phenothiazine usage or other drug that compromises vasomotor tone.

COMT inhibitors: (Major) Concomitant use of opioid agonists with COMT inhibitors may cause excessive sedation and somnolence. Limit the use of opioid pain medications with COMT inhibitors to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. Dopaminergic agents like entacapone and tolcapone have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment.

Conivaptan: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of conivaptan is necessary. If conivaptan is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like conivaptan

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can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If conivaptan is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Crizotinib: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of crizotinib is necessary. If crizotinib is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like crizotinib can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If crizotinib is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Crofelemer: (Moderate) Pharmacodynamic interactions between crofelemer and opiate agonists are theoretically possible. Crofelemer does not affect GI motility mechanisms, but does have antidiarrheal effects. Patients taking medications that decrease GI motility, such as opiate agonists, may be at greater risk for serious complications from crofelemer, such as constipation with chronic use. Use caution and monitor GI symptoms during coadministration.

Cyclizine: (Moderate) Concomitant use of opioid agonists with cyclizine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with cyclizine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Cyclobenzaprine: (Major) Concomitant use of oxycodone with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.

Cyclosporine: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of cyclosporine is necessary. If cyclosporine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like cyclosporine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If cyclosporine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Cyproheptadine: (Moderate) Concomitant use of opioid agonists with cyproheptadine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with cyproheptadine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Dabrafenib: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with dabrafenib is necessary; consider increasing the dose of oxycodone as needed. If dabrafenib is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and dabrafenib is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.

Dalfopristin; Quinupristin: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of dalfopristin; quinupristin is necessary. If dalfopristin; quinupristin is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like dalfopristin; quinupristin can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If dalfopristin; quinupristin is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Danazol: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of danazol is necessary. If danazol is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like danazol can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If danazol is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Dantrolene: (Major) Concomitant use of oxycodone with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.

Dapsone: (Moderate) Coadministration of dapsone with acetaminophen may increase the risk of developing methemoglobinemia. Advise patients to discontinue treatment and seek immediate medical attention with any signs or symptoms of methemoglobinemia.

Darifenacin: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when darifenacin, an anticholinergic drug for overactive bladder, is used with opiate agonists. The concomitant use of these drugs together may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect. Both agents may also cause drowsiness or blurred vision, and patients should use care in driving or performing other hazardous tasks until the effects of the drugs are known.

Darunavir: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of darunavir is necessary. If darunavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like darunavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If darunavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Darunavir; Cobicistat: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of cobicistat is necessary. If cobicistat is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like cobicistat can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If cobicistat is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone. (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of darunavir is necessary. If darunavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like darunavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If darunavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Darunavir; Cobicistat; Emtricitabine; Tenofovir alafenamide: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of cobicistat is necessary. If cobicistat is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like cobicistat can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If cobicistat is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone. (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of darunavir is necessary. If darunavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like darunavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression,

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particularly when an inhibitor is added to a stable dose of oxycodone. If darunavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Dasabuvir; Ombitasvir; Paritaprevir; Ritonavir: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ritonavir is necessary. If ritonavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like ritonavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ritonavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Deferasirox: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with deferasirox is necessary; consider increasing the dose of oxycodone as needed. If deferasirox is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and deferasirox is a weak CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Delavirdine: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of delavirdine is necessary. If delavirdine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like delavirdine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If delavirdine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Desflurane: (Moderate) Concurrent use with opiate agonists can decrease the minimum alveolar concentration (MAC) of desflurane needed to produce anesthesia.
Desipramine: (Major) Concomitant use of opioid agonists with tricyclic antidepressants may cause excessive sedation, somnolence, and increased risk of serotonin syndrome. The anticholinergic properties of tricyclic antidepressants may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Limit the use of opioid pain medications with tricyclic antidepressants to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and serotonin syndrome. Monitor for signs of urinary retention and reduced gastric motility.
Desmopressin: (Major) Additive hyponatremic effects may be seen in patients treated with desmopressin and drugs associated with water intoxication, hyponatremia, or SIADH including opiate agonists. Use combination with caution, and monitor patients for signs and symptoms of hyponatremia.
Deutetrabenazine: (Major) Concomitant use of opiate agonists with deutetrabenazine may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with deutetrabenazine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If extended-release oxycodone or oxycodone; naloxone is initiated in a patient taking a barbiturate, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage and titrate to clinical response; reduced initial doses of immediate-release oxycodone, oxycodone; naltrexone, aspirin, ASA; oxycodone, and ibuprofen; oxycodone are also recommended. If a decision is made to start treatment with acetaminophen; oxycodone extended-release tablets, start with 1 tablet every 12 hours. If a barbituate is prescribed for a patient taking an opioid agonist, use a lower initial dose of the barbituate and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Dexamethasone: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with dexamethasone is necessary; consider increasing the dose of oxycodone as needed. If dexamethasone is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and dexamethasone is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Dexchlorpheniramine: (Moderate) Concomitant use of opioid agonists with dexchlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with dexchlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Dexchlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Concomitant use of opioid agonists with dexchlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with dexchlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Dexmedetomidine: (Moderate) Co-administration of dexmedetomidine with opiate agonists likely to lead to an enhancement of CNS depression.
Dexpanthenol: (Moderate) Use caution when using dexpanthenol with drugs that decrease gastrointestinal motility, such as opiate agonists, as it may decrease the effectiveness of dexpanthenol.
Dextromethorphan; Diphenhydramine; Phenylephrine: (Moderate) Concomitant use of opioid agonists with diphenhydramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with diphenhydramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Dextromethorphan; Promethazine: (Moderate) Concomitant use of oxycodone with phenothiazines may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. Furthermore, oxycodone is metabolized in part by 2D6 to oxymorphone, which represents < 15% of the total administered dose. Concurrent use of some agents that inhibit CYP2D6 (e.g., quinidine) has not been shown to result in clinically significant interactions. However, many phenothiazines are inhibitors of CYP2D6 (e.g., chlorpromazine, perphenazine, thioridazine) and may potentially increase the effects of oxycodone. Also, severe hypotension may be potentiated with concurrent phenothiazine usage or other drug that compromises vasomotor tone.
Dextromethorphan; Quinidine: (Moderate) Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone, which represents < 15% of the total administered dose. Potent inhibitors of CYP2D6, such as quinidine, may potentially increase the effects of oxycodone; however, such blockade has not been shown to be of clinical significance during oxycodone treatment. Clinicians should be aware of this possible interaction.
Diazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. If parental diazepam is used with an opiate agonist, reduce the opiate agonist dosage by at least 1/3. Educate patients about the risks and symptoms of respiratory depression and sedation.
Diflunisal: (Moderate) Acetaminophen plasma concentrations can increase by approximately 50% following administration of diflunisal. Acetaminophen has no effect on diflunisal concentrations. Acetaminophen in high doses has been associated with severe hepatotoxic reactions; therefore, caution should be exercised when using these agents concomitantly.
Dihydrocodeine; Guaifenesin; Pseudoephedrine: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the

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patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.

Diltiazem: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of diltiazem is necessary. If diltiazem is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like diltiazem can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If diltiazem is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Dimenhydrinate: (Moderate) Concomitant use of opioid agonists with dimenhydrinate may cause excessive sedation and somnolence. Limit the use of opioid pain medications with dimenhydrinate to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Diphenhydramine: (Moderate) Concomitant use of opioid agonists with diphenhydramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with diphenhydramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Diphenhydramine; Hydrocodone; Phenylephrine: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression. (Moderate) Concomitant use of opioid agonists with diphenhydramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with diphenhydramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Diphenhydramine; Ibuprofen: (Moderate) Concomitant use of opioid agonists with diphenhydramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with diphenhydramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Diphenhydramine; Naproxen: (Moderate) Concomitant use of opioid agonists with diphenhydramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with diphenhydramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Diphenhydramine; Phenylephrine: (Moderate) Concomitant use of opioid agonists with diphenhydramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with diphenhydramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Dolasetron: (Moderate) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as serotonin-receptor antagonists. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.

Doxacurium: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of alfentanil on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.

Doxepin: (Major) Concomitant use of opioid agonists with tricyclic antidepressants may cause excessive sedation, somnolence, and increased risk of serotonin syndrome. The anticholinergic properties of tricyclic antidepressants may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Limit the use of opioid pain medications with tricyclic antidepressants to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and serotonin syndrome. Monitor for signs of urinary retention and reduced gastric motility.

Doxylamine: (Moderate) Concomitant use of opioid agonists with doxylamine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with doxylamine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Doxylamine; Pyridoxine: (Moderate) Concomitant use of opioid agonists with doxylamine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with doxylamine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Dronabinol: (Moderate) Concomitant use of opiate agonists and other CNS depressants such as dronabinol, THC may result in respiratory depression, CNS depression, and/or hypotension. Prior to concurrent use of opiate agonists in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. When concomitant treatment is necessary, reduce the dose of 1 or both drugs. When levorphanol is used with dronabinol, reduce the initial levorphanol dose by approximately 50% or more.

Dronedarone: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of dronedarone is necessary. If dronedarone is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like dronedarone can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If dronedarone is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Droperidol: (Major) Concomitant use of opioid agonists with droperidol may cause excessive sedation and somnolence. Limit the use of opioid pain medications with droperidol to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Drospirenone; Ethinyl Estradiol: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.

Drospirenone; Ethinyl Estradiol; Levomefolate: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.

Duvelisib: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of duvelisib is necessary. If duvelisib is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like duvelisib can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If duvelisib is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Efavirenz: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with efavirenz is necessary; consider increasing the dose of oxycodone as needed. If efavirenz is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and efavirenz is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in

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patients who have developed physical dependence. (Minor) Drugs that induce the hepatic isoenzymes CYP2E1 and CYP1A2, such as efavirenz, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolite, NAPQI. Also, the analgesic activity of acetaminophen may be reduced.

Efavirenz; Emtricitabine; Tenofovir: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with efavirenz is necessary; consider increasing the dose of oxycodone as needed. If efavirenz is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and efavirenz is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. (Minor) Drugs that induce the hepatic isoenzymes CYP2E1 and CYP1A2, such as efavirenz, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolite, NAPQI. Also, the analgesic activity of acetaminophen may be reduced.

Efavirenz; Lamivudine; Tenofovir Disoproxil Fumarate: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with efavirenz is necessary; consider increasing the dose of oxycodone as needed. If efavirenz is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and efavirenz is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. (Minor) Drugs that induce the hepatic isoenzymes CYP2E1 and CYP1A2, such as efavirenz, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolite, NAPQI. Also, the analgesic activity of acetaminophen may be reduced.

Elagolix: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with elagolix is necessary; consider increasing the dose of oxycodone as needed. If elagolix is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and elagolix is a weak to moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.

Elbasvir; Grazoprevir: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of grazoprevir is necessary. If grazoprevir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like grazoprevir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If grazoprevir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Eletriptan: (Moderate) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as serotonin-receptor agonists. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.

Elexacaftor; tezacaftor; ivacaftor: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ivacaftor is necessary. If ivacaftor is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like ivacaftor can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ivacaftor is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Eliglustat: (Minor) Coadministration of oxycodone and eliglustat may result in increased concentrations of oxycodone, although the interaction does not appear to be clinically significant unless a 3A4 inhibitor is used concomitantly. Eliglustat is a CYP2D6 inhibitor. Although primarily metabolized by CYP3A, CYP2D6 also contributes to conversion of oxycodone to oxymorphone. If coadministration is necessary, use caution and monitor patients closely for opioid-related adverse effects such as respiratory depression and sedation at frequent intervals. Consider reducing the dosage of oxycodone until stable drug effects are achieved, and titrating to clinical effect.

Eltrombopag: (Moderate) Eltrombopag is a UDP-glucuronyltransferase inhibitor. Acetaminophen is a substrate of UDP-glucuronyltransferases. The significance or effect of this interaction is not known; however, elevated concentrations of acetaminophen are possible. Monitor patients for adverse reactions if these drugs are coadministered. (Moderate) Eltrombopag is a UDP-glucuronyltransferase inhibitor. Opiate agonists are a substrate of UDP-glucuronyltransferases. The significance or effect of this interaction is not known; however, elevated concentrations of the opiate agonist is possible. Monitor patients for adverse reactions if eltrombopag is administered with an opiate agonist.

Eluxadoline: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of eluxadoline is necessary. If eluxadoline is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like eluxadoline can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If eluxadoline is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Alafenamide: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of cobicistat is necessary. If cobicistat is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like cobicistat can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If cobicistat is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Disoproxil Fumarate: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of cobicistat is necessary. If cobicistat is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like cobicistat can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If cobicistat is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Enalapril; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Enflurane: (Major) Concomitant use of oxycodone with a general anesthetic may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a general anesthetic to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.

Enzalutamide: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with enzalutamide is necessary; consider increasing the dose of oxycodone as needed. If enzalutamide is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and enzalutamide is a strong CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.

Eprosartan; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Erythromycin: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of erythromycin is necessary. If erythromycin is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like erythromycin can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If erythromycin is discontinued, oxycodone plasma concentrations will decrease resulting in

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reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Erythromycin; Sulfisoxazole: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of erythromycin is necessary. If erythromycin is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like erythromycin can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If erythromycin is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Escitalopram: (Moderate) The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue the suspected drugs if serotonin syndrome is suspected and manage clinically. There has been a case report of possible serotonin syndrome caused by the combination of oxycodone and selective serotonin reuptake inhbitors (SSRIs).
Esketamine: (Major) Concomitant use of opioid agonists with esketamine may cause excessive sedation and somnolence. Limit the use of opioid pain medication with esketamine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Patients who have received a dose of esketamine should be instructed not to drive or engage in other activities requiring complete mental alertness until the next day after a restful sleep. Educate patients about the risks and symptoms of excessive CNS depression.
Eslicarbazepine: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with eslicarbazepine is necessary; consider increasing the dose of oxycodone as needed. If eslicarbazepine is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and eslicarbazepine is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Estazolam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Eszopiclone: (Moderate) Concomitant use of oxycodone with eszopiclone may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. In addition, the risk of next-day psychomotor impairment is increased during co-administration of eszopiclone and other CNS depressants, which may decrease the ability to perform tasks requiring full mental alertness such as driving. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If eszopiclone is used concurrently with oxycodone, a reduced dosage of oxycodone and/or eszopiclone is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.
Ethacrynic Acid: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when loop diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Ethanol: (Major) Alcohol is associated with CNS depression. The combined use of alcohol and CNS depressants can lead to additive CNS depression, which could be dangerous in tasks requiring mental alertness and fatal in overdose. Alcohol taken with other CNS depressants can lead to additive respiratory depression, hypotension, profound sedation, or coma. Consider the patient's use of alcohol or illicit drugs when prescribing CNS depressant medications. In many cases, the patient should receive a lower dose of the CNS depressant initially if the patient is not likely to be compliant with avoiding alcohol. (Major) The risk of developing hepatotoxicity from acetaminophen appears to be increased in patients who regularly consume ethanol. Patients who drink more than 3 alcoholic drinks a day and take acetaminophen are at increased risk of developing hepatotoxicity. Acute or chronic ethanol use increases acetaminophen-induced hepatotoxicity by inducing cytochrome P450 CYP 2E1 leading to increased formation of the hepatotoxic metabolite of acetaminophen. Also, chronic alcohol use can deplete liver glutathione stores. Administration of acetaminophen should be limited or avoided altogether in patients with alcoholism or patients who consume ethanol regularly.
Ethinyl Estradiol: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.
Ethinyl Estradiol; Desogestrel: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.
Ethinyl Estradiol; Ethynodiol Diacetate: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.
Ethinyl Estradiol; Etonogestrel: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.
Ethinyl Estradiol; Levonorgestrel: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.
Ethinyl Estradiol; Levonorgestrel; Ferrous bisglycinate: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.
Ethinyl Estradiol; Levonorgestrel; Folic Acid; Levomefolate: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.
Ethinyl Estradiol; Norelgestromin: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.
Ethinyl Estradiol; Norethindrone Acetate: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.
Ethinyl Estradiol; Norethindrone Acetate; Ferrous fumarate: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.
Ethinyl Estradiol; Norethindrone: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.
Ethinyl Estradiol; Norethindrone; Ferrous fumarate: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.
Ethinyl Estradiol; Norgestimate: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.
Ethinyl Estradiol; Norgestrel: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.
Etomidate: (Major) Concomitant use of oxycodone with a general anesthetic may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a general anesthetic to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.
Etravirine: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with etravirine is necessary; consider increasing the dose of oxycodone as needed. If etravirine is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and etravirine is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Everolimus: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of everoliumus is necessary. If everoliumus is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like everoliumus can

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increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If everolimus is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Exenatide: (Minor) Although an interaction is possible, these drugs may be used together. To avoid potential pharmacokinetic interactions that might alter effectiveness of acetaminophen, it may be advisable for patients to take acetaminophen at least 1 hour prior to an exenatide injection. When 1,000 mg acetaminophen elixir was given with 10 mcg exenatide (at 0 hours) and at 1, 2 and 4 hours after exenatide injection, acetaminophen AUCs were decreased by 21%, 23%, 24%, and 14%, respectively; Cmax was decreased by 37%, 56%, 54%, and 41%, respectively. Additionally, acetaminophen Tmax was delayed from 0.6 hours in the control period to 0.9, 4.2, 3.3, and 1.6 hours, respectively. Acetaminophen AUC, Cmax, and Tmax were not significantly changed when acetaminophen was given 1 h before exenatide injection. The mechanism of this interaction is not available (although it may be due to delayed gastric emptying from exenatide use) and the clinical impact has not been assessed.

Fedratinib: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of fedratinib is necessary. If fedratinib is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with moderate CYP3A4 inhibitors like fedratinib can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If fedratinib is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Fentanyl: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.

Fesoterodine: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when fesoterodine, an anticholinergic drug for overactive bladder. is used with opiate agonists. The concomitant use of these drugs together may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect. Both agents may also cause drowsiness or blurred vision, and patients should use care in driving or performing other hazardous tasks until the effects of the drugs are known.

Flibanserin: (Moderate) The concomitant use of flibanserin with CNS depressants, such as opiate agonists, may increase the risk of CNS depression (e.g., dizziness, somnolence) compared to the use of flibanserin alone. Patients should avoid activities requiring full alertness (e.g., operating machinery or driving) until at least 6 hours after each dose and until they know how flibanserin affects them.

Fluconazole: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of fluconazole is necessary. If fluconazole is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like fluconazole can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If fluconazole is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Fluoxetine: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression, sedation, and serotonin syndrome if concurrent use of fluoxetine is necessary. If fluoxetine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system like fluoxetine has resulted in serotonin syndrome. In addition, oxycodone is a CYP3A4 substrate, and coadministration with CYP3A4 inhibitors like fluoxetine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If fluoxetine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Fluoxetine; Olanzapine: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as olanzapine, can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of oxycodone in patients taking olanzapine, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Oxycodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate oxycodone at one-third to one-half the usual dosage in patients that are concurrently receiving another CNS depressant. Also, consider using a lower olanzapine dose. Monitor patients for sedation and respiratory depression. (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression, sedation, and serotonin syndrome if concurrent use of fluoxetine is necessary. If fluoxetine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system like fluoxetine has resulted in serotonin syndrome. In addition, oxycodone is a CYP3A4 substrate, and coadministration with CYP3A4 inhibitors like fluoxetine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If fluoxetine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Fluphenazine: (Moderate) Concomitant use of oxycodone with phenothiazines may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. Furthermore, oxycodone is metabolized in part by 2D6 to oxymorphone, which represents < 15% of the total administered dose. Concurrent use of some agents that inhibit CYP2D6 (e.g., quinidine) has not been shown to result in clinically significant interactions. However, many phenothiazines are inhibitors of CYP2D6 (e.g., chlorpromazine, perphenazine, thioridazine) and may potentially increase the effects of oxycodone. Also, severe hypotension may be potentiated with concurrent phenothiazine usage or other drug that compromises vasomotor tone.

Flurazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Fluvoxamine: (Major) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression, sedation, and serotonin syndrome if concurrent use of fluvoxamine is necessary. If fluvoxamine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system like fluvoxamine has resulted in serotonin syndrome. In addition, oxycodone is a CYP3A4 substrate, and coadministration with CYP3A4 inhibitors like fluvoxamine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If fluvoxamine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Fosamprenavir: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of fosamprenavir is necessary. If fosamprenavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like fosamprenavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If fosamprenavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to

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oxycodone.
Fosinopril; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Fosphenytoin: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with fosphenytoin is necessary; consider increasing the dose of oxycodone as needed. If fosphenytoin is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and fosphenytoin is a strong CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Fospropofol: (Major) Concomitant use of oxycodone with a general anesthetic may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a general anesthetic to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.
Fostamatinib: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of fostamatinib is necessary. If fostamatinib is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like fostamatinib can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If fostamatinib is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Frovatriptan: (Moderate) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as serotonin-receptor agonists. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.
Furosemide: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when loop diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Gabapentin: (Major) Concomitant use of opioid agonists with gabapentin may cause excessive sedation, somnolence, and respiratory depression. Limit the use of opioid pain medications with gabapentin to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, initiate gabapentin at the lowest recommended dose and monitor patients for symptoms of respiratory depression and sedation. Use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and respiratory depression.
Gefitinib: (Moderate) Monitor for an increased incidence of oxycodone-related adverse effects if gefitinib and oxycodone are used concomitantly. At high concentrations, gefitinib is an inhibitor of CYP2D6, which is partially responsible for the metabolism of oxycodone. As < 15% of the total administered dose is metabolized by CYP2D6 to oxymorphone, concurrent use of some agents that inhibit CYP2D6 has not been shown to result in clinically significant interactions. However, potent inhibitors of CYP2D6, such as ritonavir, may potentially increase the effects of oxycodone. In patients with solid tumors, exposure to metoprolol, another CYP2D6 substrate, was increased by 30% when given on day 15 of gefitinib dosing (500 mg daily); the effect of gefitinib on CYP2D6-dependent drugs is only likely to be clinically relevant when given with CYP2D6 substrates with a narrow therapeutic index or that are individually dose titrated such as oxycodone.
General anesthetics: (Major) Concomitant use of oxycodone with a general anesthetic may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a general anesthetic to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.
Granisetron: (Moderate) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as serotonin-receptor antagonists. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.
Grapefruit juice: (Moderate) Patients should not significantly alter their intake of grapefruit or grapefruit juice during therapy with oxycodone. Grapefruit juice, a strong CYP3A4 inhibitor, may increase plasma concentrations of oxycodone, a CYP3A4 substrate. This may increase or prolong oxycodone-related toxicities including respiratory depression. Advise patients accordingly; patient monitoring and dosage adjustments may be necessary if grapefruit is consumed regularly.
Guaifenesin; Hydrocodone: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression.
Guaifenesin; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression.
Guanabenz: (Moderate) Guanabenz is associated with sedative effects. Guanabenz can potentiate the effects of CNS depressants such as opiate agonists, when administered concomitantly.
Guanfacine: (Moderate) Central-acting adrenergic agonists like guanfacine have CNS depressive effects and can potentiate the actions of other CNS depressants including opiate agonists.
Haloperidol: (Moderate) Haloperidol can potentiate the actions of other CNS depressants such as opiate agonists. Caution should be exercised with simultaneous use of these agents due to potential excessive CNS effects.
Halothane: (Major) Concomitant use of oxycodone with a general anesthetic may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a general anesthetic to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.
Homatropine; Hydrocodone: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression.
Hydantoins: (Minor) Hydantoin anticonvulsants induce hepatic microsomal enzymes and may increase the metabolism of other drugs, leading to reduced efficacy of medications like acetaminophen. In addition, the risk of hepatotoxicity from acetaminophen may be increased with the chronic dosing of acetaminophen along with phenytoin. Adhere to recommended acetaminophen dosage limits. Acetaminophen-related hepatotoxicity has occurred clinically with the concurrent use of acetaminophen 1300 mg to 6200 mg daily and phenytoin. Acetaminophen cessation led to serum transaminase normalization within 2 weeks.
Hydralazine; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are

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administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Hydrochlorothiazide, HCTZ; Irbesartan: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Hydrochlorothiazide, HCTZ; Lisinopril: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Hydrochlorothiazide, HCTZ; Losartan: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Hydrochlorothiazide, HCTZ; Methyldopa: (Moderate) Methyldopa is associated with sedative effects. Methyldopa can potentiate the effects of CNS depressants, such as opiate agonists, when administered concomitantly. (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Hydrochlorothiazide, HCTZ; Metoprolol: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Hydrochlorothiazide, HCTZ; Moexipril: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Hydrochlorothiazide, HCTZ; Olmesartan: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Hydrochlorothiazide, HCTZ; Propranolol: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Hydrochlorothiazide, HCTZ; Quinapril: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Hydrochlorothiazide, HCTZ; Spironolactone: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when spironolactone is administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone. (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Hydrochlorothiazide, HCTZ; Telmisartan: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Hydrochlorothiazide, HCTZ; Triamterene: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone. (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when triamterene is administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Hydrochlorothiazide, HCTZ; Valsartan: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Hydrocodone: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depresión and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression.

Hydrocodone; Ibuprofen: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression.

Hydrocodone; Phenylephrine: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression.

Hydrocodone; Potassium Guaiacolsulfonate: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression.

Hydrocodone; Potassium Guaiacolsulfonate; Pseudoephedrine: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression.

Hydrocodone; Pseudoephedrine: (Major) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor patients for sedation and respiratory depression.

Hydromorphone: (Major) Concomitant use of hydromorphone with other central nervous system (CNS) depressants, such as other opiate agonists, can potentiate the effects of hydromorphone and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of hydromorphone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If hydromorphone is used

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concurrently with a CNS depressant, a reduced dosage of hydromorphone and/or the CNS depressant is recommended; start with one-third to one-half of the estimated hydromorphone starting dose when using hydromorphone extended-release tablets. Use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

Hydroxyprogesterone: (Moderate) In vitro studies indicate that hydroxyprogesterone increases the metabolic rate of CYP2A6 isoenzymes. The metabolism of drugs metabolized by CYP2A6, such as acetaminophen may be increased during treatment with hydroxyprogesterone.

Hydroxyzine: (Major) Concomitant use of opioid agonists with hydroxyzine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with hydroxyzine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Hyoscyamine; Methenamine; Methylene Blue; Phenyl Salicylate; Sodium Biphosphate: (Major) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as methylene blue. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. If concomitant treatment is clinically warranted, careful observation of the patient is advised, especially during initiation of the second therapy and after dosage increases of either agent. Instruct patients to immediately report symptoms of agitation, hallucinations, tachycardia, fever, excessive sweating, shivering or shaking, muscle twitching or stiffness, trouble with coordination, nausea, vomiting, or diarrhea.

Idelalisib: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of idelalisib is necessary. If idelalisib is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like idelalisib can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If idelalisib is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Iloperidone: (Moderate) Concomitant use of iloperidone with other centrally-acting medications such as opiate agonists, may increase both the frequency and the intensity of adverse effects including drowsiness, sedation, and dizziness.

Imatinib: (Major) Imatinib, STI-571 may affect the metabolism of acetaminophen. In vitro, imatinib was found to inhibit acetaminophen O-glucuronidation at therapeutic levels. Therefore, systemic exposure to acetaminophen is expected to be increased with coadministration of imatinib. Chronic acetaminophen therapy should be avoided in patients receiving imatinib. (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of imatinib is necessary. If imatinib is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like imatinib can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If imatinib is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Imipramine: (Major) Concomitant use of opioid agonists with tricyclic antidepressants may cause excessive sedation, somnolence, and increased risk of serotonin syndrome. The anticholinergic properties of tricyclic antidepressants may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Limit the use of opioid pain medications with tricyclic antidepressants to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and serotonin syndrome. Monitor for signs of urinary retention and reduced gastric motility.

Indapamide: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when indapamide is administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Indinavir: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of indinavir is necessary. If indinavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like indinavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If indinavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Insulin Glargine; Lixisenatide: (Minor) When 1,000 mg acetaminophen was given 1 or 4 hours after 10 mcg lixisenatide, the AUC was not significantly changed, but the acetaminophen Cmax was decreased by 29% and 31%, respectively and median Tmax was delayed by 2 and 1.75 hours, respectively. Acetaminophen AUC, Cmax, and Tmax were not significantly changed when acetaminophen was given 1 h before lixisenatide injection. The mechanism of this interaction is not available (although it may be due to delayed gastric emptying) and the clinical impact has not been assessed. To avoid potential pharmacokinetic interactions that might alter effectiveness of acetaminophen, it may be advisable for patients to take acetaminophen at least one hour prior to lixisenatide subcutaneous injection.

Isavuconazonium: (Moderate) Concomitant use of isavuconazonium with acetaminophen may result in increased serum concentrations of acetaminophen. Acetaminophen is a substrate of the hepatic isoenzyme CYP3A4; isavuconazole, the active moiety of isavuconazonium, is a moderate inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are used together. (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of isavuconazonium is necessary. If isavuconazonium is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like isavuconazonium can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If isavuconazonium is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Isoflurane: (Major) Concomitant use of oxycodone with a general anesthetic may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a general anesthetic to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.

Isoniazid, INH: (Major) Agents which induce the hepatic isoenzyme CYP2E1, such as isoniazid, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolites. The combination of isoniazid and acetaminophen has caused severe hepatotoxicity in at least one patient; studies in rats have demonstrated that pre-treatment with isoniazid potentiates acetaminophen hepatotoxicity. (Major) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression, sedation, and serotonin syndrome if concurrent use of isoniazid is necessary. If isoniazid is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system like isoniazid has resulted in serotonin syndrome. In addition, oxycodone is a CYP3A4 substrate, and coadministration with CYP3A4 inhibitors like isoniazid can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If isoniazid is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Isoniazid, INH; Pyrazinamide, PZA; Rifampin: (Major) Agents which induce the hepatic isoenzyme CYP2E1, such as isoniazid, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolites. The combination of isoniazid and acetaminophen has caused severe hepatotoxicity in at least one patient; studies in rats have demonstrated that pre-treatment with isoniazid potentiates acetaminophen hepatotoxicity. (Major) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression, sedation, and serotonin syndrome if concurrent use of isoniazid is necessary. If isoniazid is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system like isoniazid has resulted in serotonin syndrome. In addition, oxycodone is a CYP3A4 substrate, and coadministration with CYP3A4 inhibitors like isoniazid can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If isoniazid is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal

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syndrome in a patient who has developed physical dependence to oxycodone. (Moderate) Agents which induce the hepatic isoenzymes CYP2E1 and CYP1A2, such as rifampin, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolites. (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with rifampin is necessary; consider increasing the dose of oxycodone as needed. If rifampin is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and rifampin is a strong CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.

Isoniazid, INH; Rifampin: (Major) Agents which induce the hepatic isoenzyme CYP2E1, such as isoniazid, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolites. The combination of isoniazid and acetaminophen has caused severe hepatotoxicity in at least one patient; studies in rats have demonstrated that pre-treatment with isoniazid potentiates acetaminophen hepatotoxicity. (Major) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression, sedation, and serotonin syndrome if concurrent use of isoniazid is necessary. If isoniazid is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system like isoniazid has resulted in serotonin syndrome. In addition, oxycodone is a CYP3A4 substrate, and coadministration with CYP3A4 inhibitors like isoniazid can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If isoniazid is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone. (Moderate) Agents which induce the hepatic isoenzymes CYP2E1 and CYP1A2, such as rifampin, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolites. (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with rifampin is necessary; consider increasing the dose of oxycodone as needed. If rifampin is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and rifampin is a strong CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.

Istradefylline: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of istradefylline 40 mg daily is necessary. If istradefylline is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate; istradefylline administered as 40 mg daily is a weak CYP3A4 inhibitor. Coadministration can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If istradefylline is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone. There was no effect on drug exposure when istradefylline 20 mg daily was coadministered with a sensitive CYP3A4 substrate.

Itraconazole: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of itraconazole is necessary. If itraconazole is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like itraconazole can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If itraconazole is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Ivacaftor: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ivacaftor is necessary. If ivacaftor is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like ivacaftor can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ivacaftor is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Ketamine: (Major) Concomitant use of oxycodone with a general anesthetic may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a general anesthetic to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.

Ketoconazole: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ketoconazole is necessary. If ketoconazole is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like ketoconazole can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ketoconazole is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Lamivudine, 3TC; Zidovudine, ZDV: (Minor) Both acetaminophen and zidovudine, ZDV undergo glucuronidation. Competition for the metabolic pathway is thought to have caused a case of acetaminophen-related hepatotoxicity. This interaction may be more clinically significant in patients with depleted glutathione stores, such as patients with acquired immunodeficiency syndrome, poor nutrition, or alcoholism.

Lamotrigine: (Major) Acetaminophen can be hepatotoxic, and lamotrigine appears to be a potential cause of progressive and fatal hepatotoxicity despite drug discontinuation. A 35 year-old developed fulminant liver failure possibly caused by lamotrigine. She was taking several other drugs including acetaminophen. In a randomized, single-dose study, the serum half-life of lamotrigine after a 300 mg dose decreased by 15% and the area under the plasma concentration-time curve decreased by 20% when given with acetaminophen 900 mg 3 times a day as compared with administration of lamotrigine with placebo. As the lamotrigine maximum serum concentration (Cmax) and time to Cmax was similar between the groups, and the lamotrigine renal clearance increased by 7%, acetaminophen appears to enhance removal of lamotrigine from the circulation.

Lanthanum Carbonate: (Minor) The manufacturer recommends that oral compounds known to interact with antacids, such as acetaminophen, should not be taken within 2 hours of dosing with lanthanum carbonate.

Lapatinib: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of lapatinib is necessary. If lapatinib is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak CYP3A4 inhibitor like lapatinib can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If lapatinib is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Larotrectinib: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of larotrectinib is necessary. If larotrectinib is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with weak CYP3A4 inhibitors like larotrectinib can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If larotrectinib is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Lasmiditan: (Moderate) Concomitant use of oxycodone with lasmiditan may cause excessive sedation, somnolence, and serotonin syndrome. Limit the use of oxycodone with lasmiditan to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and serotonin syndrome.

Lefamulin: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of oral lefamulin is necessary. If oral lefamulin is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with moderate CYP3A4 inhibitors like oral lefamulin can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone; an interaction is not expected with intravenous lefamulin. If oral lefamulin is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has

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developed physical dependence to oxycodone.
Lesinurad: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with lesinurad is necessary; consider increasing the dose of oxycodone as needed. If lesinurad is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and lesinurad is a weak CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Lesinurad; Allopurinol: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with lesinurad is necessary; consider increasing the dose of oxycodone as needed. If lesinurad is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and lesinurad is a weak CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Letermovir: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of letermovir is necessary. If letermovir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a CYP3A4 inhibitor like letermovir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If letermovir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Levobupivacaine: (Moderate) The use of these drugs together must be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Levocetirizine: (Moderate) Concomitant use of opioid agonists with cetirizine/levocetirizine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with cetirizine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Levorphanol: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.
Lidocaine: (Moderate) Coadministration of lidocaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue lidocaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. (Moderate) The use of these drugs together must be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Lincosamides: (Moderate) Lincosamides, which have been shown to exhibit neuromuscular blocking action, can enhance the effects of opiate agonists if used concomitantly, enhancing respiratory depressant effects. They should be used together with caution and the patient carefully monitored.
Linezolid: (Major) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as linezolid. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. If concomitant treatment is clinically warranted, careful observation of the patient is advised, especially during initiation of the second therapy and after dosage increases of either agent. Instruct patients to immediately report symptoms of agitation, hallucinations, tachycardia, fever, excessive sweating, shivering or shaking, muscle twitching or stiffness, trouble with coordination, nausea, vomiting, or diarrhea.
Lixisenatide: (Minor) When 1,000 mg acetaminophen was given 1 or 4 hours after 10 mcg lixisenatide, the AUC was not significantly changed, but the acetaminophen Cmax was decreased by 29% and 31%, respectively and median Tmax was delayed by 2 and 1.75 hours, respectively. Acetaminophen AUC, Cmax, and Tmax were not significantly changed when acetaminophen was given 1 h before lixisenatide injection. The mechanism of this interaction is not available (although it may be due to delayed gastric emptying) and the clinical impact has not been assessed. To avoid potential pharmacokinetic interactions that might alter effectiveness of acetaminophen, it may be advisable for patients to take acetaminophen at least one hour prior to lixisenatide subcutaneous injection.
Lofexidine: (Moderate) Monitor for excessive hypotension and sedation during coadministration of lofexidine and oxycodone. Lofexidine can potentiate the effects of CNS depressants.
Lomitapide: (Moderate) Caution should be exercised when lomitapide is used with other medications known to have potential for hepatotoxicity, such as acetaminophen (> 4 g/day PO for >= 3 days/week). The effect of concomitant administration of lomitapide with other hepatotoxic medications is unknown. More frequent monitoring of liver-related tests may be warranted.
Loop diuretics: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when loop diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Loperamide: (Moderate) Additive constipation may be seen with concurrent use of opiate agonists and antidiarrheals. Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect. Concurrent use of selected antidiarrheals (e.g., loperamide, diphenoxylate) and opiate agonists can lead to additive CNS depression.
Loperamide; Simethicone: (Moderate) Additive constipation may be seen with concurrent use of opiate agonists and antidiarrheals. Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect. Concurrent use of selected antidiarrheals (e.g., loperamide, diphenoxylate) and opiate agonists can lead to additive CNS depression.
Lopinavir; Ritonavir: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of lopinavir; ritonavir is necessary. If lopinavir; ritonavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like lopinavir; ritonavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If lopinavir; ritonavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone. (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ritonavir is necessary. If ritonavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like ritonavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ritonavir is

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discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Lorazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Lorlatinib: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with lorlatinib is necessary; consider increasing the dose of oxycodone as needed. If lorlatinib is discontinued, consider a dose reduction of lorlatinib and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and lorlatinib is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Loxapine: (Moderate) Loxapine can potentiate the actions of other CNS depressants such as opiate agonists. Caution should be exercised with simultaneous use of these agents due to potential excessive CNS effects.
Lumacaftor; Ivacaftor: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ivacaftor is necessary. If ivacaftor is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like ivacaftor can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ivacaftor is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Lumacaftor; Ivacaftor: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with lumacaftor; ivacaftor is necessary; consider increasing the dose of oxycodone as needed. If lumacaftor; ivacaftor is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and lumacaftor; ivacaftor is a strong CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Lumateperone: (Moderate) Monitor for excessive sedation and somnolence during coadministration of lumateperone and opiate agonists. Concurrent use may result in additive CNS depression.
Lurasidone: (Moderate) Due to the CNS effects of lurasidone, caution should be used when lurasidone is given in combination with other centrally acting medications such as opiate agonists.
Magnesium Salicylate: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. Although salicylates are rarely associated with nephrotoxicity, high-dose, chronic administration of salicylates combined other analgesics, including acetaminophen, significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Additive hepatic toxicity may occur, especially in combined overdose situations. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.
Magnesium Salts: (Minor) Because of the CNS-depressant effects of magnesium sulfate, additive central-depressant effects can occur following concurrent administration with CNS depressants such as opiate agonists. Caution should be exercised when using these agents concurrently.
Maprotiline: (Major) Concomitant use of opioid agonists with maprotiline may cause excessive sedation and somnolence. Limit the use of opioid pain medications with maprotiline to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Meperidine: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.
Meperidine; Promethazine: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. (Moderate) Concomitant use of oxycodone with phenothiazines may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. Furthermore, oxycodone is metabolized in part by 2D6 to oxymorphone, which represents < 15% of the total administered dose. Concurrent use of some agents that inhibit CYP2D6 (e.g., quinidine) has not been shown to result in clinically significant interactions. However, many phenothiazines are inhibitors of CYP2D6 (e.g., chlorpromazine, perphenazine, thioridazine) and may potentially increase the effects of oxycodone. Also, severe hypotension may be potentiated with concurrent phenothiazine usage or other drug that compromises vasomotor tone.
Mephobarbital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.
Mepivacaine: (Moderate) Coadministration of mepivacaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue mepivacaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. (Moderate) The use of these drugs together must be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Mepivacaine; Levonordefrin: (Moderate) Coadministration of mepivacaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue mepivacaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. (Moderate) The use of these drugs together must be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Meprobamate: (Moderate) Concomitant use of oxycodone with meprobamate may lead to additive respiratory and/or CNS depression.

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Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If meprobamate is used concurrently with oxycodone, a reduced dosage of oxycodone and/or meprobamate is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.
Mesoridazine: (Moderate) Concomitant use of oxycodone with phenothiazines may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. Furthermore, oxycodone is metabolized in part by 2D6 to oxymorphone, which represents < 15% of the total administered dose. Concurrent use of some agents that inhibit CYP2D6 (e.g., quinidine) has not been shown to result in clinically significant interactions. However, many phenothiazines are inhibitors of CYP2D6 (e.g., chlorpromazine, perphenazine, thioridazine) and may potentially increase the effects of oxycodone. Also, severe hypotension may be potentiated with concurrent phenothiazine usage or other drug that compromises vasomotor tone.
Metaxalone: (Major) Concomitant use of oxycodone with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.
Methadone: (Major) Concomitant use of methadone with another CNS depressant, such as oxycodone, can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Methadone should be used with caution and in reduced dosages if used concurrently with a CNS depressant; in opioid-naive adults, use an initial methadone dose of 2.5 mg every 12 hours. Also, consider a using a lower dose of the CNS depressant; use an initial dose of oxycodone at one-third to one-half the usual dosage. Monitor patients for sedation and respiratory depression.
Methenamine; Sodium Acid Phosphate; Methylene Blue; Hyoscyamine: (Major) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as methylene blue. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. If concomitant treatment is clinically warranted, careful observation of the patient is advised, especially during initiation of the second therapy and after dosage increases of either agent. Instruct patients to immediately report symptoms of agitation, hallucinations, tachycardia, fever, excessive sweating, shivering or shaking, muscle twitching or stiffness, trouble with coordination, nausea, vomiting, or diarrhea.
Methocarbamol: (Major) Concomitant use of opiate agonists with skeletal muscle relaxants may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with skeletal muscle relaxants to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone or oxycodone; naloxone is initiated in a patient taking a skeletal muscle relaxant, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage and titrate to clinical response; reduced initial doses of oxycodone; naltrexone, aspirin, ASA; oxycodone, and ibuprofen; oxycodone are also recommended. If a decision is made to start treatment with acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours. If a skeletal muscle relaxant is prescribed for a patient taking an opiate agonist, use a lower initial dose of the skeletal muscle relaxant and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Methohexital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.
Methyclothiazide: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Methyldopa: (Moderate) Methyldopa is associated with sedative effects. Methyldopa can potentiate the effects of CNS depressants, such as opiate agonists, when administered concomitantly.
Methylene Blue: (Major) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as methylene blue. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. If concomitant treatment is clinically warranted, careful observation of the patient is advised, especially during initiation of the second therapy and after dosage increases of either agent. Instruct patients to immediately report symptoms of agitation, hallucinations, tachycardia, fever, excessive sweating, shivering or shaking, muscle twitching or stiffness, trouble with coordination, nausea, vomiting, or diarrhea.
Metoclopramide: (Moderate) The effects of metoclopramide on gastrointestinal motility are antagonized by narcotic analgesics. Concomitant use of opioid agonists with metoclopramide may also cause excessive sedation and somnolence. Limit the use of opioid pain medications with metoclopramide to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Metolazone: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Metyrapone: (Major) Coadministration of metyrapone and acetaminophen may result in acetaminophen toxicity. Acetaminophen glucuronidation is inhibited by metyrapone. It may be advisable for patients to avoid acetaminophen while taking metyrapone. (Moderate) Metyrapone may cause dizziness and/or drowsiness. Other drugs that may also cause drowsiness, such as opiate agonists, should be used with caution. Additive drowsiness and/or dizziness is possible.
Metyrosine: (Moderate) The concomitant administration of metyrosine with opiate agonists can result in additive sedative effects.
Midazolam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Mifepristone: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of mifepristone is necessary. If mifepristone is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like mifepristone can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If mifepristone is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone. The clinical significance of this interaction with the short-term use of mifepristone for termination of pregnancy is unknown.
Minocycline: (Minor) Injectable minocycline contains magnesium sulfate heptahydrate. Because of the CNS-depressant effects of magnesium sulfate, additive central-depressant effects can occur following concurrent administration with CNS depressants such as opiate agonists. Caution should be exercised when using these agents concurrently.
Mipomersen: (Moderate) Caution should be exercised when mipomersen is used with other medications known to have potential for hepatotoxiclty, such as acetaminophen (> 4 g/day for >= 3 days/week). The effect of concomitant administration of mipomersen with other hepatotoxic medications is unknown. More frequent monitoring of liver-related tests may be warranted.
Mirabegron: (Moderate) Mirabegron is a moderate CYP2D6 inhibitor. Exposure of drugs partially metabolized by CYP2D6, such as oxycodone, may be increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary.
Mirtazapine: (Major) Concomitant use of opioid agonists with mirtazapine may cause excessive sedation, somnolence, and increased risk of serotonin syndrome. Limit the use of opioid pain medications with mirtazapine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical

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effect. Educate patients about the risks and symptoms of excessive CNS depression and serotonin syndrome.
Mitotane: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with mitotane is necessary; consider increasing the dose of oxycodone as needed. If mitotane is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and mitotane is a strong CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. (Minor) Use caution if mitotane and acetaminophen are used concomitantly, and monitor for decreased efficacy of acetaminophen. Mitotane is a strong CYP3A4 inducer and acetaminophen is a minor (10% to 15%) CYP3A4 substrate; coadministration may result in decreased plasma concentrations of acetaminophen.
Mivacurium: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of alfentanil on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.
Modafinil: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with modafinil is necessary; consider increasing the dose of oxycodone as needed. If modafinil is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and modafinil is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Molindone: (Moderate) Concomitant use of opiate agonists with other central nervous system (CNS) depressants, such as molindone, can potentiate the effects of the opiate and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of an opiate in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of the opiate and/or molindone is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.
Monoamine oxidase inhibitors: (Major) The use of oxycodone is not recommended in patients who have received a monoamine oxidase inhibitor (MAOI) within 14 days due to a risk for serotonin syndrome or opioid toxicity, including respiratory depression. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.
Morphine: (Major) Concomitant use of oxycodone with morphine may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. A reduced dosage of oxycodone and/or morphine is recommended; use an initial dose of oxycodone at one-third to one-half the usual dosage. For extended-release morphine products, start with the lowest possible dose of morphine (i.e., 15 mg PO every 12 hours, extended-release tablets; 30 mg or less PO every 24 hours; extended-release capsules). Monitor for sedation and respiratory depression.
Morphine; Naltrexone: (Major) Concomitant use of oxycodone with morphine may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. A reduced dosage of oxycodone and/or morphine is recommended; use an initial dose of oxycodone at one-third to one-half the usual dosage. For extended-release morphine products, start with the lowest possible dose of morphine (i.e., 15 mg PO every 12 hours, extended-release tablets; 30 mg or less PO every 24 hours; extended-release capsules). Monitor for sedation and respiratory depression.
Nabilone: (Moderate) Concomitant use of opiate agonists with other central nervous system (CNS) depressants, such as nabilone, can potentiate the effects of the opiate and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of an opiate in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of the opiate and/or the CNS depressant is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.
Nafcillin: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with nafcillin is necessary; consider increasing the dose of oxycodone as needed. If nafcillin is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and nafcillin is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Nalbuphine: (Major) Avoid the concomitant use of nalbuphine and opiate agonists, such as oxycodone. Nalbuphine is a mixed opiate agonist/antagonist that may block the effects of opiate agonists and reduce analgesic effects of acetaminophen; oxycodone. Nalbuphine may cause withdrawal symptoms in patients receiving chronic opiate agonists. Concurrent use of nalbuphine with other opiate agonists can cause additive CNS, respiratory, and hypotensive effects. The additive or antagonistic effects are dependent upon the dose of the opiate agonist used; antagonistic effects are more common at low to moderate doses of the opiate agonist.
Naloxone: (Major) Naloxone can antagonize the therapeutic efficacy of oxycodone in addition to precipitating withdrawal symptoms in patients who are physically dependent on opiate drugs including oxycodone.
Naltrexone: (Major) When naltrexone is used as adjuvant treatment of opiate or alcohol dependence, use is contraindicated in patients currently receiving opiate agonists. Naltrexone will antagonize the therapeutic benefits of opiate agonists and will induce a withdrawal reaction in patients with physical dependence to opioids. Also, patients should be opiate-free for at least 7-10 days prior to initiating naltrexone therapy. If there is any question of opioid use in the past 7-10 days and the patient is not experiencing opioid withdrawal symptoms and/or the urine is negative for opioids, a naloxone challenge test needs to be performed. If a patient receives naltrexone, and an opiate agonist is needed for an emergency situation, large doses of opiate agonists may ultimately overwhelm naltrexone antagonism of opiate receptors. Immediately following administration of exogenous opiate agonists, the opiate plasma concentration may be sufficient to overcome naltrexone competitive blockade, but the patient may experience deeper and more prolonged respiratory depression and thus, may be in danger of respiratory arrest and circulatory collapse. Non-receptor mediated actions like facial swelling, itching, generalized erythema, or bronchoconstriction may occur presumably due to histamine release. A rapidly acting opiate agonist is preferred as the duration of respiratory depression will be shorter. Patients receiving naltrexone may also experience opiate side effects with low doses of opiate agonists. If the opiate agonist is taken in such a way that high concentrations remain in the body beyond the time naltrexone exerts its therapeutic effects, serious side effects may occur.
Naproxen; Sumatriptan: (Moderate) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as serotonin-receptor agonists. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.
Naratriptan: (Moderate) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as serotonin-receptor agonists. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.
Nefazodone: (Major) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression, sedation, and serotonin syndrome if concurrent use of nefazodone is necessary. If nefazodone is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system like nefazodone has resulted in serotonin syndrome. In addition, oxycodone is a CYP3A4 substrate, and coadministration with CYP3A4 inhibitors like nefazodone can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If nefazodone is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Nelfinavir: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of nelfinavir is necessary. If nelfinavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like nelfinavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If nelfinavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy

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of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Nesiritide, BNP: (Major) The potential for hypotension may be increased when coadministering nesiritide with opiate agonists.
Netupitant, Fosnetupitant; Palonosetron: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of netupitant is necessary. If netupitant is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like netupitant can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If netupitant is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Neuromuscular blockers: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of alfentanil on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.
Nevirapine: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with nevirapine is necessary; consider increasing the dose of oxycodone as needed. If nevirapine is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and nevirapine is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Nicardipine: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of nicardipine is necessary. If nicardipine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like nicardipine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If nicardipine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Nilotinib: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of nilotinib is necessary. If nilotinib is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like nilotinib can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If nilotinib is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Nitroglycerin: (Minor) Nitroglycerin can cause hypotension. This action may be additive with other agents that can cause hypotension such as opiate agonists. Patients should be monitored more closely for hypotension if nitroglycerin is used concurrently with opiate agonists.
Nortriptyline: (Major) Concomitant use of opioid agonists with tricyclic antidepressants may cause excessive sedation, somnolence, and increased risk of serotonin syndrome. The anticholinergic properties of tricyclic antidepressants may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Limit the use of opioid pain medications with tricyclic antidepressants to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and serotonin syndrome. Monitor for signs of urinary retention and reduced gastric motility.
Octreotide: (Major) Octreotide can cause additive constipation with opiate agonists such as oxycodone. Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect. Monitor patients during concomitant use. Also, coadministration of octreotide, a CYP3A4 inhibitor, and oxycodone, a CYP3A4 substrate, may increase oxycodone plasma concentrations and increase or prolong related toxicities including potentially fatal respiratory depression. If therapy with both agents is necessary, monitor patient for an extended period of time and adjust dosage as necessary; oxycodone dosage adjustments may be needed if the CYP3A4 inhibitor is discontinued. Concurrent administration of oxycodone and voriconazole, another CYP3A4 inhibitor, increased oxycodone AUC by 3.6-fold and the Cmax by 1.7-fold.
Olanzapine: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as olanzapine, can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of oxycodone in patients taking olanzapine, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Oxycodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate oxycodone at one-third to one-half the usual dosage in patients that are concurrently receiving another CNS depressant. Also, consider using a lower olanzapine dose. Monitor patients for sedation and respiratory depression.
Ombitasvir; Paritaprevir; Ritonavir: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ritonavir is necessary. If ritonavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like ritonavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ritonavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Omeprazole; Amoxicillin; Rifabutin: (Moderate) As a cytochrome P450 isoenzyme inducers, rifabutin could induce the metabolism of acetaminophen. An increase in acetaminophen-induced hepatotoxicity may be seen by increasing the metabolism of acetaminophen to its toxic metabolite, NAPQI. Also, the analgesic activity of acetaminophen may be reduced. (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with rifabutin is necessary; consider increasing the dose of oxycodone as needed. If rifabutin is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and rifabutin is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Omeprazole; Sodium Bicarbonate: (Minor) Antacids can delay the oral absorption of acetaminophen, but the interactions are not likely to be clinically significant as the extent of acetaminophen absorption is not appreciably affected.
Ondansetron: (Moderate) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as serotonin-receptor antagonists. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.
Oritavancin: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with oritavancin is necessary; consider increasing the dose of oxycodone as needed. If oritavancin is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and oritavancin is a weak CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Orphenadrine: (Major) Concomitant use of oxycodone with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.
Oxazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Oxcarbazepine: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with oxcarbazepine is necessary; consider increasing the dose of oxycodone as needed. If oxcarbazepine is discontinued, consider a dose reduction of oxycodone and

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frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and oxcarbazepine is a weak CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.

Oxymorphone: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. a reduced dosage of oxymorphone (1/3 to 1/2 of the usual dose) and/or the CNS depressant is recommended. If the extended-release oxymorphone tablets are used concurrently with a CNS depressant, it is recommended to use an initial dosage of 5 mg PO every 12 hours. Monitor for sedation and respiratory depression.

Palbociclib: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of palbociclib is necessary. If palbociclib is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like palbociclib can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If palbociclib is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Paliperidone: (Moderate) Drugs that can cause CNS depression such as opiate agonists, if used concomitantly with paliperidone, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness. Monitor for signs and symptoms of CNS depression during coadministration of paliperidone and oxycodone and advise patients to avoid driving or engaging in other activities requiring mental alertness until they know how this combination affects them.

Palonosetron: (Moderate) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as serotonin-receptor antagonists. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.

Pancuronium: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of alfentanil on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.

Papaverine: (Moderate) Papaverine is a benzylisoquinoline alkaloid of opium and may have synergistic effects with opiate agonists. Concurrent use of papaverine with potent CNS depressants could lead to enhanced sedation.

Paroxetine: (Moderate) The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue the suspected drugs if serotonin syndrome is suspected and manage clinically. There has been a case report of possible serotonin syndrome caused by the combination of oxycodone and selective serotonin reuptake inhbitors (SSRIs).

Pazopanib: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of pazopanib is necessary. If pazopanib is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like pazopanib can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If pazopanib is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Peginterferon Alfa-2b: (Moderate) Oxycodone is metabolized in part by CYP2D6 to oxymorphone, which represents < 15% of the total administered dose. In theory, concurrent use of a CYP2D6 inhibitor, such as peginterferon alfa-2b, may inhibit the conversion of oxycodone to oxymorphone. In addition, concurrent use with a CYP2D6 inhibitor may increase the adverse effects of oxycodone. Close monitoring for pronounced opioid effects is advisable.

Pegvisomant: (Moderate) In clinical trials, patients taking opiate agonists often required higher serum pegvisomant concentrations to achieve appropriate IGF-I suppression compared with patients not receiving opiate agonists. The mechanism of this interaction is unknown.

Penicillin G Benzathine; Penicillin G Procaine: (Moderate) Coadministration of penicillin G procaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue penicillin G procaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

Penicillin G Procaine: (Moderate) Coadministration of penicillin G procaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue penicillin G procaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

Pentazocine: (Major) Avoid the concomitant use of pentazocine and opiate agonists, such as oxycodone. Pentazocine is a mixed opiate agonist/antagonist that may block the effects of opiate agonists and reduce analgesic effects of oxycodone. Pentazocine may cause withdrawal symptoms in patients receiving chronic opiate agonists. Concurrent use of pentazocine with other opiate agonists can cause additive CNS, respiratory, and hypotensive effects. The additive or antagonistic effects are dependent upon the dose of the opiate agonist used; antagonistic effects are more common at low to moderate doses of the opiate agonist.

Pentazocine; Naloxone: (Major) Avoid the concomitant use of pentazocine and opiate agonists, such as oxycodone. Pentazocine is a mixed opiate agonist/antagonist that may block the effects of opiate agonists and reduce analgesic effects of oxycodone. Pentazocine may cause withdrawal symptoms in patients receiving chronic opiate agonists. Concurrent use of pentazocine with other opiate agonists can cause additive CNS, respiratory, and hypotensive effects. The additive or antagonistic effects are dependent upon the dose of the opiate agonist used; antagonistic effects are more common at low to moderate doses of the opiate agonist. (Major) Naloxone can antagonize the therapeutic efficacy of oxycodone in addition to precipitating withdrawal symptoms in patients who are physically dependent on opiate drugs including oxycodone.

Pentobarbital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.

Perampanel: (Moderate) Concomitant use of opioid agonists with perampanel may cause excessive sedation and somnolence. Limit the use of opioid pain medications with perampanel to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Perindopril; Amlodipine: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of amlodipine is necessary. If amlodipine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like amlodipine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If amlodipine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Perphenazine: (Moderate) Concomitant use of oxycodone with phenothiazines may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. Furthermore, oxycodone is metabolized in part by 2D6 to oxymorphone, which represents < 15% of the total administered dose. Concurrent use of some agents that inhibit CYP2D6 (e.g., quinidine) has not been shown to result in clinically significant interactions. However, many phenothiazines are inhibitors of CYP2D6 (e.g., chlorpromazine, perphenazine, thioridazine) and may potentially increase the effects of oxycodone. Also, severe hypotension may be potentiated with concurrent phenothiazine usage or other drug that compromises vasomotor tone.

Perphenazine; Amitriptyline: (Major) Concomitant use of opioid agonists with tricyclic antidepressants may cause excessive sedation,

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somnolence, and increased risk of serotonin syndrome. The anticholinergic properties of tricyclic antidepressants may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Limit the use of opioid pain medications with tricyclic antidepressants to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and serotonin syndrome. Monitor for signs of urinary retention and reduced gastric motility. (Moderate) Concomitant use of oxycodone with phenothiazines may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. Furthermore, oxycodone is metabolized in part by 2D6 to oxymorphone, which represents < 15% of the total administered dose. Concurrent use of some agents that inhibit CYP2D6 (e.g., quinidine) has not been shown to result in clinically significant interactions. However, many phenothiazines are inhibitors of CYP2D6 (e.g., chlorpromazine, perphenazine, thioridazine) and may potentially increase the effects of oxycodone. Also, severe hypotension may be potentiated with concurrent phenothiazine usage or other drug that compromises vasomotor tone.

Phenobarbital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.

Phenothiazines: (Moderate) Concomitant use of oxycodone with phenothiazines may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. Furthermore, oxycodone is metabolized in part by 2D6 to oxymorphone, which represents < 15% of the total administered dose. Concurrent use of some agents that inhibit CYP2D6 (e.g., quinidine) has not been shown to result in clinically significant interactions. However, many phenothiazines are inhibitors of CYP2D6 (e.g., chlorpromazine, perphenazine, thioridazine) and may potentially increase the effects of oxycodone. Also, severe hypotension may be potentiated with concurrent phenothiazine usage or other drug that compromises vasomotor tone.

Phentermine; Topiramate: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with topiramate is necessary; consider increasing the dose of oxycodone as needed. If topiramate is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and topiramate is a weak CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.

Phenylephrine; Promethazine: (Moderate) Concomitant use of oxycodone with phenothiazines may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. Furthermore, oxycodone is metabolized in part by 2D6 to oxymorphone, which represents < 15% of the total administered dose. Concurrent use of some agents that inhibit CYP2D6 (e.g., quinidine) has not been shown to result in clinically significant interactions. However, many phenothiazines are inhibitors of CYP2D6 (e.g., chlorpromazine, perphenazine, thioridazine) and may potentially increase the effects of oxycodone. Also, severe hypotension may be potentiated with concurrent phenothiazine usage or other drug that compromises vasomotor tone.

Phenytoin: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with phenytoin is necessary; consider increasing the dose of oxycodone as needed. If phenytoin is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and phenytoin is a strong CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.

Pimozide: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as pimozide, can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of oxycodone in patients taking pimozide, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Oxycodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate oxycodone at one-third to one-half the usual dosage in patients that are concurrently receiving another CNS depressant. Also, consider using a lower pimozide dose. Monitor patients for sedation and respiratory depression.

Pneumococcal Vaccine, Polyvalent: (Moderate) Concomitant administration of antipyretics, such as acetaminophen, may decrease an individual's immunological response to the pneumococcal vaccine. A post-marketing study conducted in Poland using a non-US vaccination schedule (2, 3, 4, and 12 months of age) evaluated the impact of prophylactic oral acetaminophen on antibody responses to Prevnar 13. Data show that acetaminophen, given at the time of vaccination and then dosed at 6 to 8 hour intervals for 3 doses on a scheduled basis, reduced the antibody response to some serotypes after the third dose of Prevnar 13 when compared to the antibody responses of infants who only received antipyretics 'as needed' for treatment. However, reduced antibody responses were not observed after the fourth dose of Prevnar 13 with prophylactic acetaminophen.

Posaconazole: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of posaconazole is necessary. If posaconazole is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like posaconazole can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If posaconazole is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone. (Moderate) Posaconazole and acetaminophen should be coadministered with caution due to an increased potential for acetaminophen-related adverse events. Posaconazole is a potent inhibitor of CYP3A4, an isoenzyme partially responsible for the metabolism of acetaminophen. These drugs used in combination may result in elevated acetaminophen plasma concentrations, causing an increased risk for acetaminophen-related adverse events.

Pramipexole: (Major) Concomitant use of opioid agonists with pramipexole may cause excessive sedation and somnolence. Limit the use of opioid pain medications with pramipexole to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. Dopaminergic agents like pramipexole have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment.

Pramlintide: (Major) Pramlintide slows gastric emptying and the rate of nutrient delivery to the small intestine. Medications with the potential to slow GI motility, such as opiate agonists, should be used with caution, if at all, with pramlintide until more data are available from the manufacturer. Monitor blood glucose. (Minor) Because pramlintide has the potential to delay the absorption of concomitantly administered medications, medications should be administered at least 1 hour before or 2 hours after pramlintide injection when the rapid onset of a concomitantly administered oral medication is a critical determinant of effectiveness (i.e., analgesics).

Prasugrel: (Moderate) Consider the use of a parenteral anti-platelet agent for patients with acute coronary syndrome who require concomitant opioid agonists. Coadministration of opioid agonists with prasugrel delays and reduces the absorption of prasugrel's active metabolite due to slowed gastric emptying.

Pregabalin: (Major) Concomitant use of opioid agonists with pregabalin may cause excessive sedation, somnolence, and respiratory depression. Limit the use of opioid pain medications with pregabalin to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, initiate pregabalin at the lowest recommended dose and monitor patients for symptoms of respiratory depression and sedation. Use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and respiratory depression.

Prilocaine: (Moderate) Coadministration of prilocaine with oxidizing agents, such as acetaminophen, may increase the risk of developing

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methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue prilocaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. (Moderate) The use of these drugs together must be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Prilocaine; Epinephrine: (Moderate) Coadministration of prilocaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue prilocaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. (Moderate) The use of these drugs together must be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Primidone: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.

Procaine: (Minor) Due to the CNS depression potential of all local anesthetics, they should be used with caution with other agents that can cause respiratory depression, such as opiate agonists.

Procarbazine: (Moderate) Opiate agonists may cause additive sedation or other CNS effects when given in combination with procarbazine.

Prochlorperazine: (Moderate) Concomitant use of oxycodone with phenothiazines may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. Furthermore, oxycodone is metabolized in part by 2D6 to oxymorphone, which represents < 15% of the total administered dose. Concurrent use of some agents that inhibit CYP2D6 (e.g., quinidine) has not been shown to result in clinically significant interactions. However, many phenothiazines are inhibitors of CYP2D6 (e.g., chlorpromazine, perphenazine, thioridazine) and may potentially increase the effects of oxycodone. Also, severe hypotension may be potentiated with concurrent phenothiazine usage or other drug that compromises vasomotor tone.

Promethazine: (Moderate) Concomitant use of oxycodone with phenothiazines may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. Furthermore, oxycodone is metabolized in part by 2D6 to oxymorphone, which represents < 15% of the total administered dose. Concurrent use of some agents that inhibit CYP2D6 (e.g., quinidine) has not been shown to result in clinically significant interactions. However, many phenothiazines are inhibitors of CYP2D6 (e.g., chlorpromazine, perphenazine, thioridazine) and may potentially increase the effects of oxycodone. Also, severe hypotension may be potentiated with concurrent phenothiazine usage or other drug that compromises vasomotor tone.

Propafenone: (Moderate) Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone, which represents < 15% of the total administered dose. Potent inhibitors of CYP2D6, such as propafenone, may potentially increase the effects of oxycodone; however, such blockade has not been shown to be of clinical significance during oxycodone treatment. Clinicians should be aware of this possible interaction.

Propofol: (Major) Concomitant use of oxycodone with a general anesthetic may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a general anesthetic to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.

Propoxyphene: (Major) Propoxyphene is a weak mu-opiate receptor agonist. As other opiate agonists bind to mu-opiate receptors, concurrent use of an opiate agonist with propoxyphene is not desirable. Also, propoxyphene will only partially suppress the withdrawal syndrome in patients physically dependent on morphine or other narcotics. The choice of one mu-opiate receptor agonist needs to be made to avoid duplicate therapy and possible adverse effects. For example, concomitant use of propoxyphene with other CNS depressants (e.g., other opiate agonists) can potentiate the effects of respiratory depression and/or sedation. Propoxyphene in combination with other CNS depressants is a major cause of drug-related death. Fatalities within the first hour of overdosage are not uncommon. Extreme caution is needed during concomitant use of any CNS-depressant drug and propoxyphene. Assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.

Protriptyline: (Major) Concomitant use of opioid agonists with tricyclic antidepressants may cause excessive sedation, somnolence, and increased risk of serotonin syndrome. The anticholinergic properties of tricyclic antidepressants may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Limit the use of opioid pain medications with tricyclic antidepressants to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and serotonin syndrome. Monitor for signs of urinary retention and reduced gastric motility.

Quazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Quetiapine: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as quetiapine, can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of oxycodone in patients taking quetiapine, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Oxycodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate oxycodone at one-third to one-half the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider using a lower quetiapine dose. Monitor patients for sedation and respiratory depression.

Quinidine: (Moderate) Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone, which represents < 15% of the total administered dose. Potent inhibitors of CYP2D6, such as quinidine, may potentially increase the effects of oxycodone; however, such blockade has not been shown to be of clinical significance during oxycodone treatment. Clinicians should be aware of this possible interaction.

Quinine: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of quinine is necessary. If quinine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like quinine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If quinine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid

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and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Ramelteon: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Ranolazine: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ranolazine is necessary. If ranolazine is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like ranolazine can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ranolazine is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Rapacuronium: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of alfentanil on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.
Rasagiline: (Moderate) Opiate agonists (e.g., alfentanil, codeine, hydrocodone, morphine, sufentanil, etc.) may cause additive CNS depression, drowsiness, dizziness or hypotension, so use with MAOIs should be cautious; lower initial dosages of the opiate are recommended followed by careful titration.
Remifentanil: (Major) Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.
Ribociclib: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ribociclib is necessary. If ribociclib is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like ribociclib can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ribociclib is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Ribociclib; Letrozole: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ribociclib is necessary. If ribociclib is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like ribociclib can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ribociclib is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Rifabutin: (Moderate) As a cytochrome P450 isoenzyme inducers, rifabutin could induce the metabolism of acetaminophen. An increase in acetaminophen-induced hepatotoxicity may be seen by increasing the metabolism of acetaminophen to its toxic metabolite, NAPQI. Also, the analgesic activity of acetaminophen may be reduced. (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with rifabutin is necessary; consider increasing the dose of oxycodone as needed. If rifabutin is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and rifabutin is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Rifampin: (Moderate) Agents which induce the hepatic isoenzymes CYP2E1 and CYP1A2, such as rifampin, may potentially increase the risk for acetaminophen-induced hepatotoxicity via generation of a greater percentage of acetaminophen's hepatotoxic metabolites. (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with rifampin is necessary; consider increasing the dose of oxycodone as needed. If rifampin is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and rifampin is a strong CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Rifapentine: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with rifapentine is necessary; consider increasing the dose of oxycodone as needed. If rifapentine is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and rifapentine is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Rifaximin: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with rifaximin is necessary; consider increasing the dose of oxycodone as needed. If rifaximin is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and rifaximin is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Risperidone: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as risperidone, can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of oxycodone in patients taking risperidone, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Oxycodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate oxycodone at one-third to one-half the usual dosage in patients that are concurrently receiving another CNS depressant. Also, consider using a lower risperidone dose. Monitor patients for sedation and respiratory depression.
Ritonavir: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ritonavir is necessary. If ritonavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like ritonavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ritonavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Rizatriptan: (Moderate) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as serotonin-receptor agonists. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.
Rocuronium: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of alfentanil on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.
Rolapitant: (Major) Use caution if oxycodone and rolapitant are used concurrently, and monitor for oxycodone-related adverse effects. Oxycodone is a CYP2D6 substrate where an increase in exposure may significantly increase adverse effects, and rolapitant is a moderate CYP2D6 inhibitor; the inhibitory effect of rolapitant is expected to persist beyond 28 days for an unknown duration. Exposure to another CYP2D6 substrate, following a single dose of rolapitant increased about 3-fold on Days 8 and Day 22. The inhibition of CYP2D6 persisted on Day 28 with a 2.3-fold increase in the CYP2D6 substrate concentrations, the last time point measured.
Ropinirole: (Moderate) Concomitant use of opiate agonists with other central nervous system (CNS) depressants such as ropinirole can potentiate the effects of the opiate and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of an opiate in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of the

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opiate and/or the CNS depressant is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.
Ropivacaine: (Moderate) Coadministration of ropivacaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue ropivacaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. (Moderate) The use of these drugs together must be approached with caution. Although commonly used together for additive analgesic effects, the patient must be monitored for respiratory depression, hypotension, and excessive sedation due to additive effects on the CNS and blood pressure. In rare instances, serious morbidity and mortality has occurred. Limit the use of opiate pain medications with local anesthetics to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. The use of the local anesthetic will allow for the use a lower initial dose of the opiate and then the doses can be titrated to proper clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Rotigotine: (Major) Concomitant use of opioid agonists with rotigotine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with rotigotine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. Dopaminergic agents like rotigotine have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment.
Rucaparib: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of rucaparib is necessary. If rucaparib is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate and rucaparib is a weak CYP3A4 inhibitor. Coadministration can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If rucaparib is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Salsalate: (Moderate) Prolonged concurrent use of acetaminophen and salicylates is not recommended. Although salicylates are rarely associated with nephrotoxicity, high-dose, chronic administration of salicylates combined other analgesics, including acetaminophen, significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. Additive hepatic toxicity may occur, especially in combined overdose situations. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.
Saquinavir: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of saquinavir is necessary. If saquinavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like saquinavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If saquinavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Secobarbital: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.
Segesterone Acetate; Ethinyl Estradiol: (Moderate) Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. Patients taking acetaminophen concomitantly may experience an increase in estrogen related side effects.
Selective norepinephrine reuptake inhibitors: (Major) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as serotonin norepinephrine reuptake inhibitors (SNRIs). Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. If concomitant treatment is clinically warranted, careful observation of the patient is advised, especially during initiation of the second therapy and after dosage increases of either agent. Instruct patients to immediately report symptoms of agitation, hallucinations, tachycardia, fever, excessive sweating, shivering or shaking, muscle twitching or stiffness, trouble with coordination, nausea, vomiting, or diarrhea.
Serotonin-Receptor Agonists: (Moderate) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as serotonin-receptor agonists. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.
Serotonin-Receptor Antagonists: (Moderate) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as serotonin-receptor antagonists. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.
Sertraline: (Moderate) The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue the suspected drugs if serotonin syndrome is suspected and manage clinically. There has been a case report of possible serotonin syndrome caused by the combination of oxycodone and selective serotonin reuptake inhbitors (SSRIs).
Sevoflurane: (Major) Concomitant use of oxycodone with a general anesthetic may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a general anesthetic to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.
Sildenafil: (Moderate) Prolonged erections have been reported in two patients taking sildenafil with dihydrocodeine. Although more data are needed, use caution when prescribing opiate agonists and sildenafil concomitantly.
Simeprevir: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of simeprevir is necessary. If simeprevir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like simeprevir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If simeprevir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Skeletal Muscle Relaxants: (Major) Concomitant use of oxycodone with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.
Sodium Bicarbonate: (Minor) Antacids can delay the oral absorption of acetaminophen, but the interactions are not likely to be clinically significant as the extent of acetaminophen absorption is not appreciably affected.
Sodium Oxybate: (Major) Additive CNS depressant effects may be possible when sodium oxybate is used concurrently with opiate agonists.
Solifenacin: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when oxycodone is used concomitantly with an anticholinergic drug, such as solifenacin. The concomitant use of oxycodone and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Spironolactone: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when spironolactone is administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
St. John's Wort, Hypericum perforatum: (Major) Consider an increased dose of oxycodone and monitor for evidence of opioid withdrawal and serotonin syndrome if coadministration with St. John's Wort is necessary. If St. John's Wort is discontinued, consider reducing the oxycodone dose until stable drug effects are achieved and monitor for evidence of respiratory depression. The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system like St. John's Wort has resulted in serotonin syndrome. In addition, oxycodone is a CYP3A4 substrate, and coadministration with a CYP3A4 inducer like St. John's Wort can decrease oxycodone concentrations; this may result in decreased

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efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. (Minor) St. John's wort, Hypericum perforatum induces cytochrome P450 1A2. About 10 to 15% of the acetaminophen dose undergoes oxidative metabolism via cytochrome P450 isoenzymes CYP2E1, 3A4 and 1A2, which produces the hepatotoxic metabolite, N-acetyl-p-benzoquinonimine. Thus, theoretically St. John's wort might increase the risk of acetaminophen-induced hepatotoxicity by increasing the metabolism of acetaminophen to NAPQI.

Streptogramins: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of dalfopristin; quinupristin is necessary. If dalfopristin; quinupristin is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like dalfopristin; quinupristin can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If dalfopristin; quinupristin is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Succinylcholine: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of alfentanil on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.

Sulfinpyrazone: (Minor) Sulfinpyrazone can induce hepatic oxidative microsomal enzymes and the drug has been shown to increase acetaminophen clearance by roughly 23%. Theoretically, it is thought that the induction of acetaminophen metabolism by sulfinpyrazone may increase the risk of acetaminophen hepatotoxicity due to the formation of increased amounts of toxic acetaminophen metabolites, but there is no confirmatory evidence.

Sumatriptan: (Moderate) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as serotonin-receptor agonists. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.

Suvorexant: (Moderate) Concomitant use of opioid agonists with suvorexant may cause excessive sedation and somnolence. Limit the use of opioid pain medications with suvorexant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Tapentadol: (Major) Additive CNS depressive effects are expected if tapentadol is used in conjunction with other CNS depressants, including other opiate agonists. Severe hypotension, profound sedation, coma, or respiratory depression may occur. Prior to concurrent use of tapentadol in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If an opiate agonist is used concurrently with tapentadol, a reduced dosage of tapentadol and/or the opiate agonist is recommended. If the extended-release tapentadol tablets are used concurrently with a CNS depressant, it is recommended to use an initial tapentadol dose of 50 mg PO every 12 hours. Monitor patients for sedation and respiratory depression.

Tasimelteon: (Moderate) Concomitant use of opioid agonists with tasimelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with tasimelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Telaprevir: (Moderate) Close clinical monitoring is advised when administering acetaminophen with telaprevir due to an increased potential for acetaminophen-related adverse events. If acetaminophen dose adjustments are made, re-adjust the dose upon completion of telaprevir treatment. Although this interaction has not been studied, predictions about the interaction can be made based on the metabolic pathway of acetaminophen. Acetaminophen is partially metabolized by the hepatic isoenzyme CYP3A4; telaprevir inhibits this isoenzyme. Coadministration may result in elevated acetaminophen plasma concentrations. (Moderate) Close clinical monitoring is advised when administering oxycodone with telaprevir due to an increased potential for oxycodone-related adverse events. If oxycodone dose adjustments are made, re-adjust the dose upon completion of telaprevir treatment. Although this interaction has not been studied, predictions about the interaction can be made based on the metabolic pathway of oxycodone. Oxycodone is partially metabolized by the hepatic isoenzyme CYP3A4; telaprevir inhibits this isoenzyme. Coadministration may result in elevated oxycodone plasma concentrations.

Telithromycin: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of telithromycin is necessary. If telithromycin is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like telithromycin can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If telithromycin is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.

Telotristat Ethyl: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with telotristat ethyl is necessary; consider increasing the dose of oxycodone as needed. If telotristat ethyl is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and telotristat ethyl is a weak CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. (Moderate) Use telotristat ethyl and CYP3A4 substrates, such as acetaminophen, together with caution; the systemic exposure of acetaminophen may be decreased resulting in reduced efficacy. If these drugs are used together, monitor patients for suboptimal efficacy of acetaminophen; consider increasing the dose of acetaminophen if necessary. The systemic exposure of a sensitive CYP3A4 substrate was significantly decreased (by 48%) when it was coadministered with telotristat ethyl. The mechanism of this drug interaction appears to be that telotristat ethyl increases the glucuronidation of the CYP3A4 substrate.

Temazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Terbinafine: (Moderate) Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone, which represents < 15% of the total administered dose. Potent inhibitors of CYP2D6, such as terbinafine, may potentially increase the effects of oxycodone; however, such blockade has not been shown to be of clinical significance during oxycodone treatment. Clinicians should be aware of this possible interaction.

Tetrabenazine: (Moderate) Additive effects are possible when tetrabenazine is combined with other drugs that cause CNS depression. Concurrent use of tetrabenazine and drugs that can cause CNS depression, such as opiate agonists, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, dizziness, and orthostatic hypotension.

Tetracaine: (Major) Due to the central nervous system depression potential of local anesthetics, they should be used with caution with other agents that can cause respiratory depression, such as opiate agonists. Excitation or depression of the CNS may be the first manifestation of CNS toxicity. Restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of CNS toxicity. After each local anesthetic injection, careful and constant monitoring of ventilation adequacy, cardiovascular vital signs, and the patient's state of consciousness is advised. (Moderate) Coadministration of tetracaine with oxidizing agents, such as acetaminophen, may increase the risk of developing methemoglobinemia. Monitor patients closely for signs and symptoms of methemoglobinemia if coadministration is necessary. If methemoglobinemia occurs or is suspected, discontinue tetracaine and any other oxidizing agents. Depending on the severity of symptoms, patients may respond to supportive care; more severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

Tezacaftor; Ivacaftor: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ivacaftor is necessary. If ivacaftor is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like ivacaftor can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ivacaftor is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of

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the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Thalidomide: (Major) Avoid the concomitant use of thalidomide with opiate agonists; antihistamines; antipsychotics; anxiolytics, sedatives, and hypnotics; and other central nervous system depressants due to the potential for additive sedative effects.
Thiazide diuretics: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Thiethylperazine: (Moderate) Concomitant use of oxycodone with phenothiazines may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. Furthermore, oxycodone is metabolized in part by 2D6 to oxymorphone, which represents < 15% of the total administered dose. Concurrent use of some agents that inhibit CYP2D6 (e.g., quinidine) has not been shown to result in clinically significant interactions. However, many phenothiazines are inhibitors of CYP2D6 (e.g., chlorpromazine, perphenazine, thioridazine) and may potentially increase the effects of oxycodone. Also, severe hypotension may be potentiated with concurrent phenothiazine usage or other drug that compromises vasomotor tone.
Thiopental: (Minor) Chronic therapy with barbiturates can increase the metabolism and decrease the effectiveness of acetaminophen. During acute overdoses, barbiturates can enhance the formation of toxic acetaminophen metabolites.
Thioridazine: (Moderate) Concomitant use of oxycodone with phenothiazines may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. Furthermore, oxycodone is metabolized in part by 2D6 to oxymorphone, which represents < 15% of the total administered dose. Concurrent use of some agents that inhibit CYP2D6 (e.g., quinidine) has not been shown to result in clinically significant interactions. However, many phenothiazines are inhibitors of CYP2D6 (e.g., chlorpromazine, perphenazine, thioridazine) and may potentially increase the effects of oxycodone. Also, severe hypotension may be potentiated with concurrent phenothiazine usage or other drug that compromises vasomotor tone.
Thiothixene: (Moderate) Concomitant use of opiate agonists with other central nervous system (CNS) depressants can potentiate the effects of the opiate and may lead to additive CNS or respiratory depression, profound sedation, or coma. Examples of drugs associated with CNS depression include thiothixene. Prior to concurrent use of an opiate in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of the opiate and/or the CNS depressant is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.
Ticagrelor: (Moderate) Coadministration of opioid agonists may delay and reduce the absorption of ticagrelor resulting in reduced exposure and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Mean ticagrelor exposure decreased up to 36% in ACS patients undergoing PCI when intravenous morphine was administered with a loading dose of ticagrelor; mean platelet aggregation was higher up to 3 hours post loading dose. Similar effects on ticagrelor exposure and platelet inhibition were observed when fentanyl was administered with a ticagrelor loading dose in ACS patients undergoing PCI. Although exposure to ticagrelor was decreased up to 25% in healthy adults administered intravenous morphine with a loading dose of ticagrelor, platelet inhibition was not delayed or decreased in this population.
Tipranavir: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of tipranavir is necessary. If tipranavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like tipranavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If tipranavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Tizanidine: (Major) Concomitant use of oxycodone with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. (Minor) Tizanidine delays the time to attain peak concentrations of acetaminophen by about 16 minutes. The clinical significance of this interaction is unknown.
Tobacco: (Moderate) Tobacco smoking induces the cytochrome P450 isoenzyme CYP1A2 and may potentially increase the risk for acetaminophen-induced hepatotoxicity during overdose via enhanced generation of acetaminophen's hepatotoxic metabolite, NAPQI. In one study, current tobacco smoking was found to be very frequent in patients admitted with acetaminophen poisoning. Tobacco smoking appears to be an independent risk factor of severe hepatotoxicity, acute liver failure and death following acetaminophen overdose.
Tolterodine: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when oxycodone is used concomitantly with an anticholinergic drug, such as tolterodine. The concomitant use of oxycodone and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Topiramate: (Moderate) Monitor for reduced efficacy of oxycodone and signs of opioid withdrawal if coadministration with topiramate is necessary; consider increasing the dose of oxycodone as needed. If topiramate is discontinued, consider a dose reduction of oxycodone and frequently monitor for signs of respiratory depression and sedation. Oxycodone is a CYP3A4 substrate and topiramate is a weak CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease oxycodone levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Torsemide: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when loop diuretics are administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Tramadol: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Trandolapril; Verapamil: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of verapamil is necessary. If verapamil is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like verapamil can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If verapamil is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Trazodone: (Major) Concomitant use of opioid agonists with trazodone may cause excessive sedation, somnolence, and increased risk of serotonin syndrome. Limit the use of opioid pain medications with trazodone to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and serotonin syndrome.
Triamterene: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when triamterene is administered with oxycodone. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Triazolam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at 1/3 to 1/2

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the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Tricyclic antidepressants: (Major) Concomitant use of opioid agonists with tricyclic antidepressants may cause excessive sedation, somnolence, and increased risk of serotonin syndrome. The anticholinergic properties of tricyclic antidepressants may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Limit the use of opioid pain medications with tricyclic antidepressants to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and serotonin syndrome. Monitor for signs of urinary retention and reduced gastric motility.
Trifluoperazine: (Moderate) Concomitant use of oxycodone with phenothiazines may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to use of oxycodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxycodone, a reduced dosage of oxycodone and/or the CNS depressant is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression. Furthermore, oxycodone is metabolized in part by 2D6 to oxymorphone, which represents < 15% of the total administered dose. Concurrent use of some agents that inhibit CYP2D6 (e.g., quinidine) has not been shown to result in clinically significant interactions. However, many phenothiazines are inhibitors of CYP2D6 (e.g., chlorpromazine, perphenazine, thioridazine) and may potentially increase the effects of oxycodone. Also, severe hypotension may be potentiated with concurrent phenothiazine usage or other drug that compromises vasomotor tone.
Trimethobenzamide: (Moderate) The concurrent use of trimethobenzamide with other medications that cause CNS depression, like opiate agonists, may potentiate the effects of either trimethobenzamide or the opiate agonist.
Trimetrexate: (Moderate) Acetaminophen can inhibit oxidative hepatic enzymes responsible for metabolizing trimetrexate. Concurrent use can decrease the clearance of trimetrexate and thus increase its plasma levels.
Trimipramine: (Major) Concomitant use of opioid agonists with tricyclic antidepressants may cause excessive sedation, somnolence, and increased risk of serotonin syndrome. The anticholinergic properties of tricyclic antidepressants may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Limit the use of opioid pain medications with tricyclic antidepressants to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and serotonin syndrome. Monitor for signs of urinary retention and reduced gastric motility.
Triprolidine: (Moderate) Concomitant use of opioid agonists with triprolidine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with triprolidine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Trospium: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when trospium, an anticholinergic drug for overactive bladder. is used with opiate agonists. The concomitant use of these drugs together may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect. Both agents may also cause drowsiness or blurred vision, and patients should use care in driving or performing other hazardous tasks until the effects of the drugs are known.
Tubocurarine: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of alfentanil on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.
Valerian, Valeriana officinalis: (Moderate) Any substances that act on the CNS may theoretically interact with valerian, Valeriana officinalis. The valerian derivative, dihydrovaltrate, binds at barbiturate binding sites; valerenic acid has been shown to inhibit enzyme-induced breakdown of GABA in the brain; the non-volatile monoterpenes (valepotriates) have sedative activity. The sedative effect may be additive to other drugs with sedative actions, such as the opiate agonists. Consider the patient's use of alcohol or illicit drugs. If valerian is used concurrently with a CNS depressant, a reduced dosage of the CNS depressant may be required, or, the valerian supplement may be discontinued. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression.
Valproic Acid, Divalproex Sodium: (Moderate) Concomitant use of opioid agonists with valproic acid may cause excessive sedation and somnolence. Limit the use of opioid pain medications with valproic acid to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Vecuronium: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as neuromuscular blockers, can potentiate the effects of alfentanil on respiration, alertness, and blood pressure. A dose reduction of one or both drugs may be warranted.
Vemurafenib: (Moderate) Concomitant use of vemurafenib and acetaminophen may result in altered concentrations of acetaminophen. Vemurafenib is an inhibitor of CYP1A2 and CYP2A6, and an inducer of CYP3A4. Acetaminophen is a substrate of CYP1A2, CYP2A6, and CYP3A4. Use caution and monitor patients for toxicity and efficacy. (Moderate) Concomitant use of vemurafenib and oxycodone may result in altered concentrations of oxycodone. Vemurafenib is a weak inhibitor of CYP2D6 and an inducer of CYP3A4. Oxycodone is a substrate of CYP2D6 and CYP3A4. Use caution and monitor patients for toxicity and efficacy.
Verapamil: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of verapamil is necessary. If verapamil is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a moderate inhibitor like verapamil can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If verapamil is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Vigabatrin: (Moderate) Vigabatrin may cause somnolence and fatigue. Drugs that can cause CNS depression, if used concomitantly with vigabatrin, may increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness. Caution should be used when vigabatrin is given with opiate agonists.
Vilazodone: (Moderate) Due to the CNS effects of vilazodone, caution should be used when vilazodone is given in combination with other centrally acting medications such as opiate agonists.
Voriconazole: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of voriconazole is necessary. If voriconazole is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like voriconazole can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If voriconazole is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Voxelotor: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of voxelotor is necessary. If voxelotor is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with weak CYP3A4 inhibitors like voxelotor can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If voxelotor is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Warfarin: (Minor) Although acetaminophen is routinely considered safer than aspirin and agent of choice when a mild analgesic/antipyretic is necessary for a patient receiving therapy with warfarin, acetaminophen has also been shown to augment the hypoprothrombinemic response to warfarin. Concomitant acetaminophen ingestion may result in increases in the INR in a dose-related fashion. Clinical bleeding has been reported. Single doses or short (i.e., several days) courses of treatment with acetaminophen are probably safe in most patients taking warfarin. Clinicians should be alert for an increased INR if acetaminophen is administered in large daily doses for longer than 10 to 14 days.
Zafirlukast: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of zafirlukast is necessary. If zafirlukast is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a weak inhibitor like zafirlukast can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If zafirlukast is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the

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opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone.
Zaleplon: (Moderate) Concomitant use of oxycodone with zaleplon may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If zaleplon is used concurrently with oxycodone, a reduced dosage of oxycodone and/or zaleplon is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. Monitor for sedation and respiratory depression.
Ziconotide: (Moderate) Concurrent use of ziconotide and opiate agonists may result in an increased incidence of dizziness and confusion. Ziconotide neither interacts with opiate receptors nor potentiates opiate-induced respiratory depression. However, in animal models, ziconotide did potentiate gastrointestinal motility reduction by opioid agonists.
Zidovudine, ZDV: (Minor) Both acetaminophen and zidovudine, ZDV undergo glucuronidation. Competition for the metabolic pathway is thought to have caused a case of acetaminophen-related hepatotoxicity. This interaction may be more clinically significant in patients with depleted glutathione stores, such as patients with acquired immunodeficiency syndrome, poor nutrition, or alcoholism.
Ziprasidone: (Moderate) Ziprasidone has the potential to impair cognitive and motor skills. Additive CNS depressant effects are possible when ziprasidone is used concurrently with any CNS depressant, including oxycodone.
Zolmitriptan: (Moderate) Serotonin syndrome can occur during concomitant use of opiate agonists with serotonergic drugs, such as serotonin-receptor agonists. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs. (Minor) Zolmitriptan can delay the Tmax of acetaminophen by one hour. A single 1 g dose of acetaminophen does not alter the pharmacokinetics of zolmitriptan and its active metabolite. The interaction between zolmitriptan and acetaminophen is not likely to be clinically significant.
Zolpidem: (Major) Concomitant use of oxycodone with zolpidem may lead to additive respiratory and/or CNS depression. Hypotension, profound sedation, coma, respiratory depression, or death may occur. In addition, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of zolpidem and other CNS depressants than with zolpidem alone. Prior to concurrent use, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If zolpidem is used concurrently with oxycodone, a reduced dosage of oxycodone and/or zolpidem is recommended; use an initial dose of oxycodone at 1/3 to 1/2 the usual dosage. For Intermezzo brand of sublingual zolpidem tablets, reduce the dose to 1.75 mg/night. Monitor for sedation and respiratory depression.

PREGNANCY AND LACTATION

Pregnancy

Acetaminophen; oxycodone is classified as FDA pregnancy risk category C. No well-controlled studies in pregnant women have been performed. Some experts suggest increased risk of oxycodone if used for prolonged periods or at high doses near term. Chronic maternal use of opioids during pregnancy may result in neonatal opioid withdrawal syndrome. This syndrome can be life-threatening and includes symptoms such as poor feeding, irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, rigidity, and seizures. Neonates whose mothers have been taking oxycodone chronically may show some respiratory depression and/or withdrawal symptoms at birth or within a few days. Neonatal opioid withdrawal syndrome may be life-threatening and should be treated according to protocols developed by neonatology experts. Acetaminophen; oxycodone should not be used immediately prior to or during labor or obstetric delivery due to the potential for respiratory depression in the newborn. No overall increase in fetal mortality, as determined by pregnancy outcomes of mothers that overdosed on various amounts of acetaminophen, was apparent amongst 300 women. Treatment with acetylcysteine or methionine did not appear to affect fetal or neonatal toxicity. Of 235 babies exposed to an overdose of only acetaminophen, 168 were normal, 8 had malformations, 16 were spontaneously aborted, and 43 were electively terminated. Of 67 babies exposed to an overdose of a combination acetaminophen product, 51 were normal, 3 had malformations, 2 were spontaneously aborted (late fetal deaths), and 11 were electively terminated. None of the babies with malformations were exposed during the first trimester, but all of the spontaneous abortions and one of the late fetal deaths were subsequent to first trimester exposure.

MECHANISM OF ACTION

Mechanism of Action: Acetaminophen-oxycodone combination produces analgesia through two different mechanisms leading to a synergistic analgesic effect.•Oxycodone: Oxycodone is a potent μ-opiate receptor agonist. Opioid analgesia is mediated through changes in the perception of pain at the spinal cord and higher levels in the CNS. Opioids also alter the emotional response to pain. The stimulatory effects of opioids are the result of 'disinhibition' as the release of inhibitory neurotransmitters such as GABA and acetylcholine is blocked.•Acetaminophen: Acetaminophen acts primarily in the CNS and increases the pain threshold by inhibiting cyclooxygenase, an enzyme involved in prostaglandin (PG) synthesis. Acetaminophen inhibits both isoforms of cyclooxygenase, COX-1 and COX-2, but does so centrally; acetaminophen does not inhibit PG synthesis in peripheral tissues, which is the reason for its lack of peripheral anti-inflammatory effects. The antipyretic activity of acetaminophen is exerted by blocking the effects of endogenous pyrogen on the hypothalamic heat-regulating center via inhibition of PG synthesis.

PHARMACOKINETICS

Acetaminophen; oxycodone is administered orally. Both acetaminophen and oxycodone are metabolized in the liver via cytochrome P450 (CYP) isoenzymes and excreted through the kidney. Administration of other drugs which affect these isoenzymes may affect the efficacy and incidence of adverse reactions from the acetaminophen-oxycodone combination.
Oxycodone: The metabolism of oxycodone is mediated through CYP2D6.
Acetaminophen: Acetaminophen primarily undergoes glucuronidation and sulfate conjugation; however, a small percentage of the dose is metabolized via CYP2E1 and CYP1A2 to a hepatotoxic metabolite. The elimination half-life of this compound is approximately 4 hours. Depletion of glucuronide and sulfate stores due to chronic ethanol use or acute acetaminophen overdose may increase oxidative metabolism of acetaminophen leading to hepatotoxicity.

Oral Route

For immediate-release formulations, the onset of analgesia is within 30 minutes with peak analgesic effects in about 90 minutes. The duration of analgesia is 3—4 hours. After administration of the extended-release tablets, maximum plasma concentrations of acetaminophen and oxycodone occur in approximately 1 and 3 hours, respectively. Steady state concentrations are achieved within 24 hours of initiation.

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Exhibit 2

Exhibit 2

PDR.net

CLASSES

Compounding Kits Miscellaneous
Opioid Agonists

BOXED WARNING

Accidental exposure, acute intoxication of CNS depressants, ethanol ingestion, ethanol intoxication, potential for overdose or poisoning

Use of tramadol is associated with a significant potential for overdose or poisoning. Tramadol in excessive doses, either alone or in combination with other CNS depressants such as alcohol, is a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. Many of the tramadol-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts, as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of tramadol alone or in combination with other drugs. Tramadol should be kept out of the reach of pediatric patients, others for whom the drug was not prescribed, and pets as accidental exposure or improper use may cause respiratory failure and a fatal overdose. The use of immediate-release tramadol, tramadol orally disintegrating tablets (Rybix), and extended-release tablets (specifically Ultram ER and generic equivalents) is contraindicated in cases of acute intoxication of CNS depressants including ethanol intoxication and/or intoxication with opiate agonists, hypnotics, centrally-acting analgesics, or psychotropic drugs. Note that while Ryzolt extended-release tablets (and generic equivalents) and extended-release capsules are not specifically contraindicated, use during acute intoxication is not recommended. Tramadol may worsen central nervous system depression and decrease the respiratory rate in these patients. Tell patients not to exceed the recommended tramadol dose and to avoid ethanol ingestion during tramadol therapy. Advise patients of the additive depressant effects of tramadol and alcohol.

Asthma, coadministration with other CNS depressants, respiratory depression

As with other opioid agonists, tramadol should be avoided in patients with severe pulmonary disease. Additionally, avoid coadministration with other CNS depressants unless no other alternatives are available, as this significantly increases the risk for respiratory depression, low blood pressure, and death. As tramadol use is contraindicated in any situation where opioid agonist are contraindicated, do not use in patients with severe respiratory depression. Further, the manufacturers of dual-matrix extended-release tablets (e.g., Ryzolt) and extended-release capsules (e.g., ConZip) specifically contraindicate use in patients with acute or severe asthma or hypercapnia in unmonitored care settings or in the absence of resuscitate equipment. Consider alternative non-opioid analgesics instead of tramadol. Respiratory depression is possible with large doses of tramadol, especially when given concurrently with ethanol and anesthetic agents. Concurrent administration with other respiratory depressants exacerbates this risk. If respiratory depression occurs, treat as an overdose; however, administer naloxone cautiously in these situations due to an increased risk of seizures.

Alcoholism, depression, substance abuse, suicidal ideation

Do not prescribe tramadol for patients who have depression, suicidal ideation, or addiction problems such as patients with alcoholism. Consider use of non-narcotic analgesics in these patients. Tramadol is an opioid agonist and therefore has abuse potential and risk of fatal overdose from respiratory failure. Addiction may occur in patients who obtain tramadol illicitly or in those appropriately prescribed the drug. The risk of addiction in any individual is unknown. However, patients with mental illness (e.g., major depression) or a family history of substance abuse (including alcoholism) have an increased risk of opioid abuse. Assess patients for risks of addiction, abuse, or misuse before drug initiation, and monitor patients who receive opioids routinely for development of these behaviors or conditions. A potential risk of abuse should not preclude appropriate pain management in any patient, but requires more intensive counseling and monitoring. Abuse and addiction are separate and distinct from physical dependence and tolerance; patients with addiction may not exhibit tolerance and symptoms of physical dependence. The misuse of tramadol extended-release tablets or extended-release capsules by splitting, breaking, crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery and can result in overdose and death. To discourage abuse, the smallest appropriate quantity of tramadol should be dispensed, and proper disposal instructions for unused drug should be given to patients.

Labor, neonatal opioid withdrawal syndrome, obstetric delivery, pregnancy

Data are insufficient to inform a drug-associated risk for major birth defects or miscarriage with tramadol use in human pregnancy. Tramadol crosses the placenta. Based on animal data, tramadol may cause fetal harm; advise pregnant women of the potential risk to the fetus. In animal studies of tramadol, decreased fetal weights and reduced ossification were observed in mice, rats, and rabbits at 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD). Decreased body weight and increased mortality were observed in pups at tramadol doses of 1.2 and 1.9 times the MRHD. Tramadol is not recommended for use in women during and immediately prior to labor and obstetric delivery because oral opioid agonists may cause respiratory depression in the newborn. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women treated with tramadol during labor. Opioid analgesics can prolong labor by reducing the strength and frequency of uterine contractions; however, this effect may be offset by an increased rate of cervical dilation. Further, prolonged maternal use of tramadol during pregnancy may result in neonatal opioid withdrawal syndrome (NOWS). This syndrome can be life-threatening. Severe symptoms may require pharmacologic therapy managed by clinicians familiar with neonatal opioid withdrawal. Monitor the neonate for withdrawal symptoms including irritability, hyperactivity, abnormal sleep pattern, high-pitched crying, tremor, vomiting, diarrhea, and failure to gain weight. Onset, duration, and severity of opioid withdrawal may vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination by the newborn. Neonatal seizures, neonatal withdrawal syndrome, fetal death, and still birth have been reported during postmarketing experience with tramadol.

Adenoidectomy, children, infants, neonates, neuromuscular disease, obesity, pulmonary disease, sleep apnea, tonsillectomy

Tramadol is contraindicated in neonates, infants, and children younger than 12 years and for postoperative pain management in pediatric patients younger than 18 years after a tonsillectomy and/or adenoidectomy. Avoid use in patients 12 to 18 years of age who have other risk factors for respiratory depression unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other respiratory depressants. When prescribing tramadol for adolescents, choose the lowest effective dose for the shortest period of time, and inform patients and caregivers of the risks and the signs of opioid overdose. Ultra-rapid metabolizers of CYP2D6 substrates may convert tramadol to its active metabolite, O-desmethyltramadol, more quickly and completely than usual, leading to higher than normal opioid blood concentrations that can result in fatal respiratory depression. Because some children who are normal metabolizers can covert opioids at similar rates to ultra-rapid metabolizers, this

concern extends to all pediatric patients.The safety and efficacy of tramadol in patients younger than 16 years of age have not been established for any dosage form.

DEA CLASS

Rx, schedule IV

DESCRIPTION

Centrally-active oral analgesic, acts as mu-opioid receptor agonist and weak norepinephrine/serotonin reuptake inhibitor.
Used to treat acute and chronic moderate to moderately severe pain.
Compared to typical opioids has lower abuse and respiratory depression potential and higher risk potential for serotonin syndrome.

COMMON BRAND NAMES

Active-Tramadol Kit for Compounding, ConZip, EnovaRX, Ryzolt, Ultram, Ultram ER

HOW SUPPLIED

Active-Tramadol Kit for Compounding Topical Pwd: 8%
ConZip/Tramadol/Tramadol Hydrochloride Oral Cap ER: 100mg, 150mg, 200mg, 300mg
EnovaRX Topical Pwd F/Recon: 3g, 6g
Ryzolt/Tramadol/Tramadol Hydrochloride/Ultram ER Oral Tab ER: 100mg, 200mg, 300mg
Tramadol/Tramadol Hydrochloride/Ultram Oral Tab: 50mg

DOSAGE & INDICATIONS

For the treatment of moderate pain or moderately severe pain.

For moderate chronic pain or moderately severe chronic pain in patients requiring continuous, around-the-clock treatment for an extended period of time.

Oral dosage (coated extended-release tablets; i.e., Ultram ER ONLY, or generic equivalents)

Adults

NOT CURRENTLY RECEIVING TRAMADOL: Initially, 100 mg PO once daily; titrate in 100 mg increments every 5 days, if needed. Dose no more frequently than every 24 hours. Maximum: 300 mg PO once daily. Dose no more frequently than every 24 hours. CONVERSION FROM IMMEDIATE-RELEASE: Calculate the 24-hour tramadol dose, and initiate a total daily dose of the extended-release tablets rounded down to the next lowest 100 mg increment. Individualize dose titration as needed. Maximum: 300 mg PO once daily; the clinical benefit higher doses has not been demonstrated. Consider lower doses in geriatric patients over 65 years of age, particularly in those greater than 75 years of age. The concomitant use of the extended-release tablets with other tramadol products is not recommended. Different formulations of extended-release tramadol are not interchangable; pharmacokinetics and dosage titration schedules differ.

Oral dosage (dual-matrix extended-release tablets; i.e., Ryzolt ONLY)

Adults and Adolescents 16 years and older

NOT CURRENTLY RECEIVING TRAMADOL: Initially, 100 mg PO once daily; titrate in 100 mg increments every 2 to 3 days. Dose no more frequently than every 24 hours. Maximum: 300 mg PO once daily. CONVERSION FROM IMMEDIATE-RELEASE: Calculate the 24-hour tramadol dose, and initiate a total daily dose of the extended-release tablets rounded down to the next lowest 100 mg increment. Individualize dose titration as needed. Maximum: 300 mg PO once daily; clinical benefit of higher doses has not been demonstrated. Consider lower doses in geriatric adults above 65 years of age, particularly those older than 75 years of age. The concomitant use of the dual-matrix extended-release tablets with other tramadol products is not recommended. Different formulations of extended-release tramadol are not interchangable; pharmacokinetics and dosage titration schedules differ.

Oral dosage (extended biphasic-release capsules; i.e., ConZip ONLY, or generic equivalents)

Adults

NOT CURRENTLY RECEIVING TRAMADOL: Initially, 100 mg PO once daily; titrate upwards to 150 mg, 200 mg, and 300 mg every 5 days. Dose no more frequently than every 24 hours. Maximum: 300 mg PO once daily. CONVERSION FROM IMMEDIATE-RELEASE: Calculate the 24-hour tramadol dose, and initiate a total daily dose rounded down to the next lowest 100 mg increment. Individualize dose titration as needed. Maximum: 300 mg PO once daily; clinical benefit of higher doses has not been demonstrated. Consider lower doses in geriatric adults above 65 years of age, particularly those older than 75 years of age. The concomitant use of the biphasic extended-release capsules with other tramadol products is not recommended. Different formulations of extended-release tramadol are not interchangable; pharmacokinetics and dosage titration schedules differ. When the patient no longer requires tramadol, taper the dose gradually to prevent withdrawal.

Oral dosage (immediate-release tablets; i.e., Ultram, or generic equivalents)

Adults and Adolescents 17 years and older

If rapid onset of analgesia is not required, initiate with 25 mg PO once daily and titrate in 25 mg increments every 3 days to reach a dose of 100 mg/day PO (i.e., 25 mg PO 4 times daily) to improve tolerability. Thereafter, the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day PO (i.e., 50 mg PO 4 times daily). After titration, a dose of 50 to 100 mg PO every 4 to 6 hours may be administered as needed. For rapid relief of moderate to moderately severe pain in patients where more rapid titration is necessary, give 50 to 100 mg PO every 4 to 6 hours as needed. In general, geriatric patients require care in dose selection and titration. Maximum (age up to 75 years): 400 mg/day PO. Maximum (75 years and older): 300 mg/day PO.

Oral dosage (immediate-release orally disintegrating tablets; i.e., Rybix ODT ONLY)

Adults and Adolescents 17 years and older

If rapid onset of analgesia not required, initiate with 50 mg PO once daily and titrate in 50 mg increments every 3 days to reach a dose of 200 mg/day PO (i.e., 50 mg PO 4 times daily) to improve tolerability. After titration, may administer 50 to 100 mg every 4 to 6 hours as needed. For rapid relief of moderate to moderately severe pain in patients where more rapid titration is necessary, give 50 to 100 mg PO every 4 to 6 hours as needed. In general, geriatric patients require care in dose selection and titration. Maximum (age up to 75 years): 400 mg/day PO. Maximum (75 years and older): 300 mg/day PO.

For the adjuvant treatment of arthralgia† associated with osteoarthritis†.

Oral dosage (immediate-release tablets)

Adults and Geriatrics 74 years and younger

50 mg to 100 mg PO every 4 to 6 hours as needed. Maximum: 400 mg/day. Dosage titration may improve tolerability. Tramadol has been shown to be effective in controlling breakthrough pain in patients receiving NSAIDs. A trial of tramadol versus diclofenac in patients with osteoarthritis of the hip and/or knee showed that the drugs were comparable. Tramadol may be an alternative to NSAIDs in patients who do not tolerate or have preexisting conditions that limit NSAID use or in patients with a limited inflammatory component to their osteoarthritis.

Geriatrics 75 years and older

50 mg to 100 mg PO every 4 to 6 hours as needed. Maximum: 300 mg/day PO. Dosage titration may improve tolerability. Tramadol has been shown to be effective in controlling breakthrough pain in patients receiving NSAIDs. A trial of tramadol versus diclofenac in patients with osteoarthritis of the hip and/or knee showed that the drugs were comparable. Tramadol may be an alternative to NSAIDs in patients who do not tolerate or have preexisting conditions that limit NSAID use or in patients with a limited inflammatory component to their osteoarthritis.

For the treatment of diabetic neuropathy†.

Oral dosage (immediate-release tablets)

Adults

In one study, treatment was initiated at 50 mg/day PO and increased in 50 mg increments every 3 days up to 200 mg/day by Day 10 (i.e., 50 mg PO four times daily). During Days 14 through 28, patients could increase their dose of study medication by 50 mg/day to obtain optimal pain relief, not to exceed 400 mg/day in divided doses. A more rapid titration was permitted if patients were experiencing inadequate pain relief at any time. The mean effective dose in clinical trials was 210 mg/day, in divided doses. The American Academy of Neurology considers tramadol probably effective in lessening the pain of diabetic neuropathy.

For postherpetic neuralgia†.

Oral dosage (immediate-release tablets)

Adults

Usual doses range from 50 mg/day PO during initial titration, up to 200 mg/day, in divided doses (i.e., 50 mg PO four times daily). Further titration by 50 mg/day to obtain optimal pain relief has been used. Maximum: 400 mg/day PO, in divided doses. Tramadol is not considered a first-line therapy for postherpetic neuralgia and is often recommended only for short-term pain relief. Tricyclic antidepressants, gabapentin, pregabalin, and lidocaine patches are effective in reducing the pain of postherpetic neuralgia and are usually first line treatments.

For the treatment of postoperative shivering†.

Intravenous dosage (not commercially available in US)†

Adults

1 mg/kg to 2 mg/kg IV stopped shivering within 5 minutes in post-anesthetic patients.

†Indicates off-label use

MAXIMUM DOSAGE

Adults

400 mg/day PO for immediate-release and orally disintegrating tablets; 300 mg/day PO for extended-release formulations.

Geriatric

65 to 75 years: 400 mg/day PO for immediate-release and orally disintegrating tablets; 300 mg/day PO for extended-release formulations.
Older than 75 years: 300 mg/day PO.

Adolescents

17 years: 400 mg/day PO for immediate-release and orally disintegrating tablets; 300 mg/day PO for dual-matrix extended-release tablets (Ryzolt). Safety and efficacy of other formulations have not been established.
16 years: 300 mg/day PO for dual-matrix extended-release tablets (Ryzolt). Safety and efficacy of other formulations have not been established.
13 to 16 years: Safety and efficacy have not been established.

Children

12 years: Safety and efficacy have not been established.
1 to 11 years: Use is contraindicated.

Infants

Use is contraindicated.

DOSING CONSIDERATIONS

Hepatic Impairment

Do not use the extended-release tramadol formulations in patients with severe hepatic impairment (Child-Pugh Class C); specific guidelines for dosage adjustments in mild to moderate hepatic impairment are not available. For the immediate-release and orally disintegrating tablets, a dose of 50 mg PO every 12 hours is recommended in patients with cirrhosis.

Renal Impairment

CrCl 30—80 ml/min: Specific guidelines for dosage adjustments are not available; decreased rate and extent of drug and metabolite excretion is expected.
CrCl < 30 ml/min: Do not use the extended-release tramadol formulations. For the immediate-release and orally disintegrating tablets, increase dosage interval to 12 hours; maximum daily dose not to exceed 200 mg/day PO.

Intermittent hemodialysis
Approximately 7% of a tramadol dose is removed during a standard hemodialysis session. Therefore, no additional dosing adjustments of immediate-release and orally disintegrating tablets are needed on the day of dialysis. Do not use extended-release tramadol formulations in patients with CrCl < 30 ml/min.

ADMINISTRATION

Oral Administration

Slow titration of tramadol to the effective analgesic dose may improve tolerability (see Dosage).

Oral Solid Formulations

Immediate-release tablets (e.g., Ultram)
Administer tramadol immediate-release tablets with or without food.

Orally disintegrating tablets (Rybix ODT)
Administer with or without food.
Remove tablet from the blister pack by peeling back foil from the blister; do not attempt to push the tablet through the foil.
Do not break, chew, split, or crush the tablets.
Place tablet in the mouth on the tongue; it will dissolve within one minute.
May be taken with or without water.

Extended-release tablets and capsules (e.g., Ryzolt, ConZip, Ultram ER)
NOTE: Different formulations of extended-release tramadol are NOT interchangable; pharmacokinetics and dosage titration schedules differ.
Administer tramadol dual-matrix extended-release tablets (Ryzolt) and extended-release capsules (ConZip) without regard for meals.
Administer the coated extended-release tablets (Ultram ER) in a consistent manner, taken regularly either with food or without food.
Swallow whole; do not break, chew, dissolve, or crush. Taking broken, chewed, dissolved, or crushed extended-release products leads to rapid release and absorption of a potentially fatal dose of tramadol.

STORAGE

Generic:
- Store between 68 to 77 degrees F, excursions permitted 59 to 86 degrees F
Active-Tramadol Kit for Compounding:
- Prior to compounding, store at room temperature (between 59 to 86 degrees F)
ConZip:
- Store at 77 degrees F; excursions permitted to 59-86 degrees F
EnovaRX:
- Store at 77 degrees F; excursions permitted to 59-86 degrees F
- Store in a cool, dry place
Rybix:
- Store at 77 degrees F; excursions permitted to 59-86 degrees F
Ryzolt:
- Store at controlled room temperature (between 68 and 77 degrees F)
Ultram:
- Store between 68 to 77 degrees F, excursions permitted 59 to 86 degrees F
Ultram ER:
- Store between 68 to 77 degrees F, excursions permitted 59 to 86 degrees F

CONTRAINDICATIONS / PRECAUTIONS

Lactase deficiency

Tramadol immediate-release tablets contain lactose; patients with lactase deficiency should take appropriate precautions with use.

Opiate agonist hypersensitivity, polysorbate 80 hypersensitivity

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol, including reports of anaphylactoid reactions after the initial tramadol dose, particularly in patients with a history of codeine hypersensitivity. Tramadol is contraindicated in patients with known tramadol hypersensitivity, opiate agonist hypersensitivity, or hypersensitivity to any other ingredient of the specific product formulation. Some tramadol immediate-release tablets contain polysorbate 80; do not use in patients with polysorbate 80 hypersensitivity.

Accidental exposure, acute intoxication of CNS depressants, ethanol ingestion, ethanol intoxication, potential for overdose or poisoning

Use of tramadol is associated with a significant potential for overdose or poisoning. Tramadol in excessive doses, either alone or in combination with other CNS depressants such as alcohol, is a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. Many of the tramadol-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts, as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of tramadol alone or in combination with other drugs. Tramadol should be kept out of the reach of pediatric patients, others for whom the drug was not prescribed, and pets as accidental exposure or improper use may cause respiratory failure and a fatal overdose. The use of immediate-release tramadol, tramadol orally disintegrating tablets (Rybix), and extended-release tablets (specifically Ultram ER and generic equivalents) is contraindicated in cases of acute intoxication of CNS depressants including ethanol intoxication and/or intoxication with opiate agonists, hypnotics, centrally-acting analgesics, or psychotropic drugs. Note that while Ryzolt extended-release tablets (and generic equivalents) and extended-release capsules are not specifically contraindicated, use during acute intoxication is not recommended. Tramadol may worsen central nervous system depression and decrease the respiratory rate in these patients. Tell patients not to

exceed the recommended tramadol dose and to avoid ethanol ingestion during tramadol therapy. Advise patients of the additive depressant effects of tramadol and alcohol.

Asthma, coadministration with other CNS depressants, respiratory depression

As with other opioid agonists, tramadol should be avoided in patients with severe pulmonary disease. Additionally, avoid coadministration with other CNS depressants unless no other alternatives are available, as this significantly increases the risk for respiratory depression, low blood pressure, and death. As tramadol use is contraindicated in any situation where opioid agonist are contraindicated, do not use in patients with severe respiratory depression. Further, the manufacturers of dual-matrix extended-release tablets (e.g., Ryzolt) and extended-release capsules (e.g., ConZip) specifically contraindicate use in patients with acute or severe asthma or hypercapnia in unmonitored care settings or in the absence of resuscitate equipment. Consider alternative non-opioid analgesics instead of tramadol. Respiratory depression is possible with large doses of tramadol, especially when given concurrently with ethanol and anesthetic agents. Concurrent administration with other respiratory depressants exacerbates this risk. If respiratory depression occurs, treat as an overdose; however, administer naloxone cautiously in these situations due to an increased risk of seizures.

Head trauma, increased intracranial pressure, seizure disorder, seizures

Seizures have been reported in patients receiving tramadol within the recommended dosage range (see Adverse Reactions). Tramadol should be used with caution in patients who are at risk of seizures including those who have a pre-existing seizure disorder or a history of seizures, are receiving medications that reduce the seizure threshold (see Drug Interactions), who have certain medical conditions (i.e., metabolic disorders, increased intracranial pressure, CNS infection, head trauma), or who are experiencing ethanol or illicit drug withdrawal. The risk of seizures may increase in these patients. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. In tramadol overdose, naloxone administration may increase the risk of seizure. In addition, administration of tramadol to patients with increased intracranial pressure or head trauma may obscure the existence, extent, or course of intracranial pathology because tramadol induces pupillary changes (miosis). Further, the respiratory depressant effects of opioids such as carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in these patients. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving tramadol.

Acute abdomen, biliary tract disease, constipation, diarrhea, GI disease, GI obstruction, ileus, pancreatitis, ulcerative colitis

Tramadol use is contraindicated in patients with known or suspected GI obstruction, including paralytic ileus. Due to the effects of opioid agonists on the gastrointestinal tract, tramadol should be used cautiously in patients with pre-existing biliary tract or GI disease, ulcerative colitis (UC), or pre-existing constipation. Patients with UC or other inflammatory bowel disease may be more sensitive to the constipating effects of opioid agonists. Also, use with caution in patients with pancreatic or biliary tract disease, including acute pancreatitis, as mu-opioid agonists are known to cause spasm of the sphincter of Oddi. Opioid agonists may obscure the diagnosis or clinical course in patients with an acute abdomen. Although opioid agonists are not desirable for use in patients with diarrhea secondary to poisoning or infectious diarrhea, antimotility agents have been used successfully in these patients. If possible, opioid agonists should not be given until the toxic substance has been eliminated.

Alcoholism, depression, substance abuse, suicidal ideation

Do not prescribe tramadol for patients who have depression, suicidal ideation, or addiction problems such as patients with alcoholism. Consider use of non-narcotic analgesics in these patients. Tramadol is an opioid agonist and therefore has abuse potential and risk of fatal overdose from respiratory failure. Addiction may occur in patients who obtain tramadol illicitly or in those appropriately prescribed the drug. The risk of addiction in any individual is unknown. However, patients with mental illness (e.g., major depression) or a family history of substance abuse (including alcoholism) have an increased risk of opioid abuse. Assess patients for risks of addiction, abuse, or misuse before drug initiation, and monitor patients who receive opioids routinely for development of these behaviors or conditions. A potential risk of abuse should not preclude appropriate pain management in any patient, but requires more intensive counseling and monitoring. Abuse and addiction are separate and distinct from physical dependence and tolerance; patients with addiction may not exhibit tolerance and symptoms of physical dependence. The misuse of tramadol extended-release tablets or extended-release capsules by splitting, breaking, crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery and can result in overdose and death. To discourage abuse, the smallest appropriate quantity of tramadol should be dispensed, and proper disposal instructions for unused drug should be given to patients.

Abrupt discontinuation

To prevent withdrawal symptoms, avoid abrupt discontinuation of tramadol. Withdrawal symptoms may include anxiety, sweating, nausea, tremors, diarrhea, upper respiratory symptoms, insomnia, rigors, pain, piloerection, panic attacks, paresthesias, and hallucinations (rarely). Clinical experience suggests that withdrawal symptoms may be relieved by tapering the dosage of tramadol.

Renal disease, renal failure, renal impairment

Administer tramadol with caution to patients with renal disease, renal impairment, or renal failure. Impaired renal function affects the rate and extent of excretion of both tramadol and its active metabolite, M1. It may take several days for elevated plasma concentrations and toxicity to develop. Dosage reductions of the immediate-release tablets are recommended if creatinine clearance falls below 30 mL/minute. The extended-release tablets are not recommended for use in patients with a creatinine clearance below 30 mL/minute. The extended-release tablets have not been studied in patients with a creatinine clearance below 30 mL/minute, and the limited availability of dose strengths and once daily dosing do not permit the dosing flexibility required for safe use in patients with severe renal impairment.

Hepatic disease

Dosage reductions and an increased dosage interval are recommended for patients with hepatic disease (see Dosage). Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. It may take several days for elevated plasma concentrations and toxicity to develop. The extended-release tablets are not recommended for use in patients with severe hepatic impairment. The pharmacokinetics of the extended-release tablets have not been studied in patients with severe hepatic impairment, and the limited availability of dose strengths and once daily dosing do not permit the dosing flexibility required for safe use in patients with severe hepatic impairment.

Labor, neonatal opioid withdrawal syndrome, obstetric delivery, pregnancy

Data are insufficient to inform a drug-associated risk for major birth defects or miscarriage with tramadol use in human pregnancy. Tramadol crosses the placenta. Based on animal data, tramadol may cause fetal harm; advise pregnant women of the potential risk to the fetus. In animal studies of tramadol, decreased fetal weights and reduced ossification were observed in mice, rats, and rabbits at 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD). Decreased body weight and increased mortality were observed in pups at tramadol doses of 1.2 and 1.9 times the MRHD. Tramadol is not recommended for use in women during and immediately prior to labor and obstetric delivery because oral opioid agonists may cause respiratory depression in the newborn. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women treated with tramadol during labor. Opioid analgesics can prolong labor by reducing the strength and frequency of uterine contractions; however, this effect may be offset by an increased rate of cervical dilation. Further, prolonged maternal use of tramadol during pregnancy may result in neonatal opioid withdrawal syndrome (NOWS). This syndrome can be life-threatening. Severe symptoms may require pharmacologic therapy managed by clinicians familiar with neonatal opioid withdrawal. Monitor the neonate for withdrawal symptoms including irritability, hyperactivity, abnormal sleep pattern, high-pitched crying, tremor, vomiting, diarrhea, and failure to gain weight. Onset, duration, and severity of opioid withdrawal may vary based on the specific opioid used, duration of use, timing and amount of last maternal use,

and rate of elimination by the newborn. Neonatal seizures, neonatal withdrawal syndrome, fetal death, and still birth have been reported during postmarketing experience with tramadol.

Breast-feeding

Breast-feeding is not recommended during treatment with tramadol because of the potential for serious adverse events, including excess sedation and respiratory depression in the breastfed infant. If an infant is exposed to tramadol through breast milk, they should be monitored for excessive sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal use of an opioid is stopped or when breast-feeding is stopped. Alternative analgesics that previous American Academy of Pediatrics recommendations considered as usually compatible with breast-feeding include acetaminophen, ibuprofen, and morphine. There is no information on the effects of tramadol on milk production. Tramadol and its metabolite (M1) are excreted into human milk. An infant nursing from an ultra-rapid metabolizer mother taking tramadol could potentially be exposed to high metabolite concentrations and experience life-threatening respiratory depression. In women with normal tramadol metabolism (normal CYP2D6 activity), the amount of tramadol secreted into human milk is low and dose-dependent. After a single IV dose of tramadol 100 mg, the cumulative excretion in breast milk within 16 hours was 100 mcg of tramadol (0.1% of the maternal dose) and 27 mcg of M1. Samples of breast milk taken from 75 women 2 to 4 days postpartum after receiving at least 4 doses of tramadol indicated that an exclusively breast-fed infant would receive 2.24% of the maternal weight adjusted dose of tramadol and 0.64% of its metabolite. Assessments of the infants of these mothers using the Neurologic and Adaptive Capacity Score found no difference when compared to infants in a control group. Forty-nine percent of mothers in the tramadol group and 100% of mothers in the control group were also receiving other opioids (mostly oxycodone).

Infertility, reproductive risk

Chronic opioid use may influence the hypothalamic-pituitary-gonadal axis, leading to hormonal changes that may manifest as hypogonadism (gonadal suppression) and pose a reproductive risk. Although the exact causal role of opioids in the clinical manifestations of hypogonadism is unknown, patients could experience libido decrease, impotence, amenorrhea, or infertility. It is not known whether the effects on fertility are reversible. Monitor patients for symptoms of opioid-induced endocrinopathy. Patients presenting with signs or symptoms of androgen deficiency should undergo laboratory evaluation.

Geriatric

Geriatric patients vary in their tolerance of tramadol. Use all forms of tramadol with caution in patients 65 years and older, with consideration of the greater frequency of decreased organ function, concomitant disease, and other drug therapy. Age-based dosage adjustments are recommended in patients older than 75 years of age.[28314] [32475] [40255] [43297] In clinical trials, higher general incidence rates of constipation, fatigue, weakness, postural hypotension, and dyspepsia were observed for geriatric patients as compared with younger patients.[28314] According to the Beers Criteria, caution is recommended when using tramadol in older adults because the drug can cause or exacerbate hyponatremia and SIADH and the elderly are at increased risk of developing these conditions. Sodium levels should be closely monitored when starting or changing dosages in older adults. In addition, the Expert Panel recommends reducing the dose of immediate-release tramadol in geriatric patients with a creatinine clearance less than 30 mL/minute due to the potential for adverse CNS effects. Opiate agonists are considered potentially inappropriate medications (PIMs) in geriatric patients with a history of falls or fractures and should be avoided in these patient populations, except in the setting of severe acute pain, since opiates can produce ataxia, impaired psychomotor function, syncope, and additional falls. If an opiate must be used, consider reducing the use of other CNS-active medications that increase the risk of falls and fractures and implement strategies to reduce fall risk. In patients receiving palliative care or hospice, the balance of benefits and harms of medication management may differ from those of the general population of older adults.[63923] The federal Omnibus Budget Reconciliation Act (OBRA) regulates medication use in residents of long-term care facilities (LTCFs). OBRA cautions that opioids may cause constipation, nausea, vomiting, sedation, lethargy, weakness, confusion, dysphoria, physical and psychological dependency, hallucinations, and unintended respiratory depression, especially in individuals with compromised pulmonary function. These adverse effects can lead to other consequences such as falls. The initiation of longer-acting opioids is not recommended unless shorter-acting opioids have been unsuccessful, or titration of shorter-acting doses has established a clear daily dose of opioid analgesic that can be provided by using a long-acting form.[60742]

Adenoidectomy, children, infants, neonates, neuromuscular disease, obesity, pulmonary disease, sleep apnea, tonsillectomy

Tramadol is contraindicated in neonates, infants, and children younger than 12 years and for postoperative pain management in pediatric patients younger than 18 years after a tonsillectomy and/or adenoidectomy. Avoid use in patients 12 to 18 years of age who have other risk factors for respiratory depression unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other respiratory depressants. When prescribing tramadol for adolescents, choose the lowest effective dose for the shortest period of time, and inform patients and caregivers of the risks and the signs of opioid overdose. Ultra-rapid metabolizers of CYP2D6 substrates may convert tramadol to its active metabolite, O-desmethyltramadol, more quickly and completely than usual, leading to higher than normal opioid blood concentrations that can result in fatal respiratory depression. Because some children who are normal metabolizers can covert opioids at similar rates to ultra-rapid metabolizers, this concern extends to all pediatric patients.The safety and efficacy of tramadol in patients younger than 16 years of age have not been established for any dosage form.

Driving or operating machinery

Patients should be warned against driving or operating machinery until they know how tramadol may affect them.

MAOI therapy

Use of tramadol is contraindicated in patients who are receiving or who have received MAOI therapy within the past 14 days. Additive CNS depression, drowsiness, dizziness, or hypotension may occur. Concomitant use may also increase the risk for serotonin syndrome.

Phenylketonuria

Orally disintegrating tablets contain phenylalanine; do not prescribe this dosage form for patients with phenylketonuria or other phenylketone-related sensitivity.

Adrenal insufficiency, hypothyroidism, myxedema

Use tramadol with caution in patients with adrenal insufficiency (i.e., Addison's disease), hypothyroidism, or myxedema. Such patients may be at increased risk of adverse events. Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH); however, the thyroid stimulating hormone may be either stimulated or inhibited by opioids. Rarely, adrenal insufficiency has been reported in association with opioid use. Patients should seek immediate medical attention if they experience symptoms such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or hypotension. If adrenocortical insufficiency is suspected, confirm with diagnostic testing as soon as possible. If diagnosed, the patient should be treated with physiologic replacement doses of corticosteroids, and if appropriate, weaned off of opioid therapy. If the opioid can be discontinued, a follow-up assessment of adrenal function should be performed to determine if corticosteroid treatment can be discontinued. Other opioids may be tried; some cases reported use of a different opioid with no recurrence of adrenocortical insufficiency. It is unclear which, if any, opioids are more likely to cause adrenocortical insufficiency. In addition, chronic opioid use may lead to symptoms of hypogonadism, resulting from changes in the hypothalamic-pituitary-gonadal axis. Monitor patients for symptoms of opioid-induced endocrinopathy, particularly those receiving a daily dose equivalent to 100 mg or more of morphine. Patients presenting with signs or symptoms of androgen deficiency should undergo laboratory evaluation.

ADVERSE REACTIONS

Severe

visual impairment / Early / 1.0-4.9
hepatic failure / Delayed / 0-1.0
pancreatitis / Delayed / 0-1.0
GI bleeding / Delayed / 0-1.0
bradycardia / Rapid / 0-1.0
serotonin syndrome / Delayed / 0-1.0
seizures / Delayed / 0-1.0
suicidal ideation / Delayed / 0-1.0
Stevens-Johnson syndrome / Delayed / 0-1.0
toxic epidermal necrolysis / Delayed / 0-1.0
proteinuria / Delayed / 0-1.0
cholecystitis / Delayed / 0-1.0
hearing loss / Delayed / 0-1.0
myocardial infarction / Delayed / 0.5-0.9
pulmonary embolism / Delayed / Incidence not known
pulmonary edema / Early / Incidence not known
torsade de pointes / Rapid / Incidence not known
bronchospasm / Rapid / Incidence not known
anaphylactoid reactions / Rapid / Incidence not known
angioedema / Rapid / Incidence not known
fetal death / Delayed / Incidence not known
neonatal opioid withdrawal syndrome / Delayed / Incidence not known
SIADH / Delayed / Incidence not known

Moderate

constipation / Delayed / 9.3-46.0
euphoria / Early / 0-14.0
hallucinations / Early / 0-14.0
orthostatic hypotension / Delayed / 0-5.4
peripheral vasodilation / Rapid / 0-5.0
hypertension / Early / 0-5.0
hypertonia / Delayed / 0-5.0
depression / Delayed / 0-5.0
dyspnea / Early / 0-5.0
urinary retention / Early / 0-5.0
hyperglycemia / Delayed / 0-5.0
peripheral edema / Delayed / 1.0-4.9
hot flashes / Early / 1.0-4.9
blurred vision / Early / 1.0-4.9
confusion / Early / 1.0-4.9
withdrawal / Early / 0.5-4.9
dysphagia / Delayed / 0-1.0
hepatitis / Delayed / 0-1.0
stomatitis / Delayed / 0-1.0
hypotension / Rapid / 0-1.0
amnesia / Delayed / 0-1.0
ataxia / Delayed / 0-1.0
impaired cognition / Early / 0-1.0
migraine / Early / 0-1.0
dysuria / Early / 0-1.0
hematuria / Delayed / 0-1.0
cystitis / Delayed / 0-1.0
anemia / Delayed / 0-1.0
thrombocytopenia / Delayed / 0-1.0
elevated hepatic enzymes / Delayed / 0-1.0
cholelithiasis / Delayed / 0-1.0
cataracts / Delayed / 0-1.0
impotence (erectile dysfunction) / Delayed / 0-1.0
palpitations / Early / 0.5-0.9
sinus tachycardia / Rapid / 0.5-0.9
gout / Delayed / 0.5-0.9
QT prolongation / Rapid / Incidence not known
dysphonia / Delayed / Incidence not known
respiratory depression / Rapid / Incidence not known
physiological dependence / Delayed / Incidence not known
psychological dependence / Delayed / Incidence not known
hyponatremia / Delayed / Incidence not known
infertility / Delayed / Incidence not known
adrenocortical insufficiency / Delayed / Incidence not known

Mild

nausea / Early / 13.0-40.0
vertigo / Early / 0.5-33.0
dizziness / Early / 7.0-33.0
headache / Early / 3.0-32.0
drowsiness / Early / 5.0-25.0
vomiting / Early / 3.0-17.0
flushing / Rapid / 0-15.8
agitation / Early / 0-14.0
tremor / Early / 0-14.0
anxiety / Delayed / 0-14.0
emotional lability / Early / 0-14.0
xerostomia / Early / 1.0-13.1

dyspepsia / Early / 1.0-13.0
asthenia / Delayed / 0-12.0
pruritus / Rapid / 3.0-11.9
insomnia / Early / 1.0-10.9
diarrhea / Early / 0-10.0
diaphoresis / Early / 0-9.0
anorexia / Delayed / 0.7-5.9
arthralgia / Delayed / 1.0-5.4
malaise / Early / 0-5.0
syncope / Early / 0-5.0
paresthesias / Delayed / 0-5.0
increased urinary frequency / Early / 0-5.0
infection / Delayed / 0-5.0
fever / Early / 0-5.0
weight loss / Delayed / 0-5.0
myalgia / Early / 0-5.0
flatulence / Early / 0.5-4.9
abdominal pain / Early / 1.0-4.9
fatigue / Early / 1.0-4.9
weakness / Early / 1.0-4.9
lethargy / Early / 1.0-4.9
sneezing / Early / 1.0-4.9
nasal congestion / Early / 1.0-4.9
rhinorrhea / Early / 1.0-4.9
cough / Delayed / 1.0-4.9
hypoesthesia / Delayed / 1.0-4.9
miosis / Early / 1.0-4.9
restlessness / Early / 1.0-4.9
rash / Early / 1.0-4.9
chills / Rapid / 1.0-4.9
rhinitis / Early / 1.0-4.9
pharyngitis / Delayed / 1.0-4.9
sinusitis / Delayed / 1.0-4.9
influenza / Delayed / 1.0-4.9
back pain / Delayed / 1.0-4.9
gastroesophageal reflux / Delayed / 0-1.0
dental pain / Delayed / 0-1.0
yawning / Early / 0-1.0
hyperkinesis / Delayed / 0-1.0
night sweats / Early / 0-1.0
irritability / Delayed / 0-1.0
pallor / Early / 0-1.0
urticaria / Rapid / 0-1.0
menstrual irregularity / Delayed / 0-1.0
tinnitus / Delayed / 0-1.0
libido decrease / Delayed / 0-1.0
ecchymosis / Delayed / 0.5-0.9
muscle cramps / Delayed / 0.5-0.9
gonadal suppression / Delayed / Incidence not known
amenorrhea / Delayed / Incidence not known

DRUG INTERACTIONS

Abiraterone: (Moderate) Monitor for reduced efficacy of tramadol and signs of opioid withdrawal if coadministration with abiraterone is necessary; also monitor for tramadol-related adverse reactions, including seizures and serotonin syndrome. Consider increasing the dose of tramadol if clinically appropriate. If abiraterone is discontinued, consider a dose reduction of tramadol and frequently monitor for signs or respiratory depression and sedation. Tramadol is metabolized by CYP2D6 to its active metabolite, M1; M1 is critical to the activity of tramadol. Abiraterone is a moderate CYP2D6 inhibitor. Concomitant use with CYP2D6 inhibitors may result in an increase in tramadol plasma levels and a decrease in the levels of the active metabolite, M1. In patients who have developed physical dependence to tramadol, decreased M1 levels may result in opioid withdrawal or reduced efficacy while increased tramadol levels may cause serotonin syndrome or seizures.
Acetaminophen; Butalbital: (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate.
Acetaminophen; Butalbital; Caffeine: (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate.
Acetaminophen; Butalbital; Caffeine; Codeine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate.

Acetaminophen; Caffeine; Dihydrocodeine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Acetaminophen; Codeine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Acetaminophen; Dextromethorphan; Doxylamine: (Moderate) Concomitant use of opioid agonists with doxylamine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with doxylamine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Acetaminophen; Dextromethorphan; Phenylephrine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Acetaminophen; Diphenhydramine: (Moderate) Concomitant use of opioid agonists with diphenhydramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with diphenhydramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Acetaminophen; Hydrocodone: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Acetaminophen; Oxycodone: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Acetaminophen; Pentazocine: (Major) Avoid the concomitant use of pentazocine and opiate agonists, such as tramadol. Pentazocine is a mixed opiate agonist/antagonist that may block the effects of opiate agonists and reduce analgesic effects. Pentazocine may cause withdrawal symptoms in patients receiving chronic opiate agonists. There is also a potential increased risk of seizures if tramadol and pentazocine are given concurrently. Concurrent use of pentazocine with other opiate agonists can cause additive CNS, respiratory, and hypotensive effects. The additive or antagonistic effects are dependent upon the dose of the opiate agonist used; antagonistic effects are more common at low to moderate doses of the opiate agonist.
Acetaminophen; Propoxyphene: (Major) As propoxyphene is a moderate CYP2D6 inhibitor and tramadol is primarily metabolized by CYP2D6 (and CYP3A4), concurrent therapy may decrease tramadol metabolism. This interaction may result in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of either or both CYP2D6 and CYP3A4 is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.
Alfentanil: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Aliskiren; Amlodipine: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with amlodipine is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of amlodipine, a weak CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Aliskiren; Amlodipine; Hydrochlorothiazide, HCTZ: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with amlodipine is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of amlodipine, a weak CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist. (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Aliskiren; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Almotriptan: (Moderate) Caution is advised when tramadol is coadministered with serotonin-receptor agonists because of the potential for serotonin syndrome. If concomitant treatment of tramadol and a serotonin-receptor agonist is clinically warranted, careful observation of the patient is advised, especially during the initial time both drugs are used together and during a dose increase of either tramadol or the serotonin-receptor agonist.
Alprazolam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Amifampridine: (Major) Carefully consider the need for concomitant treatment with tramadol and amifampridine, as coadministration may increase the risk of seizures. If coadministration occurs, closely monitor patients for seizure activity. Seizures have been observed in patients without a history of seizures taking amifampridine at recommended doses. Tramadol may increase the risk of seizures.
Amiloride: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when potassium-sparing diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Amiloride; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when potassium-sparing diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone. (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Amiodarone: (Moderate) Use of amiodarone concurrently with tramadol may inhibit tramadol metabolism. Decreased efficacy and possibly increased side effects may occur due to increased tramadol serum concentrations and decreased serum concentrations of the active metabolite.
Amitriptyline; Chlordiazepoxide: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Amlodipine: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with amlodipine is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of amlodipine, a weak CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Amlodipine; Atorvastatin: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with amlodipine is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of amlodipine, a weak CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Amlodipine; Benazepril: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with amlodipine is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of amlodipine, a weak CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Amlodipine; Hydrochlorothiazide, HCTZ; Olmesartan: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with amlodipine is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of amlodipine, a weak CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist. (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Amlodipine; Hydrochlorothiazide, HCTZ; Valsartan: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with amlodipine is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of amlodipine, a weak CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist. (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Amlodipine; Olmesartan: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with amlodipine is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of amlodipine, a weak CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Amlodipine; Telmisartan: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with amlodipine is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of amlodipine, a weak CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Amlodipine; Valsartan: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with amlodipine is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of amlodipine, a weak CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Amobarbital: (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate.
Amoxapine: (Major) Concomitant use of tramadol with amoxapine may cause excessive sedation and somnolence and increase the risk for seizures. Limit the use of tramadol with amoxapine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and the potential increased risk for seizures.
Amphetamine; Dextroamphetamine Salts: (Major) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering amphetamines with other drugs that have serotonergic properties such as tramadol. Serotonin syndrome is characterized by the rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Further study is needed to fully elucidate the severity and frequency of adverse effects that may occur from concomitant administration of amphetamines and tramadol. Patients receiving tramadol and an amphetamine should be monitored for the emergence of serotonin syndrome, particularly during treatment initiation and during dosage increases. The amphetamine and tramadol should be discontinued if serotonin syndrome occurs and supportive symptomatic treatment should be initiated. In addition, the risk of seizures from the use of tramadol may be increased with concomitant use of CNS stimulants that may induce seizures, including the amphetamines. Extreme caution and close clinical monitoring is recommended if these agents must be used together.
Anticholinergics: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Apalutamide: (Moderate) Monitor for reduced efficacy of tramadol and signs of opioid withdrawal if coadministration with apalutamide is necessary; consider increasing the dose of tramadol as needed. If apalutamide is discontinued, consider a dose reduction of tramadol and frequently monitor for signs or respiratory depression and sedation. Tramadol is a CYP3A4 substrate and apalutamide is a strong CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease tramadol levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Apomorphine: (Major) Concomitant use of opioid agonists with apomorphine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with apomorphine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. Dopaminergic agents like apomorphine have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment.

Aprepitant, Fosaprepitant: (Moderate) Use caution if tramadol and aprepitant, fosaprepitant are used concurrently and monitor for an increase in tramadol-related adverse effects for several days after administration of a multi-day aprepitant regimen. Tramadol is a CYP3A4 substrate. Aprepitant, when administered as a 3-day oral regimen (125 mg/80 mg/80 mg), is a moderate CYP3A4 inhibitor and inducer and may increase plasma concentrations of tramadol. For example, a 5-day oral aprepitant regimen increased the AUC of another CYP3A4 substrate, midazolam (single dose), by 2.3-fold on day 1 and by 3.3-fold on day 5. After a 3-day oral aprepitant regimen, the AUC of midazolam (given on days 1, 4, 8, and 15) increased by 25% on day 4, and then decreased by 19% and 4% on days 8 and 15, respectively. As a single 125 mg or 40 mg oral dose, the inhibitory effect of aprepitant on CYP3A4 is weak, with the AUC of midazolam increased by 1.5-fold and 1.2-fold, respectively. After administration, fosaprepitant is rapidly converted to aprepitant and shares many of the same drug interactions. However, as a single 150 mg intravenous dose, fosaprepitant only weakly inhibits CYP3A4 for a duration of 2 days; there is no evidence of CYP3A4 induction. Fosaprepitant 150 mg IV as a single dose increased the AUC of midazolam (given on days 1 and 4) by approximately 1.8-fold on day 1; there was no effect on day 4. Less than a 2-fold increase in the midazolam AUC is not considered clinically important.
Aripiprazole: (Moderate) Concomitant use of tramadol with aripiprazole may cause excessive sedation, somnolence, and increased risk of seizure. Limit the use of tramadol with aripiprazole to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and seizures.
Artemether; Lumefantrine: (Moderate) Lumefantrine is an inhibitor and tramadol is a substrate/inhibitor of the CYP2D6 isoenzyme; therefore, coadministration may lead to increased tramadol concentrations. Concomitant use warrants caution due to the potential for increased side effects.
Asenapine: (Moderate) Concomitant use of tramadol with asenapine may cause excessive sedation, somnolence, and increased risk of seizure. Limit the use of tramadol with asenapine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and seizures.
Aspirin, ASA; Butalbital; Caffeine: (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate.
Aspirin, ASA; Butalbital; Caffeine; Codeine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate.
Aspirin, ASA; Caffeine; Dihydrocodeine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Aspirin, ASA; Caffeine; Orphenadrine: (Major) Concomitant use of tramadol with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.
Aspirin, ASA; Carisoprodol: (Major) Concomitant use of tramadol with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.
Aspirin, ASA; Carisoprodol; Codeine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Major) Concomitant use of tramadol with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.
Aspirin, ASA; Oxycodone: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Atazanavir; Cobicistat: (Major) As cobicistat is a CYP2D6 and CYP3A4 inhibitor and tramadol is primarily metabolized by CYP2D6 and CYP3A4, concurrent therapy may decrease tramadol metabolism; reduced tramadol dose may be needed during coadministration. This interaction may result in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of either or both CYP2D6 and CYP3A4 is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.
Atenolol; Chlorthalidone: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Atropine: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Atropine; Benzoic Acid; Hyoscyamine; Methenamine; Methylene Blue; Phenyl Salicylate: (Severe) Tramadol use is contraindicated in patients who are receiving or who have received monoamine oxidase inhibitors (MAOIs) within the previous 14 days. Methylene blue is a reversible inhibitor of MAO. Concomitant use of tramadol with other serotonergic drugs such as MAOIs may result in serious adverse effects including serotonin syndrome or seizures. MAOIs may cause additive CNS depression, respiratory depression, drowsiness, dizziness, or hypotension when used with opiate agonists such as tramadol. (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Atropine; Difenoxin: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Atropine; Diphenoxylate: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used

concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Atropine; Edrophonium: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Atropine; Hyoscyamine; Phenobarbital; Scopolamine: (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate. (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Azelastine: (Major) Concomitant use of opioid agonists with azelastine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with azelastine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Azelastine; Fluticasone: (Major) Concomitant use of opioid agonists with azelastine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with azelastine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Azilsartan; Chlorthalidone: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Baclofen: (Major) Concomitant use of tramadol with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.

Barbiturates: (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate.

Belladonna Alkaloids; Ergotamine; Phenobarbital: (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate. (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Belladonna; Opium: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Benazepril; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Bendroflumethiazide; Nadolol: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Benzhydrocodone; Acetaminophen: (Major) Concomitant use of other opiate agonists with tramadol may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of other opiate pain medications with tramadol to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If benzhydrocodone is initiated in a patient taking tramadol, reduce the initial dosage and titrate to clinical response. If tramadol is prescribed in a patient taking benzhydrocodone, use a lower initial dose of tramadol and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Careful monitoring, particularly during treatment initiation and dose adjustment, is recommended during coadministration of benzhydrocodone and tramadol because of the potential risk of serotonin syndrome. Discontinue benzhydrocodone if serotonin syndrome is suspected. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome. Concomitant use of tramadol increases the seizure risk in patients taking other opiate agonists.

Benzoic Acid; Hyoscyamine; Methenamine; Methylene Blue; Phenyl Salicylate: (Severe) Tramadol use is contraindicated in patients who are receiving or who have received monoamine oxidase inhibitors (MAOIs) within the previous 14 days. Methylene blue is a reversible inhibitor of MAO. Concomitant use of tramadol with other serotonergic drugs such as MAOIs may result in serious adverse effects including serotonin syndrome or seizures. MAOIs may cause additive CNS depression, respiratory depression, drowsiness, dizziness, or hypotension when used with opiate agonists such as tramadol. (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Benzphetamine: (Moderate) Serotonin syndrome may occur during coadministration of serotonergic drugs such as amphetamines and tramadol. At high doses, amphetamines can increase serotonin release, as well as act as serotonin agonists. An additive risk of seizures is also possible.

Inform patients taking this combination of the possible increased risk of serotonin syndrome and seizures and monitor for adverse effects particularly after a dose increase or the addition of interacting medications. Discontinue all serotonergic agents if serotonin syndrome occurs and implement appropriate medical management.
Benztropine: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Bisoprolol; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Boceprevir: (Moderate) Close clinical monitoring is advised when administering tramadol with boceprevir due to an increased potential for tramadol-related adverse events. If tramadol dose adjustments are made, re-adjust the dose upon completion of boceprevir treatment. Although this interaction has not been studied, predictions about the interaction can be made based on the metabolic pathway of tramadol. Tramadol is partially metabolized by the hepatic isoenzyme CYP3A4; boceprevir inhibits this isoenzyme. Coadministration may result in elevated tramadol plasma concentrations.
Brexpiprazole: (Major) Concomitant use of tramadol with brexpiprazole may cause excessive sedation, somnolence, and increased risk of seizures. Limit the use of opioid pain medications with brexpiprazole to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and seizures.
Brigatinib: (Moderate) Monitor for reduced efficacy of tramadol and signs of opioid withdrawal if coadministration with brigatinib is necessary; consider increasing the dose of tramadol as needed. If brigatinib is discontinued, consider a dose reduction of tramadol and frequently monitor for seizures, serotonin syndrome, and signs of respiratory depression and sedation. Tramadol is a CYP3A4 substrate. At clinically relevant concentrations, brigatinib induced CYP3A via activation of the pregnane X receptor (PXR); this may decrease concentrations of sensitive CYP3A substrates. Concomitant use with CYP3A4 inducers can decrease tramadol levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Brompheniramine: (Moderate) Concomitant use of opioid agonists with brompheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with brompheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Brompheniramine; Carbetapentane; Phenylephrine: (Moderate) Concomitant use of opioid agonists with brompheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with brompheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including tramadol.
Brompheniramine; Dextromethorphan; Guaifenesin: (Moderate) Concomitant use of opioid agonists with brompheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with brompheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Brompheniramine; Guaifenesin; Hydrocodone: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Moderate) Concomitant use of opioid agonists with brompheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with brompheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Brompheniramine; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Moderate) Concomitant use of opioid agonists with brompheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with brompheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Brompheniramine; Pseudoephedrine: (Moderate) Concomitant use of opioid agonists with brompheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with brompheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Bumetanide: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when loop diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Buprenorphine: (Major) Buprenorphine is a mixed opiate agonist/antagonist with strong affinity for the mu-receptor that may partially block the effects of full mu-receptor opiate agonists and reduce analgesic effects. In some cases of acute pain, trauma, or during surgical management, opiate-dependent patients receiving buprenorphine maintenance therapy may require concurrent treatment with opiate agonists, such as tramadol. In these cases, health care professionals must exercise caution in opiate agonist dose selection, as higher doses of an opiate agonist may be required to compete with buprenorphine at the mu-receptor. Management strategies may include adding a short-acting opiate agonist to achieve analgesia in the presence of buprenorphine, discontinuation of buprenorphine and use of an opiate agonist to avoid withdrawal and achieve analgesia, or conversion of buprenorphine to methadone while using additional opiate agonists if needed. Closely monitor patients for CNS or respiratory depression. When buprenorphine is used for analgesia, avoid co-use with opiate agonists. Buprenorphine may cause withdrawal symptoms in patients receiving chronic opiate agonists as well as possibly potentiate CNS, respiratory, and hypotensive effects. The additive or antagonistic effects are dependent upon the dose of the opiate agonist used; antagonistic effects are more common at low to moderate doses of the opiate agonist. Additionally, concurrent use of opiates with other drugs that modulate serotonergic function, such as tramadol, has resulted in serotonin syndrome in some cases. Serotonin syndrome is characterized by the rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. If combination treatment is required, patients should be carefully observed, particularly during treatment initiation and during dose adjustments of the serotonergic drug; discontinue buprenorphine if serotonin syndrome is suspected. Consider a dose reduction of one or both drugs because of the potential for additive pharmacological effects. There is also a potential for increased risk of seizures if tramadol is given with other opiates.
Buprenorphine; Naloxone: (Major) Buprenorphine is a mixed opiate agonist/antagonist with strong affinity for the mu-receptor that may partially block the effects of full mu-receptor opiate agonists and reduce analgesic effects. In some cases of acute pain, trauma, or during surgical management, opiate-dependent patients receiving buprenorphine maintenance therapy may require concurrent treatment with opiate agonists, such as tramadol. In these cases, health care professionals must exercise caution in opiate agonist dose selection, as higher doses of an opiate agonist may be required to compete with buprenorphine at the mu-receptor. Management strategies may include adding a short-acting opiate agonist to achieve analgesia in the presence of buprenorphine, discontinuation of buprenorphine and use of an opiate agonist to avoid withdrawal and achieve analgesia, or conversion of buprenorphine to methadone while using additional opiate agonists if needed. Closely monitor patients for CNS or respiratory depression. When buprenorphine is used for analgesia, avoid co-use with opiate agonists. Buprenorphine may cause withdrawal symptoms in patients receiving chronic opiate agonists as well as possibly potentiate CNS, respiratory, and hypotensive effects. The additive or antagonistic effects are dependent upon the dose of the opiate agonist used; antagonistic effects are more common at low to moderate doses of the opiate agonist. Additionally, concurrent use of opiates with other drugs that modulate serotonergic function, such as tramadol, has resulted in serotonin syndrome in some cases. Serotonin syndrome is characterized by the rapid development of hyperthermia, hypertension,

myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. If combination treatment is required, patients should be carefully observed, particularly during treatment initiation and during dose adjustments of the serotonergic drug; discontinue buprenorphine if serotonin syndrome is suspected. Consider a dose reduction of one or both drugs because of the potential for additive pharmacological effects. There is also a potential for increased risk of seizures if tramadol is given with other opiates. (Moderate) Naloxone should be used cautiously in situations of tramadol overdose. Naloxone administration may increase the risk of seizures in these patients. Furthermore, naloxone will reverse some but not all symptoms caused by tramadol overdosage. It is not clear if such precautions would also apply to the use of other opiate antagonists with tramadol.

Bupropion: (Major) Increased serum concentrations of tramadol and reduced serum concentrations of the O-desmethyltramadol metabolite (M1) would be expected from concurrent use of tramadol and a CYP2D6 inhibitor such as bupropion. As the analgesic activity of tramadol is due to both the parent drug and M1, inhibition of CYP2D6 by bupropion may affect the analgesic effect of tramadol; reduced analgesic effects are possible. Also, administration of tramadol may enhance the seizure risk in patients taking other medications that decrease the seizure threshold such as bupropion.

Bupropion; Naltrexone: (Major) Increased serum concentrations of tramadol and reduced serum concentrations of the O-desmethyltramadol metabolite (M1) would be expected from concurrent use of tramadol and a CYP2D6 inhibitor such as bupropion. As the analgesic activity of tramadol is due to both the parent drug and M1, inhibition of CYP2D6 by bupropion may affect the analgesic effect of tramadol; reduced analgesic effects are possible. Also, administration of tramadol may enhance the seizure risk in patients taking other medications that decrease the seizure threshold such as bupropion. (Moderate) Naloxone should be used cautiously in situations of tramadol overdose. Naloxone administration may increase the risk of seizures in these patients. Furthermore, naloxone will reverse some but not all symptoms caused by tramadol overdosage. It is not clear if such precautions would also apply to the use of other opiate antagonists with tramadol.

Buspirone: (Moderate) Tramadol can cause additive CNS depression when used with other agents that are CNS depressants including buspirone.

Butabarbital: (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate.

Butorphanol: (Major) Avoid the concomitant use of butorphanol and opiate agonists, such as tramadol. Butorphanol is a mixed opiate agonist/antagonist that may block the effects of opiate agonists and reduce analgesic effects. Butorphanol may cause withdrawal symptoms in patients receiving chronic opiate agonists. Concurrent use of butorphanol with other opiate agonists can cause additive CNS, respiratory, and hypotensive effects. The additive or antagonistic effects are dependent upon the dose of the opiate agonist used; antagonistic effects are more common at low to moderate doses of the opiate agonist. There is also a potential increased risk of seizures if tramadol is given with other opiates.

Candesartan; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Cannabidiol: (Moderate) Concomitant use of opioid agonists with cannabidiol may cause excessive sedation and somnolence. Limit the use of opioid pain medications with cannabidiol to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Capsaicin; Metaxalone: (Major) Concomitant use of tramadol with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.

Captopril; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Carbamazepine: (Moderate) Monitor for reduced efficacy of tramadol and signs of opioid withdrawal if coadministration with carbamazepine is necessary; consider increasing the dose of tramadol as needed. If carbamazepine is discontinued, consider a dose reduction of tramadol and frequently monitor for seizures, serotonin syndrome, and signs of respiratory depression and sedation. Tramadol is a CYP3A4 substrate and carbamazepine is a strong CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease tramadol levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.

Carbetapentane; Chlorpheniramine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including tramadol.

Carbetapentane; Chlorpheniramine; Phenylephrine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including tramadol.

Carbetapentane; Diphenhydramine; Phenylephrine: (Moderate) Concomitant use of opioid agonists with diphenhydramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with diphenhydramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including tramadol.

Carbetapentane; Guaifenesin: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including tramadol.

Carbetapentane; Guaifenesin; Phenylephrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including tramadol.

Carbetapentane; Phenylephrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including tramadol.

Carbetapentane; Phenylephrine; Pyrilamine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including tramadol.

Carbetapentane; Pseudoephedrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including tramadol.

Carbetapentane; Pyrilamine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including tramadol.

Carbinoxamine; Hydrocodone; Phenylephrine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.

Carbinoxamine; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.

Cariprazine: (Moderate) Concurrent use of tramadol and cariprazine should be avoided if possible. Antipsychotics may enhance the seizure risk of tramadol. Additive CNS depression may also be seen with the concomitant use of tramadol and cariprazine.
Carisoprodol: (Major) Concomitant use of tramadol with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.
Celecoxib: (Moderate) Monitor for reduced efficacy of tramadol and signs of opioid withdrawal if coadministration with celecoxib is necessary; also monitor for tramadol-related adverse reactions, including seizures and serotonin syndrome. Consider increasing the dose of tramadol if clinically appropriate. If celecoxib is discontinued, consider a dose reduction of tramadol and frequently monitor for signs or respiratory depression and sedation. Tramadol is metabolized by CYP2D6 to its active metabolite, M1; M1 is critical to the activity of tramadol. Celecoxib is a CYP2D6 inhibitor. Concomitant use with CYP2D6 inhibitors may result in an increase in tramadol plasma concentrations and a decrease in the concentrations of the active metabolite, M1. In patients who have developed physical dependence to tramadol, decreased M1 concentrations may result in opioid withdrawal or reduced efficacy while increased tramadol concentrations may cause serotonin syndrome or seizures.
Ceritinib: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with ceritinib is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of ceritinib, a strong CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Cetirizine: (Moderate) Concomitant use of opioid agonists with cetirizine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with cetirizine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Cetirizine; Pseudoephedrine: (Moderate) Concomitant use of opioid agonists with cetirizine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with cetirizine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Chloral Hydrate: (Major) Concomitant use of opioid agonists with chloral hydrate may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chloral hydrate to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Chlordiazepoxide: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Chlordiazepoxide; Clidinium: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Chlorothiazide: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Chlorpheniramine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Chlorpheniramine; Codeine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Chlorpheniramine; Dextromethorphan: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Chlorpheniramine; Dihydrocodeine; Phenylephrine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Chlorpheniramine; Dihydrocodeine; Pseudoephedrine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Chlorpheniramine; Guaifenesin; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Chlorpheniramine; Hydrocodone: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also,

tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpheniramine; Hydrocodone; Phenylephrine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpheniramine; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpheniramine; Phenylephrine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpheniramine; Pseudoephedrine: (Moderate) Concomitant use of opioid agonists with chlorpheniramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with chlorpheniramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Chlorpromazine: (Moderate) Concurrent use of tramadol and chlorpromazine should be avoided if possible. Antipsychotics may enhance the seizure risk of tramadol. In addition, in vitro data suggest that chlorpromazine has CYP2D6 inhibitory effects and has the potential to decrease the metabolism of CYP2D6 substrates such as tramadol. Although the full pharmacologic impact of increased tramadol exposure is unknown, close monitoring for serious adverse effects, such as seizures, is advisable. In addition, serotonin syndrome may occur during use of tramadol with medications that impair its metabolism. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, hyperreflexia, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Because the analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), CYP2D6 inhibition by chlorpromazine may alter the analgesic response to tramadol. Additive CNS depression may also be seen with the concomitant use of tramadol and chlorpromazine.

Chlorthalidone: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Chlorthalidone; Clonidine: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Chlorzoxazone: (Major) Concomitant use of tramadol with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.

Cinacalcet: (Moderate) Coadministration of cinacalcet, a strong CYP2D6 inhibitor, with tramadol, a CYP2D6 substrate, may decrease tramadol metabolism. This interaction may result in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of CYP2D6 metabolism is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.

Citalopram: (Moderate) Serotonin syndrome can occur during concomitant use of opiate agonists like tramadol with serotonergic drugs, such as citalopram. Several cases of serotonin syndrome have been reported after the administration of tramadol with an SSRI. Post-marketing reports implicate the concurrent use of SSRIs with tramadol in some cases of seizures. Lastly, citalopram is a weak inhibitor of CYP2D6. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of CYP2D6 metabolism is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. If serotonin syndrome is suspected, citalopram and concurrent serotonergic agents should be discontinued.

Clemastine: (Moderate) Concomitant use of opioid agonists with clemastine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with clemastine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Clobazam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, in vivo data suggest clobazam is a CYP2D6 inhibitor. Because the analgesic activity of tramadol is due to both the parent drug and O-desmethyltramadol (M1), inhibition of CYP2D6 by clobazam may affect the analgesic response to tramadol. Reduced analgesic effects of tramadol are possible, and the risk for serious adverse effects such as seizures may be increased.

Clonazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Clopidogrel: (Moderate) Coadministration of opioid agonists, such as tramadol, delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Clorazepate: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a

benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Clozapine: (Moderate) Concurrent use of tramadol and clozapine should be avoided if possible. Antipsychotics may enhance the seizure risk of tramadol. In addition, in vitro data suggest that clozapine has CYP2D6 inhibitory effects and may increase plasma concentrations of CYP2D6 substrates such as tramadol. Although the full pharmacologic impact of increased tramadol exposure is unknown, close monitoring for serious adverse effects, such as seizures, is advisable. In addition, serotonin syndrome may occur during use of tramadol with medications that impair its metabolism. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, hyperreflexia, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Because the analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), CYP2D6 inhibition by clozapine may alter the analgesic response to tramadol. Additive CNS depression may also be seen with the concomitant use of tramadol and clozapine.
Cobicistat: (Major) As cobicistat is a CYP2D6 and CYP3A4 inhibitor and tramadol is primarily metabolized by CYP2D6 and CYP3A4, concurrent therapy may decrease tramadol metabolism; reduced tramadol dose may be needed during coadministration. This interaction may result in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of either or both CYP2D6 and CYP3A4 is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.
Cocaine: (Major) Cocaine use has been associated with precipitating seizures. Since tramadol decreases the seizure threshold, an increased risk of seizures may be seen with concomitant use of these two drugs.
Codeine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Codeine; Guaifenesin: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Codeine; Phenylephrine; Promethazine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Moderate) Caution is advisable during concurrent use of tramadol and promethazine. Seizures have been reported in patients receiving monotherapy with both tramadol and promethazine at recommended doses. Concomitant use of tramadol and promethazine may increase the risk of seizures. In addition, due to the primary CNS effects of promethazine, caution is advisable during use of other centrally acting medications such as tramadol. Impairment of metabolism of tramadol by CYP2D6 inhibitors, such as promethazine, may increase the risk of serotonin syndrome. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6 inhibitor may decrease tramadol analgesic efficacy.
Codeine; Promethazine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Moderate) Caution is advisable during concurrent use of tramadol and promethazine. Seizures have been reported in patients receiving monotherapy with both tramadol and promethazine at recommended doses. Concomitant use of tramadol and promethazine may increase the risk of seizures. In addition, due to the primary CNS effects of promethazine, caution is advisable during use of other centrally acting medications such as tramadol. Impairment of metabolism of tramadol by CYP2D6 inhibitors, such as promethazine, may increase the risk of serotonin syndrome. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6 inhibitor may decrease tramadol analgesic efficacy.
COMT inhibitors: (Major) Concomitant use of opioid agonists with COMT inhibitors may cause excessive sedation and somnolence. Limit the use of opioid pain medications with COMT inhibitors to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. Dopaminergic agents like entacapone and tolcapone have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment.
Crizotinib: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with crizotinib is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of crizotinib, a moderate CYP3A inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Cyclobenzaprine: (Major) Concomitant use of tramadol with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Additionally, concurrent use of tramadol and cyclobenzaprine increases the possibility of developing serotonin syndrome and enhances the risk of seizures in patients taking tramadol. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Closely monitor the patient for signs and symptoms of serotonin syndrome. Immediately discontinue concurrent use if serotonin syndrome occurs. Educate patients about the risks and symptoms of respiratory depression and sedation.
Cyproheptadine: (Moderate) Concomitant use of opioid agonists with cyproheptadine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with cyproheptadine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Dacomitinib: (Moderate) Coadministration of dacomitinib with tramadol may decrease tramadol metabolism resulting in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. Tramadol is a CYP2D6 substrate; dacomitinib is a strong CYP2D6 inhibitor. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of CYP2D6 metabolism is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.
Dantrolene: (Major) Concomitant use of tramadol with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.
Darifenacin: (Moderate) Coadministration of darifenacin with tramadol may decrease tramadol metabolism resulting in decreased tramadol efficacy and/or increased tramadol-induced risks for respiratory depression, serotonin syndrome, or seizures. Tramadol is a CYP2D6 substrate; darifenacin is a moderate CYP2D6 inhibitor. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of CYP2D6 metabolism is expected to result in reduced metabolic clearance of tramadol that may increase the risk of tramadol-related adverse events including respiratory depression, serotonin syndrome, and seizures. In addition, the concomitant use of these drugs together may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates such as tramadol increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect. Both agents may also cause drowsiness or blurred vision, and patients should use care in driving or performing other hazardous tasks until the effects of the drugs are known.
Darunavir: (Major) Concurrent use of tramadol with darunavir may decrease the CYP3A4 and CYP2D6 metabolism of tramadol; reduced tramadol

dose may be needed during coadministration. This interaction may result in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of either or both CYP2D6 and CYP3A4 is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.

Darunavir; Cobicistat: (Major) As cobicistat is a CYP2D6 and CYP3A4 inhibitor and tramadol is primarily metabolized by CYP2D6 and CYP3A4, concurrent therapy may decrease tramadol metabolism; reduced tramadol dose may be needed during coadministration. This interaction may result in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of either or both CYP2D6 and CYP3A4 is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. (Major) Concurrent use of tramadol with darunavir may decrease the CYP3A4 and CYP2D6 metabolism of tramadol; reduced tramadol dose may be needed during coadministration. This interaction may result in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of either or both CYP2D6 and CYP3A4 is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.

Darunavir; Cobicistat; Emtricitabine; Tenofovir alafenamide: (Major) As cobicistat is a CYP2D6 and CYP3A4 inhibitor and tramadol is primarily metabolized by CYP2D6 and CYP3A4, concurrent therapy may decrease tramadol metabolism; reduced tramadol dose may be needed during coadministration. This interaction may result in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of either or both CYP2D6 and CYP3A4 is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. (Major) Concurrent use of tramadol with darunavir may decrease the CYP3A4 and CYP2D6 metabolism of tramadol; reduced tramadol dose may be needed during coadministration. This interaction may result in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of either or both CYP2D6 and CYP3A4 is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.

Dasabuvir; Ombitasvir; Paritaprevir; Ritonavir: (Major) Tramadol is primarily metabolized by CYP2D6 and CYP3A4; drugs that inhibit these enzymes, such as ritonavir, may decrease the metabolism of tramadol. This may result in a decreased concentration of the active metabolite (O-desmethyltramadol) leading to decreased analgesic effects and possibly increased side effects (seizures and serotonin syndrome) due to higher tramadol concentrations.

Delavirdine: (Moderate) Since tramadol is primarily metabolized by cytochrome P450 isoenzyme CYP2D6, agents that inhibit this enzyme, such as delavirdine, decrease the metabolism of tramadol. Concomitant use of these agents and tramadol may increase plasma levels of tramadol and decrease concentration of the active metabolite leading to decreased analgesic effects and possibly increased side effects due to higher tramadol concentrations.

Desvenlafaxine: (Major) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering serotonin norepinephrine reuptake inhibitors (SNRIs) with other drugs that have serotonergic properties such as tramadol. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. In one case, the addition of tramadol to extended-release venlafaxine (300 mg/day) and mirtazapine (30 mg/day) likely caused serotonin syndrome. A patient developed agitation, confusion, severe shivering, diaphoresis, myoclonus, hyperreflexia, mydriasis, tachycardia, and fever within 7 weeks of taking tramadol 400 mg daily. He had taken 300 mg tramadol without difficulty. Discontinuation of the 3 drugs and rehydration led to symptom resolution over 36 hours. Reinstitution of the antidepressants 3 days after patient presentation was uneventful. In addition, although clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 inhibition at doses of 100 mg/day, the manufacturer recommends that primary substrates of CYP2D6, such as tramadol, be dosed at the original level when coadministered with desvenlafaxine 100 mg or lower, or when desvenlafaxine is discontinued. The dose of these CYP2D6 substrates should be reduced by up to one-half if coadministered with desvenlafaxine 400 mg/day.

Deutetrabenazine: (Major) Concomitant use of opiate agonists with deutetrabenazine may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with deutetrabenazine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking deutetrabenazine, use a lower initial dose of the opiate and titrate to clinical response. If deutetrabenazine is prescribed for a patient taking an opiate agonist, use a lower initial dose of deutetrabenazine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Dexmedetomidine: (Moderate) Concurrent use of dexmedetomidine with other CNS depressants, such as tramadol, could result in additive sedative effects and possibly prolong recovery from anesthesia.

Dextromethorphan; Diphenhydramine; Phenylephrine: (Moderate) Concomitant use of opioid agonists with diphenhydramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with diphenhydramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Dextromethorphan; Promethazine: (Moderate) Caution is advisable during concurrent use of tramadol and promethazine. Seizures have been reported in patients receiving monotherapy with both tramadol and promethazine at recommended doses. Concomitant use of tramadol and promethazine may increase the risk of seizures. In addition, due to the primary CNS effects of promethazine, caution is advisable during use of other centrally acting medications such as tramadol. Impairment of metabolism of tramadol by CYP2D6 inhibitors, such as promethazine, may increase the risk of serotonin syndrome. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6 inhibitor may decrease tramadol analgesic efficacy.

Dextromethorphan; Quinidine: (Moderate) As quinidine is a potent inhibitor of CYP2D6 and tramadol is partially metabolized by CYP2D6, concurrent therapy may decrease tramadol metabolism. This interaction may result in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of CYP2D6 metabolism is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.

Diazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If parental

diazepam is used with an opiate agonist, reduce the opiate agonist dosage by at least 1/3. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Dicyclomine: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Digoxin: (Moderate) An increased incidence of digoxin toxicity has been reported in some patients during post-marketing reports with the concurrent use of tramadol and digoxin.
Dihydrocodeine; Guaifenesin; Pseudoephedrine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Dimenhydrinate: (Moderate) Concomitant use of opioid agonists with dimenhydrinate may cause excessive sedation and somnolence. Limit the use of opioid pain medications with dimenhydrinate to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Diphenhydramine: (Moderate) Concomitant use of opioid agonists with diphenhydramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with diphenhydramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Diphenhydramine; Hydrocodone; Phenylephrine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Moderate) Concomitant use of opioid agonists with diphenhydramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with diphenhydramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Diphenhydramine; Ibuprofen: (Moderate) Concomitant use of opioid agonists with diphenhydramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with diphenhydramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Diphenhydramine; Naproxen: (Moderate) Concomitant use of opioid agonists with diphenhydramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with diphenhydramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Diphenhydramine; Phenylephrine: (Moderate) Concomitant use of opioid agonists with diphenhydramine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with diphenhydramine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Dolasetron: (Major) Because of the potential risk and severity of serotonin syndrome, use caution when administering dolasetron with other drugs that have serotonergic properties such as tramadol. If serotonin syndrome is suspected, discontinue dolasetron and concurrent serotonergic agents and initiate appropriate medical treatment. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.
Doxylamine: (Moderate) Concomitant use of opioid agonists with doxylamine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with doxylamine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Doxylamine; Pyridoxine: (Moderate) Concomitant use of opioid agonists with doxylamine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with doxylamine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Dronabinol: (Moderate) Dronabinol, THC can cause CNS depression. Tramadol use increases the risk of CNS depression and respiratory depression when used with other agents that are CNS depressants. Extreme caution is needed in using tramadol at the same time as other CNS depressants. A reduced dose of tramadol is recommended when used with another CNS depressant.
Dronedarone: (Moderate) Dronedarone is metabolized by CYP3A and is an inhibitor of CYP2D6 and CYP3A. Tramadol is a substrate for CYP2D6 and CYP3A4. The concomitant administration of dronedarone with CYP2D6 and CYP3A substrates may result in increased exposure of the substrate and should, therefore, be undertaken with caution.
Droperidol: (Major) Concomitant use of opioid agonists with droperidol may cause excessive sedation and somnolence. Limit the use of opioid pain medications with droperidol to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Duloxetine: (Major) Because of the potential risk and severity of serotonin syndrome or neuroleptic malignant syndrome-like reactions, caution should be observed when administering serotonin norepinephrine reuptake inhibitors (SNRIs) with other drugs that have serotonergic properties such as tramadol. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome. In one case, the addition of tramadol to extended-release venlafaxine (300 mg/day) and mirtazapine (30 mg/day) likely caused serotonin syndrome. A patient developed agitation, confusion, severe shivering, diaphoresis, myoclonus, hyperreflexia, mydriasis, tachycardia, and fever within 7 weeks of taking tramadol 400 mg daily. He had taken 300 mg tramadol without difficulty. Discontinuation of the 3 drugs and rehydration led to symptom resolution over 36 hours. Reinstitution of the antidepressants 3 days after patient presentation was uneventful. Also, duloxetine may inhibit the formation of the active M1 metabolite of tramadol by inhibiting CYP2D6. The inhibition of this metabolite may decrease the analgesic effectiveness of tramadol but increase the level of the parent compound, which has more serotonergic activity than the metabolite. The risk for serious adverse effects such as seizures and serotonin syndrome may be increased. Patients receiving tramadol in combination with an SNRI should be monitored for the emergence of serotonin syndrome, neuroleptic malignant syndrome-like reactions, or other adverse effects.
Efavirenz: (Moderate) The (+) enantiomer of tramadol preferentially undergoes N-demethylation, which is mediated by CYP3A4 and CYP2B6. Efavirenz is an inducer of CYP3A4 and CYP2B6. Coadministration may affect the metabolism of tramadol leading to altered tramadol exposure. Decreased serum tramadol concentrations and reduced efficacy may occur. In addition, both medications have been associated with the development of seizures; caution is advised.
Efavirenz; Emtricitabine; Tenofovir: (Moderate) The (+) enantiomer of tramadol preferentially undergoes N-demethylation, which is mediated by CYP3A4 and CYP2B6. Efavirenz is an inducer of CYP3A4 and CYP2B6. Coadministration may affect the metabolism of tramadol leading to altered tramadol exposure. Decreased serum tramadol concentrations and reduced efficacy may occur. In addition, both medications have been associated with the development of seizures; caution is advised.
Efavirenz; Lamivudine; Tenofovir Disoproxil Fumarate: (Moderate) The (+) enantiomer of tramadol preferentially undergoes N-demethylation, which is mediated by CYP3A4 and CYP2B6. Efavirenz is an inducer of CYP3A4 and CYP2B6. Coadministration may affect the metabolism of tramadol leading to altered tramadol exposure. Decreased serum tramadol concentrations and reduced efficacy may occur. In addition, both medications have been associated with the development of seizures; caution is advised.
Elagolix: (Moderate) Monitor for reduced efficacy of tramadol and signs of opioid withdrawal if coadministration with elagolix is necessary; consider increasing the dose of tramadol as needed. If elagolix is discontinued, consider a dose reduction of tramadol and frequently monitor for signs or

respiratory depression and sedation. Tramadol is a CYP3A4 substrate and elagolix is a weak to moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease tramadol levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Elbasvir; Grazoprevir: (Moderate) Administering acetaminophen; tramadol with elbasvir; grazoprevir may result in elevated tramadol plasma concentrations. Tramadol is a substrate of CYP3A; grazoprevir is a weak CYP3A inhibitor. If these drugs are used together, closely monitor for signs of adverse events.
Eletriptan: (Moderate) Caution is advised when tramadol is coadministered with serotonin-receptor agonists because of the potential for serotonin syndrome. If concomitant treatment of tramadol and a serotonin-receptor agonist is clinically warranted, careful observation of the patient is advised, especially during the initial time both drugs are used together and during a dose increase of either tramadol or the serotonin-receptor agonist.
Elexacaftor; tezacaftor; ivacaftor: (Minor) Use caution when administering ivacaftor and tramadol concurrently. Ivacaftor is an inhibitor of CYP3A and tramadol is partially metabolized by CYP3A. Co-administration can theoretically increase tramadol exposure leading to increased or prolonged therapeutic effects and adverse events; however, the clinical impact of this has not yet been determined.
Eliglustat: (Moderate) Coadministration of tramadol and eliglustat may result in a reduction in the metabolic conversion and clearance of tramadol, increasing the risk for serious adverse events including seizures and serotonin syndrome. In addition, coadministration of tramadol and eliglustat may result in decreased analgesia. If coadministration is necessary, monitor patients closely for tramadol-related adverse effects and diminished analgesic efficacy. The analgesic activity of tramadol is due to both the parent drug and the pharmacologically active metabolite M1. Because the metabolism of tramadol to M1 is dependent on CYP2D6 and eliglustat is an inhibitor of CYP2D6, therapeutic response may be affected.
Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Alafenamide: (Major) As cobicistat is a CYP2D6 and CYP3A4 inhibitor and tramadol is primarily metabolized by CYP2D6 and CYP3A4, concurrent therapy may decrease tramadol metabolism; reduced tramadol dose may be needed during coadministration. This interaction may result in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of either or both CYP2D6 and CYP3A4 is expected to result in reduced metabolic clearance of tramadol. This in tum may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.
Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Disoproxil Fumarate: (Major) As cobicistat is a CYP2D6 and CYP3A4 inhibitor and tramadol is primarily metabolized by CYP2D6 and CYP3A4, concurrent therapy may decrease tramadol metabolism; reduced tramadol dose may be needed during coadministration. This interaction may result in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of either or both CYP2D6 and CYP3A4 is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.
Enalapril; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Enzalutamide: (Moderate) Monitor for reduced efficacy of tramadol and signs of opioid withdrawal if coadministration with enzalutamide is necessary; consider increasing the dose of tramadol as needed. If enzalutamide is discontinued, consider a dose reduction of tramadol and frequently monitor for signs or respiratory depression and sedation. Tramadol is a CYP3A4 substrate and enzalutamide is a strong CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease tramadol levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Eprosartan; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Erythromycin: (Moderate) Administration of CYP3A4 inhibitors such as erythromycin with tramadol may affect the metabolism of tramadol leading to altered tramadol exposure. Increased serum tramadol concentrations may occur.
Erythromycin; Sulfisoxazole: (Moderate) Administration of CYP3A4 inhibitors such as erythromycin with tramadol may affect the metabolism of tramadol leading to altered tramadol exposure. Increased serum tramadol concentrations may occur.
Escitalopram: (Major) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering escitalopram with other drugs that have serotonergic properties such as tramadol. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome. Several cases of serotonin syndrome have been reported after the administration of tramadol with an SSRI. The combination of SSRIs and tramadol has also been associated with an increased risk of seizures. Post-marketing reports implicate the concurrent use of SSRIs with tramadol in some cases of seizures. Lastly, CYP2D6 inhibitors can prevent the formation of the active M1 metabolite of tramadol by inhibiting CYP2D6. Although escitalopram is a modest inhibitor of CYP2D6, the inhibition of the M1 metabolite may decrease the analgesic effectiveness of tramadol but increase the level of the parent compound, which has more serotonergic activity than the metabolite. Patients receiving tramadol in combination with an SSRI should be monitored for the emergence of serotonin syndrome or other adverse effects.
Esketamine: (Major) Concomitant use of opioid agonists with esketamine may cause excessive sedation and somnolence. Limit the use of opioid pain medication with esketamine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Patients who have received a dose of esketamine should be instructed not to drive or engage in other activities requiring complete mental alertness until the next day after a restful sleep. Educate patients about the risks and symptoms of excessive CNS depression.
Estazolam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Eszopiclone: (Moderate) Concomitant use of opioid agonists with eszopiclone may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Limit the use of opioid pain medications with eszopiclone to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
Ethacrynic Acid: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when loop diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Ethanol: (Major) Alcohol is associated with CNS depression. The combined use of alcohol and CNS depressants can lead to additive CNS depression, which could be dangerous in tasks requiring mental alertness and fatal in overdose. Alcohol taken with other CNS depressants can lead to additive respiratory depression, hypotension, profound sedation, or coma. Consider the patient's use of alcohol or illicit drugs when prescribing CNS depressant medications. In many cases, the patient should receive a lower dose of the CNS depressant initially if the patient is not likely to be compliant with avoiding alcohol.
Ethotoin: (Major) Tramadol may decrease the seizure threshold in some patients and thus potentially interfere with the ability of anticonvulsants to control seizures. The use of tramadol in patients on anticonvulsant medications for seizure therapy is not recommended. In addition, the hepatic metabolism of tramadol may be accelerated by the use of ethotoin, phenytoin, or fosphenytoin.
Everolimus: (Moderate) Monitor for an increase in tramadol-related adverse reactions, including serotonin syndrome, seizures, sedation, and respiratory depression, if coadministration with everolimus is necessary; the risk is greatest if everolimus is added to a stable dose of tramadol.

Consider decreasing the dose of tramadol if necessary. Everolimus is a weak CYP3A4 inhibitor as well as a CYP2D6 inhibitor. Tramadol is metabolized by both CYP3A4 and CYP2D6.

Ezogabine: (Moderate) Due to the CNS effects of ezogabine, an enhanced CNS depressant effect may occur during concurrent use of other centrally-acting medications such as tramadol. Patients should be monitored for excessive somnolence during concurrent therapy with this agent.

Fedratinib: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with fedratinib is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of fedratinib, a moderate CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.

Fentanyl: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.

Flavoxate: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Fluoxetine: (Moderate) Because of the potential risk and severity of serotonin syndrome or neuroleptic malignant syndrome-like reactions, caution should be observed when administering selective serotonin reuptake inhibitors (SSRIs) with other drugs that have serotonergic properties such as tramadol. Several cases of serotonin syndrome have been reported after the administration of tramadol with a SSRI. Concomitant use of tramadol also increases the seizure risk in patients taking selective serotonin reuptake inhibitors (SSRIs). Post-marketing reports implicate the concurrent use of SSRIs with tramadol in some cases of seizures. Lastly, SSRIs such as fluoxetine may inhibit the formation of the active M1 metabolite of tramadol by inhibiting CYP2D6. The inhibition of this metabolite may decrease the analgesic effectiveness of tramadol but increase the level of the parent compound, which has more serotonergic activity than the metabolite. Patients receiving tramadol in combination with an SSRI should be monitored for the emergence of serotonin syndrome, neuroleptic malignant syndrome-like reactions, or other adverse effects.

Fluoxetine; Olanzapine: (Moderate) Because of the potential risk and severity of serotonin syndrome or neuroleptic malignant syndrome-like reactions, caution should be observed when administering selective serotonin reuptake inhibitors (SSRIs) with other drugs that have serotonergic properties such as tramadol. Several cases of serotonin syndrome have been reported after the administration of tramadol with a SSRI. Concomitant use of tramadol also increases the seizure risk in patients taking selective serotonin reuptake inhibitors (SSRIs). Post-marketing reports implicate the concurrent use of SSRIs with tramadol in some cases of seizures. Lastly, SSRIs such as fluoxetine may inhibit the formation of the active M1 metabolite of tramadol by inhibiting CYP2D6. The inhibition of this metabolite may decrease the analgesic effectiveness of tramadol but increase the level of the parent compound, which has more serotonergic activity than the metabolite. Patients receiving tramadol in combination with an SSRI should be monitored for the emergence of serotonin syndrome, neuroleptic malignant syndrome-like reactions, or other adverse effects. (Moderate) Concurrent use of tramadol and olanzapine should be avoided if possible. Antipsychotics may enhance the seizure risk of tramadol. Additive CNS depression may also be seen with the concomitant use of tramadol and olanzapine.

Fluphenazine: (Moderate) Concurrent use of tramadol and fluphenazine should be avoided if possible. Antipsychotics may enhance the seizure risk of tramadol. In addition, in vitro data suggest that fluphenazine is a weak CYP2D6 inhibitor and has the potential to decrease the metabolism of CYP2D6 substrates such as tramadol. Although the full pharmacologic impact of increased tramadol exposure is unknown, close monitoring for serious adverse effects, such as seizures, is advisable. In addition, serotonin syndrome may occur during use of tramadol with medications that impair its metabolism. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Because the analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), CYP2D6 inhibition by fluphenazine may alter the analgesic response to tramadol. Additive CNS depression may also be seen with the concomitant use of tramadol and fluphenazine.

Flurazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Fluvoxamine: (Major) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering fluvoxamine with other drugs that have serotonergic properties such as tramadol. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome. Several cases of serotonin syndrome have been reported after the administration of tramadol with an SSRI. The combination of SSRIs and tramadol has also been associated with an increased risk of seizures.

Fosinopril; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Fosphenytoin: (Major) Tramadol may decrease the seizure threshold in some patients and thus potentially interfere with the ability of anticonvulsants to control seizures. The use of tramadol in patients on anticonvulsant medications for seizure therapy is not recommended. In addition, the hepatic metabolism of tramadol may be accelerated by the use of ethotoin, phenytoin, or fosphenytoin.

Fostamatinib: (Moderate) Monitor for tramadol toxicities that may require tramadol dose reduction if given concurrently with fostamatinib. Concomitant use of fostamatinib with a CYP3A4 substrate may increase the concentration of the CYP3A4 substrate. The active metabolite of fostamatinib, R406, is a CYP3A4 inhibitor; tramadol is a substrate for CYP3A4. Coadministration of fostamatinib with a sensitive CYP3A4 substrate increased the substrate AUC by 64% and Cmax by 113%.

Frovatriptan: (Moderate) Caution is advised when tramadol is coadministered with serotonin-receptor agonists because of the potential for serotonin syndrome. If concomitant treatment of tramadol and a serotonin-receptor agonist is clinically warranted, careful observation of the patient is advised, especially during the initial time both drugs are used together and during a dose increase of either tramadol or the serotonin-receptor agonist.

Furosemide: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when loop diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Gabapentin: (Moderate) Concomitant use of opioid agonists with gabapentin may cause excessive sedation and somnolence. Limit the use of opioid pain medications with gabapentin to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

General anesthetics: (Major) Concomitant use of tramadol with a general anesthetic may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a general anesthetic to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.

Glycopyrrolate: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Glycopyrrolate; Formoterol: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Granisetron: (Major) Because of the potential risk and severity of serotonin syndrome, use caution when administering granisetron with other drugs that have serotonergic properties such as tramadol. If serotonin syndrome is suspected, discontinue granisetron and concurrent serotonergic

agents and initiate appropriate medical treatment. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.
Guaifenesin; Hydrocodone: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Guaifenesin; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Haloperidol: (Major) Haloperidol can competitively inhibit the metabolism of tramadol by CYP2D6. Concurrent use of haloperidol and tramadol increases plasma levels of tramadol and decreases the concentration of the active tramadol metabolite. This may lead to decreased analgesic effects of tramadol and possibly increased tramadol-induced side effects, including seizures, due to increased tramadol concentrations and the decrease in seizure threshold caused by haloperidol. Additive CNS depression may also be seen with the concomitant use of tramadol and haloperidol.
Homatropine; Hydrocodone: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Hydantoins: (Major) Tramadol may decrease the seizure threshold in some patients and thus potentially interfere with the ability of anticonvulsants to control seizures. The use of tramadol in patients on anticonvulsant medications for seizure therapy is not recommended. In addition, the hepatic metabolism of tramadol may be accelerated by the use of ethotoin, phenytoin, or fosphenytoin.
Hydralazine; Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Hydrochlorothiazide, HCTZ: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Hydrochlorothiazide, HCTZ; Irbesartan: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Hydrochlorothiazide, HCTZ; Lisinopril: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Hydrochlorothiazide, HCTZ; Losartan: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Hydrochlorothiazide, HCTZ; Methyldopa: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Hydrochlorothiazide, HCTZ; Metoprolol: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Hydrochlorothiazide, HCTZ; Moexipril: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Hydrochlorothiazide, HCTZ; Olmesartan: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Hydrochlorothiazide, HCTZ; Propranolol: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Hydrochlorothiazide, HCTZ; Quinapril: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Hydrochlorothiazide, HCTZ; Spironolactone: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when potassium-sparing diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone. (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Hydrochlorothiazide, HCTZ; Telmisartan: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Hydrochlorothiazide, HCTZ; Triamterene: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when potassium-sparing diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone. (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Hydrochlorothiazide, HCTZ; Valsartan: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Hydrocodone: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Hydrocodone; Ibuprofen: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Hydrocodone; Phenylephrine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Hydrocodone; Potassium Guaiacolsulfonate: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Hydrocodone; Potassium Guaiacolsulfonate; Pseudoephedrine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Hydrocodone; Pseudoephedrine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also,

tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Hydromorphone: (Major) Tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists such as hydromorphone. Concomitant use of tramadol and opiate agonists may also increase the risk of seizures; avoid concurrent use whenever possible. Prior to concurrent use of hydromorphone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If hydromorphone is used concurrently with a CNS depressant, a reduced dosage of hydromorphone and/or the CNS depressant is recommended; start with one-third to one-half of the estimated hydromorphone starting dose when using hydromorphone extended-release tablets. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression.
Hydroxyzine: (Major) Concomitant use of opioid agonists with hydroxyzine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with hydroxyzine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Hyoscyamine: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Hyoscyamine; Methenamine; Methylene Blue; Phenyl Salicylate; Sodium Biphosphate: (Severe) Tramadol use is contraindicated in patients who are receiving or who have received monoamine oxidase inhibitors (MAOIs) within the previous 14 days. Methylene blue is a reversible inhibitor of MAO. Concomitant use of tramadol with other serotonergic drugs such as MAOIs may result in serious adverse effects including serotonin syndrome or seizures. MAOIs may cause additive CNS depression, respiratory depression, drowsiness, dizziness, or hypotension when used with opiate agonists such as tramadol. (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Ibuprofen; Oxycodone: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Idelalisib: (Major) Avoid concomitant use of idelalisib, a strong CYP3A inhibitor, with tramadol, a CYP3A substrate, as tramadol toxicities may be significantly increased. The AUC of a sensitive CYP3A substrate was increased 5.4-fold when coadministered with idelalisib.
Iloperidone: (Moderate) Coadministration should be avoided if possible. Antipsychotics may enhance the seizure risk of tramadol. Additive CNS depression may also be seen with the concomitant use of tramadol and iloperidone.
Imatinib: (Moderate) Since tramadol is primarily metabolized by cytochrome P450 isoenzyme CYP2D6, agents that inhibit this enzyme, such as imatinib, decrease the metabolism of tramadol. Concomitant use of these agents and tramadol may increase plasma levels of tramadol and decrease concentration of the active metabolite leading to decreased analgesic effects and possibly increased side effects due to higher tramadol concentrations.
Indacaterol; Glycopyrrolate: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Indapamide: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when indapamide is administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Iobenguane I 131: (Major) Discontinue tramadol for at least 5 half-lives before the administration of the dosimetry dose or a therapeutic dose of iobenguane I-131. Do not restart tramadol until at least 7 days after each iobenguane I-131 dose. Drugs that reduce catecholamine uptake or deplete catecholamine stores, such as tramadol, may interfere with iobenguane I-131 uptake into cells and interfere with dosimetry calculations resulting in altered iobenguane I-131 efficacy.
Iohexol: (Major) Tramadol lowers the seizure threshold and should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Iopamidol: (Major) Tramadol lowers the seizure threshold and should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Iopromide: (Major) Tramadol lowers the seizure threshold and should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Ioversol: (Major) Tramadol lowers the seizure threshold and should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Isavuconazonium: (Moderate) Concomitant use of isavuconazonium with tramadol may result in increased serum concentrations of tramadol. Tramadol is a substrate of the hepatic isoenzyme CYP3A4; isavuconazole, the active moiety of isavuconazonium, is a moderate inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are used together.
Isoniazid, INH: (Major) Use tramadol cautiously, if at all, in patients also receiving a MAOI or a drug with MAO-inhibiting activity such as isoniazid, INH. International recommendations contraindicate the concurrent use of tramadol and MAOIs or the use of tramadol within 14 days of discontinuing MAOI therapy. An increased risk of seizures and serotonin syndrome exists in patients receiving tramadol and MAOIs concurrently. Postmarketing reports of serotonin syndrome with use of tramadol and MAOIs and alpha-2-adrenergic blockers exist. If concomitant treatment of tramadol with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, especially during treatment initiation and dose increases.
Isoniazid, INH; Pyrazinamide, PZA; Rifampin: (Major) Use tramadol cautiously, if at all, in patients also receiving a MAOI or a drug with MAO-inhibiting activity such as isoniazid, INH. International recommendations contraindicate the concurrent use of tramadol and MAOIs or the use of tramadol within 14 days of discontinuing MAOI therapy. An increased risk of seizures and serotonin syndrome exists in patients receiving tramadol and MAOIs concurrently. Postmarketing reports of serotonin syndrome with use of tramadol and MAOIs and alpha-2-adrenergic blockers exist. If concomitant treatment of tramadol with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, especially during treatment initiation and dose increases. (Moderate) Monitor for reduced efficacy of tramadol and signs of opioid withdrawal if coadministration with rifampin is necessary; consider increasing the dose of tramadol as needed. If rifampin is discontinued, consider a dose reduction of tramadol and frequently monitor for seizures, serotonin syndrome, and signs of respiratory depression and sedation. Tramadol is a CYP3A4 substrate and rifampin is a strong CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease tramadol levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Isoniazid, INH; Rifampin: (Major) Use tramadol cautiously, if at all, in patients also receiving a MAOI or a drug with MAO-inhibiting activity such as isoniazid, INH. International recommendations contraindicate the concurrent use of tramadol and MAOIs or the use of tramadol within 14 days of discontinuing MAOI therapy. An increased risk of seizures and serotonin syndrome exists in patients receiving tramadol and MAOIs concurrently. Postmarketing reports of serotonin syndrome with use of tramadol and MAOIs and alpha-2-adrenergic blockers exist. If concomitant treatment of tramadol with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, especially during treatment initiation and dose increases. (Moderate) Monitor for reduced efficacy of tramadol and signs of opioid withdrawal if coadministration with rifampin is necessary; consider increasing the dose of tramadol as needed. If rifampin is discontinued, consider a dose reduction of tramadol and frequently monitor for seizures, serotonin syndrome, and signs of respiratory depression and sedation. Tramadol is a CYP3A4 substrate and rifampin is a strong CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease tramadol levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Isosulfan Blue: (Major) Tramadol lowers the seizure threshold and should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Istradefylline: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with istradefylline 40 mg daily is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression

from increased tramadol exposure may be fatal. Concurrent use of istradefylline 40 mg daily, a weak CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist. There was no effect on drug exposure when istradefylline 20 mg daily was coadministered with a sensitive CYP3A4 substrate.
Ivacaftor: (Minor) Use caution when administering ivacaftor and tramadol concurrently. Ivacaftor is an inhibitor of CYP3A and tramadol is partially metabolized by CYP3A. Co-administration can theoretically increase tramadol exposure leading to increased or prolonged therapeutic effects and adverse events; however, the clinical impact of this has not yet been determined.
Ketoconazole: (Moderate) Administration of CYP3A4 inhibitors such as ketoconazole with tramadol may affect the metabolism of tramadol leading to altered tramadol exposure. Increased serum tramadol concentrations may occur.
Lapatinib: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with lapatinib is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of lapatinib, a weak CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Larotrectinib: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with larotrectinib is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of larotrectinib, a weak CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Lefamulin: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with oral lefamulin is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of oral lefamulin, a moderate CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist. An interaction is not expected with intravenous lefamulin.
Letermovir: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with letermovir is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of letermovir, a CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Levocetirizine: (Moderate) Concomitant use of opioid agonists with cetirizine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with cetirizine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Levomilnacipran: (Major) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering levomilnacipran with other drugs that have serotonergic properties such as tramadol. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. If serotonin syndrome is suspected, levomilnacipran and tramadol should be discontinued.
Levorphanol: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Linezolid: (Severe) Tramadol use is contraindicated in patients who are receiving or who have received monoamine oxidase inhibitors (MAOIs) within the previous 14 days. Linezolid is a reversible, non-selective inhibitor of MAO. Concomitant use of tramadol with other serotonergic drugs such as MAOIs may result in serious adverse effects including serotonin syndrome or seizures. MAOIs may cause additive CNS depression, respiratory depression, drowsiness, dizziness, or hypotension when used with opiate agonists such as tramadol.
Lisdexamfetamine: (Moderate) Serotonin syndrome may occur during coadministration of serotonergic drugs such as amphetamines and tramadol. At high doses, amphetamines can increase serotonin release, as well as act as serotonin agonists. An additive risk of seizures is also possible. Monitor for serotonin syndrome and seizures or other adverse effects, particularly after a dose increase or the addition of interacting medications. Discontinue all serotonergic agents if serotonin syndrome occurs and implement appropriate medical management.
Lithium: (Major) There is an increased risk of serotonin syndrome during concurrent use of drugs with central serotonergic properties such as lithium and tramadol. Signs and symptoms of serotonin syndrome include autonomic instability (e.g., labile blood pressure, tachycardia, diaphoresis, dizziness, hyperthermia), mental status changes (e.g., delirium, confusion, coma), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), gastrointestinal effects (e.g., nausea, vomiting, diarrhea), seizures, and in rare cases, death. If concurrent use is necessary, monitor for the emergence of serotonin syndrome and inform patients of the increased risk. If serotonin syndrome is suspected, serotonergic agents should be discontinued and appropriate medical treatment should be implemented.
Lofexidine: (Moderate) Monitor for excessive hypotension and sedation during coadministration of lofexidine and tramadol. Lofexidine can potentiate the effects of CNS depressants.
Loop diuretics: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when loop diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Lopinavir; Ritonavir: (Major) Tramadol is primarily metabolized by CYP2D6 and CYP3A4; drugs that inhibit these enzymes, such as ritonavir, may decrease the metabolism of tramadol. This may result in a decreased concentration of the active metabolite (O-desmethyltramadol) leading to decreased analgesic effects and possibly increased side effects (seizures and serotonin syndrome) due to higher tramadol concentrations.
Lorazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Lorcaserin: (Major) Based on the mechanism of action of lorcaserin and the theoretical potential for serotonin syndrome, use with extreme caution in combination with other drugs that may affect the serotonergic neurotransmitter systems, including, tramadol. Patients receiving these combinations should be monitored for the emergence of serotonin syndrome or neuroleptic malignant syndrome (NMS) like signs and symptoms.
Lorlatinib: (Moderate) Monitor for reduced efficacy of tramadol and signs of opioid withdrawal if coadministration with lorlatinib is necessary; consider increasing the dose of tramadol as needed. If lorlatinib is discontinued, consider a dose reduction of tramadol and frequently monitor for signs or respiratory depression and sedation. Tramadol is a CYP3A4 substrate and lorlatinib is a moderate CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease tramadol levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Loxapine: (Major) Loxapine can potentiate the actions of other CNS depressants such as tramadol. Caution should be exercised with simultaneous use of these agents due to potential excessive CNS effects. In addition, loxapine therapy may be associated with an increased risk of seizures when given concurrently with tramadol due to decreases in the seizure threshold.
Lumacaftor; Ivacaftor: (Minor) Use caution when administering ivacaftor and tramadol concurrently. Ivacaftor is an inhibitor of CYP3A and tramadol is partially metabolized by CYP3A. Co-administration can theoretically increase tramadol exposure leading to increased or prolonged therapeutic effects and adverse events; however, the clinical impact of this has not yet been determined.
Lumacaftor; Ivacaftor: (Moderate) Lumacaftor; ivacaftor may reduce the analgesic effect of tramadol by decreasing its systemic exposure. If used together, monitor patients closely for loss of tramadol efficacy; a tramadol dosage adjustment may be required to obtain the desired therapeutic effect. Do not exceed the maximum recommended dose. Tramadol preferentially undergoes N-demethylation, which is mediated by CYP3A4 and CYP2B6. Lumacaftor is a strong CYP3A inducer; in vitro data also suggest that lumacaftor may induce CYP2B6.
Lurasidone: (Moderate) Concurrent use of lurasidone and tramadol or combination products containing tramadol (e.g., acetaminophen; trarnadol) should be avoided if possible. Antipsychotics may enhance the seizure risk of tramadol. Additive CNS depression may also be seen with the concomitant use of tramadol and lurasidone.
Maprotiline: (Major) Concomitant use of opioid agonists with maprotiline may cause excessive sedation and somnolence. Use of tramadol may also increase the risk of seizures in patients receiving other drugs associated with seizures such as maprotiline. Limit the use of opioid pain medications with maprotiline to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest

effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and seizures.

Melatonin: (Moderate) Concomitant use of opioid agonists with melatonin may cause excessive sedation and somnolence. Limit the use of opioid pain medications with melatonin to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Mepenzolate: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Meperidine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.

Meperidine; Promethazine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended. (Moderate) Caution is advisable during concurrent use of tramadol and promethazine. Seizures have been reported in patients receiving monotherapy with both tramadol and promethazine at recommended doses. Concomitant use of tramadol and promethazine may increase the risk of seizures. In addition, due to the primary CNS effects of promethazine, caution is advisable during use of other centrally acting medications such as tramadol. Impairment of metabolism of tramadol by CYP2D6 inhibitors, such as promethazine, may increase the risk of serotonin syndrome. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6 inhibitor may decrease tramadol analgesic efficacy.

Mephobarbital: (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate.

Meprobamate: (Moderate) Tramadol use increases the risk of CNS depression and respiratory depression when used with other agents that are CNS depressants such as meprobamate. Extreme caution is needed in using tramadol at the same time as other CNS depressants. A reduced dose of tramadol is recommended when used with another CNS depressant.

Mesoridazine: (Moderate) Due to the primary CNS effects of phenothiazines, caution should be used when given in combination with other centrally acting medications, such as tramadol. Both of these medications can lower the seizure threshold when used alone, therefore there is an even greater risk when they are used concomitantly.

Metaxalone: (Major) Concomitant use of tramadol with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.

Methadone: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.

Methamphetamine: (Moderate) Serotonin syndrome may occur during coadministration of serotonergic drugs such as methamphetamine and tramadol. Because both methamphetamine and tramadol have been associated with seizures, risk of seizure may also increase. At high doses, amphetamines can increase serotonin release, as well as act as serotonin agonists. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome particularly after a dose increase or the addition of other serotonergic medications to an existing regimen. Discontinue all serotonergic agents if serotonin syndrome occurs and implement appropriate medical management.

Methenamine; Sodium Acid Phosphate; Methylene Blue; Hyoscyamine: (Severe) Tramadol use is contraindicated in patients who are receiving or who have received monoamine oxidase inhibitors (MAOIs) within the previous 14 days. Methylene blue is a reversible inhibitor of MAO. Concomitant use of tramadol with other serotonergic drugs such as MAOIs may result in serious adverse effects including serotonin syndrome or seizures. MAOIs may cause additive CNS depression, respiratory depression, drowsiness, dizziness, or hypotension when used with opiate agonists such as tramadol. (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Methocarbamol: (Major) Concomitant use of tramadol with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.

Methohexital: (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate.

Methscopolamine: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Methyclothiazide: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Methylene Blue: (Severe) Tramadol use is contraindicated in patients who are receiving or who have received monoamine oxidase inhibitors (MAOIs) within the previous 14 days. Methylene blue is a reversible inhibitor of MAO. Concomitant use of tramadol with other serotonergic drugs such as MAOIs may result in serious adverse effects including serotonin syndrome or seizures. MAOIs may cause additive CNS depression, respiratory depression, drowsiness, dizziness, or hypotension when used with opiate agonists such as tramadol.

Metoclopramide: (Moderate) The effects of metoclopramide on gastrointestinal motility are antagonized by narcotic analgesics. Concomitant use of opioid agonists with metoclopramide may also cause excessive sedation and somnolence. Limit the use of opioid pain medications with metoclopramide to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.

Metolazone: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release

of antidiuretic hormone.
Metyrapone: (Moderate) Metyrapone may cause dizziness and/or drowsiness. Other drugs that may also cause drowsiness, such as tramadol, should be used with caution. Additive drowsiness and/or dizziness is possible.
Midazolam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Milnacipran: (Major) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering milnacipran and levomilnacipran with other drugs that have serotonergic properties such as tramadol. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. The combination of other serotonergic medications and tramadol has been associated with serotonin syndrome and seizures. Several cases of serotonin syndrome have been reported following the administration of tramadol with SSRIs such as paroxetine or sertraline. Levomilnacipran, a serotonin-norepinephrine reuptake inhibitor, has actions similar to the SSRIs and thus may also have the potential to interact with tramadol. Patients receiving this combination should be monitored for the emergence of serotonin syndrome or other adverse effects. If serotonin syndrome is suspected, levomilnacipran and concurrent serotonergic agents should be discontinued.
Mirabegron: (Moderate) Mirabegron is a moderate CYP2D6 inhibitor. Exposure of drugs metabolized by CYP2D6 such as tramadol may be increased when co-administered with mirabegron. Tramadol is primarily metabolized by CYP2D6. Therefore, appropriate monitoring and dose adjustment may be necessary.
Mirtazapine: (Major) Concomitant use of opioid agonists with mirtazapine may cause excessive sedation, somnolence, and increased risk of serotonin syndrome. Limit the use of opioid pain medications with mirtazapine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression and serotonin syndrome.
Mitotane: (Major) Use caution if mitotane and tramadol are used concomitantly, and monitor for decreased efficacy of tramadol and a possible change in dosage requirements. Mitotane is a strong CYP3A4 inducer. The metabolism of tramadol is stereoselective; the (+) enantiomer preferentially undergoes N-demethylation, mediated by CYP3A4 and CYP2B6, and the (-) enantiomer undergoes O-demethylation via CYP2D6. O-demethylation leads to the production of the active metabolite M1, which is critical to tramadol activity. Because of the role of CYP3A4 in tramadol metabolism, coadministration with mitotane may affect patient response to tramadol.
Molindone: (Moderate) Due to the primary CNS effects of molindone, caution should be used when given in combination with other centrally acting medications, such as tramadol. Both of these medications can lower the seizure threshold when used alone, therefore there is an even greater risk when they are used concomitantly.
Monoamine oxidase inhibitors: (Severe) Tramadol use is contraindicated in patients who are receiving or who have received monoamine oxidase inhibitors (MAOIs) within the previous 14 days due to a risk for serotonin syndrome or opioid toxicity, including respiratory depression.
Morphine: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, because of the potential risk and severity of serotonin syndrome, caution and careful monitoring are recommended when coadministering drugs that have serotonergic properties such as morphine and tramadol. Serotonin syndrome is characterized by the rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Morphine and tramadol should be discontinued if serotonin syndrome occurs and supportive symptomatic treatment should be initiated. Lastly, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Morphine; Naltrexone: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, because of the potential risk and severity of serotonin syndrome, caution and careful monitoring are recommended when coadministering drugs that have serotonergic properties such as morphine and tramadol. Serotonin syndrome is characterized by the rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Morphine and tramadol should be discontinued if serotonin syndrome occurs and supportive symptomatic treatment should be initiated. Lastly, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Nabilone: (Moderate) Concomitant use of nabilone with other CNS depressants, including tramadol, can potentiate the effects of nabilone on respiratory depression.
Nalbuphine: (Major) Avoid the concomitant use of nalbuphine and opiate agonists, such as tramadol. Nalbuphine is a mixed opiate agonist/antagonist that may block the effects of opiate agonists and reduce analgesic effects. Nalbuphine may cause withdrawal symptoms in patients receiving chronic opiate agonists. Concurrent use of nalbuphine with other opiate agonists can cause additive CNS, respiratory, and hypotensive effects. The additive or antagonistic effects are dependent upon the dose of the opiate agonist used; antagonistic effects are more common at low to moderate doses of the opiate agonist. There is also a potential increased risk of seizures if tramadol is given with other opiates.
Nalmefene: (Moderate) Naloxone should be used cautiously in situations of tramadol overdose. Naloxone administration may increase the risk of seizures in these patients. Furthermore, naloxone will reverse some but not all symptoms caused by tramadol overdosage. It is not clear if such precautions would also apply to the use of other opiate antagonists with tramadol.
Naloxone: (Moderate) Naloxone should be used cautiously in situations of tramadol overdose. Naloxone administration may increase the risk of seizures in these patients. Furthermore, naloxone will reverse some but not all symptoms caused by tramadol overdosage. It is not clear if such precautions would also apply to the use of other opiate antagonists with tramadol.
Naltrexone: (Moderate) Naloxone should be used cautiously in situations of tramadol overdose. Naloxone administration may increase the risk of seizures in these patients. Furthermore, naloxone will reverse some but not all symptoms caused by tramadol overdosage. It is not clear if such precautions would also apply to the use of other opiate antagonists with tramadol.
Naproxen; Sumatriptan: (Moderate) Caution is advised when tramadol is coadministered with serotonin-receptor agonists because of the potential for serotonin syndrome. If concomitant treatment of tramadol and a serotonin-receptor agonist is clinically warranted, careful observation of the patient is advised, especially during the initial time both drugs are used together and during a dose increase of either tramadol or the serotonin-receptor agonist.
Naratriptan: (Moderate) Caution is advised when tramadol is coadministered with serotonin-receptor agonists because of the potential for serotonin syndrome. If concomitant treatment of tramadol and a serotonin-receptor agonist is clinically warranted, careful observation of the patient is advised, especially during the initial time both drugs are used together and during a dose increase of either tramadol or the serotonin-receptor agonist.
Nefazodone: (Major) Although clinical data for some interactions is lacking, medications that augment release, decrease the metabolism of, or decrease the reuptake of serotonin (tramadol) may interact with nefazodone by causing serotonin-related side effects, including serotonin syndrome.
Netupitant, Fosnetupitant; Palonosetron: (Major) Because of the potential risk and severity of serotonin syndrome, use caution when administering palonosetron with other drugs that have serotonergic properties such as tramadol. If serotonin syndrome is suspected, discontinue palonosetron and concurrent serotonergic agents and initiate appropriate medical treatment. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.
Nilotinib: (Major) The concomitant use of nilotinib and tramadol may reduce the clearance of tramadol and increase the risk for serious adverse events including seizures and serotonin syndrome. If coadministration of these drugs is required, consider reducing the dose of tramadol and monitor patients for signs of toxicity. Nilotinib is a moderate CYP3A4 inhibitor and tramadol is a CYP3A4 substrate.
Non-Ionic Contrast Media: (Major) Tramadol lowers the seizure threshold and should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Olanzapine: (Moderate) Concurrent use of tramadol and olanzapine should be avoided if possible. Antipsychotics may enhance the seizure risk of tramadol. Additive CNS depression may also be seen with the concomitant use of tramadol and olanzapine.
Ombitasvir; Paritaprevir; Ritonavir: (Major) Tramadol is primarily metabolized by CYP2D6 and CYP3A4; drugs that inhibit these enzymes, such

as ritonavir, may decrease the metabolism of tramadol. This may result in a decreased concentration of the active metabolite (O-desmethyltramadol) leading to decreased analgesic effects and possibly increased side effects (seizures and serotonin syndrome) due to higher tramadol concentrations.

Ondansetron: (Moderate) Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from a few small studies indicate that ondansetron may reduce the analgesic effects of tramadol. Since adverse effects may occur when tramadol is administered in excessive dosage as patients try to obtain pain relief, clinicians should be alert to increases in the patient reported frequency of tramadol administration during concurrent use.

Opiate Antagonists: (Moderate) Naloxone should be used cautiously in situations of tramadol overdose. Naloxone administration may increase the risk of seizures in these patients. Furthermore, naloxone will reverse some but not all symptoms caused by tramadol overdosage. It is not clear if such precautions would also apply to the use of other opiate antagonists with tramadol.

Oritavancin: (Moderate) Tramadol is metabolized by CYP3A4 and CYP2D6; oritavancin is a weak CYP3A4 and CYP2D6 inducer. Plasma concentrations and efficacy of tramadol may be reduced if these drugs are administered concurrently.

Orphenadrine: (Major) Concomitant use of tramadol with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.

Oxazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Oxybutynin: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Oxycodone: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.

Oxymorphone: (Major) Tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists such as oxymorphone. Concomitant use of tramadol and opiate agonists may also increase the risk of seizures; avoid concurrent use whenever possible. Hypotension, profound sedation, coma, respiratory depression, or death may occur. Prior to concurrent use of oxymorphone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxymorphone, a reduced dosage of oxymorphone (1/3 to 1/2 of the usual dose) and/or the CNS depressant is recommended. If the extended-release oxymorphone tablets are used concurrently with a CNS depressant, it is recommended to use an initial dosage of 5 mg PO every 12 hours. Monitor for sedation or respiratory depression.

Palbociclib: (Moderate) If coadministration of palbociclib is necessary, monitor for increased tramadol-related adverse effects (e.g., seizures, serotonin syndrome and opioid toxicity including potentially fatal respiratory depression). Consider a tramadol dose reduction until stable drug effects are achieved. If palbociclib is discontinued, monitor for opioid withdrawal symptoms and consider increasing the tramadol dose. Coadministration of palbociclib, a weak time-dependent CYP3A4 inhibitor, may increase tramadol plasma concentrations and may result in increased metabolism of tramadol through 2D6 resulting in higher levels of the active metabolite, M1.

Paliperidone: (Moderate) Concurrent use of tramadol and paliperidone should be administered with caution. Antipsychotics, such as paliperidone, may enhance the seizure risk of tramadol. Additive CNS depression may also be seen with the concomitant use of tramadol and paliperidone.

Palonosetron: (Major) Because of the potential risk and severity of serotonin syndrome, use caution when administering palonosetron with other drugs that have serotonergic properties such as tramadol. If serotonin syndrome is suspected, discontinue palonosetron and concurrent serotonergic agents and initiate appropriate medical treatment. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.

Panobinostat: (Major) Avoid the concomitant use of panobinostat and tramadol as increased tramadol levels and an increased risk of adverse effects may occur if these agents are used together. If concomitant use cannot be avoided, closely monitor patients for signs and symptoms of tramadol toxicity including seizures and serotonin syndrome. Panobinostat is a CYP2D6 inhibitor and tramadol is primarily metabolized by CYP2D6. When a single-dose of a CYP2D6-sensitive substrate was administered after 3 doses of panobinostat (20 mg given on days 3, 5, and 8), the CYP2D6 substrate Cmax increased by 20% to 200% and the AUC value increased by 20% to 130% in 14 patients with advanced cancer; exposure was highly variable (coefficient of variance > 150%).

Paroxetine: (Moderate) Patients receiving tramadol in combination with an SSRI should be monitored for the emergence of serotonin syndrome, neuroleptic malignant syndrome-like reactions, seizures, and decreased analgesic effect of tramadol. Several cases of serotonin syndrome have been reported after the administration of tramadol with a SSRI. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs. Post-marketing reports also implicate the concurrent use of SSRIs with tramadol in some cases of seizures. Paroxetine may also inhibit the formation of the active M1 metabolite of tramadol by inhibiting CYP2D6. The inhibition of this metabolite may decrease the analgesic effectiveness of tramadol but increase the level of the parent compound, which has more serotonergic activity than the metabolite.

Pazopanib: (Moderate) Pazopanib is a weak inhibitor of CYP3A4. Coadministration of pazopanib and tramadol, a CYP3A4 substrate, may cause an increase in systemic concentrations of tramadol. Use caution when administering these drugs concomitantly.

Peginterferon Alfa-2b: (Moderate) Monitor for adverse effects associated with increased exposure to tramadol if peginterferon alfa-2b is coadministered. Peginterferon alfa-2b is a CYP2D6 inhibitor, while tramadol is a CYP2D6 substrate.

Pentazocine: (Major) Avoid the concomitant use of pentazocine and opiate agonists, such as tramadol. Pentazocine is a mixed opiate agonist/antagonist that may block the effects of opiate agonists and reduce analgesic effects. Pentazocine may cause withdrawal symptoms in patients receiving chronic opiate agonists. There is also a potential increased risk of seizures if tramadol and pentazocine are given concurrently. Concurrent use of pentazocine with other opiate agonists can cause additive CNS, respiratory, and hypotensive effects. The additive or antagonistic effects are dependent upon the dose of the opiate agonist used; antagonistic effects are more common at low to moderate doses of the opiate agonist.

Pentazocine; Naloxone: (Major) Avoid the concomitant use of pentazocine and opiate agonists, such as tramadol. Pentazocine is a mixed opiate agonist/antagonist that may block the effects of opiate agonists and reduce analgesic effects. Pentazocine may cause withdrawal symptoms in patients receiving chronic opiate agonists. There is also a potential increased risk of seizures if tramadol and pentazocine are given concurrently. Concurrent use of pentazocine with other opiate agonists can cause additive CNS, respiratory, and hypotensive effects. The additive or antagonistic effects are dependent upon the dose of the opiate agonist used; antagonistic effects are more common at low to moderate doses of the opiate agonist. (Moderate) Naloxone should be used cautiously in situations of tramadol overdose. Naloxone administration may increase the risk of seizures in these patients. Furthermore, naloxone will reverse some but not all symptoms caused by tramadol overdosage. It is not clear if such precautions would also apply to the use of other opiate antagonists with tramadol.

Pentobarbital: (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate.

Perampanel: (Moderate) Concomitant use of opioid agonists with perampanel may cause excessive sedation and somnolence. Limit the use of opioid pain medications with perampanel to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Perindopril; Amlodipine: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with amlodipine is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of amlodipine, a weak CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Perphenazine: (Major) Seizures have been reported in patients receiving monotherapy with tramadol or antipsychotics at recommended doses. Concomitant use of tramadol and antipsychotics may increase the risk of seizures and result in other additive CNS effects. The manufacturer of tramadol cautions that serotonin syndrome may occur during use of drugs that impair the metabolism of tramadol such as CYP2D6 inhibitors, including antipsychotics like perphenazine. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6 inhibitor may in theory also decrease tramadol efficacy.
Perphenazine; Amitriptyline: (Major) Seizures have been reported in patients receiving monotherapy with tramadol or antipsychotics at recommended doses. Concomitant use of tramadol and antipsychotics may increase the risk of seizures and result in other additive CNS effects. The manufacturer of tramadol cautions that serotonin syndrome may occur during use of drugs that impair the metabolism of tramadol such as CYP2D6 inhibitors, including antipsychotics like perphenazine. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6 inhibitor may in theory also decrease tramadol efficacy.
Phenobarbital: (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate.
Phentermine; Topiramate: (Moderate) Topiramate may contribute to the CNS depression seen with tramadol; tramadol may also decrease the seizure threshold in some patients and thus, potentially, interfere with the ability of anticonvulsants to control seizures.
Phenylephrine; Promethazine: (Moderate) Caution is advisable during concurrent use of tramadol and promethazine. Seizures have been reported in patients receiving monotherapy with both tramadol and promethazine at recommended doses. Concomitant use of tramadol and promethazine may increase the risk of seizures. In addition, due to the primary CNS effects of promethazine, caution is advisable during use of other centrally acting medications such as tramadol. Impairment of metabolism of tramadol by CYP2D6 inhibitors, such as promethazine, may increase the risk of serotonin syndrome. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6 inhibitor may decrease tramadol analgesic efficacy.
Phenytoin: (Major) Tramadol may decrease the seizure threshold in some patients and thus potentially interfere with the ability of anticonvulsants to control seizures. The use of tramadol in patients on anticonvulsant medications for seizure therapy is not recommended. In addition, the hepatic metabolism of tramadol may be accelerated by the use of ethotoin, phenytoin, or fosphenytoin.
Pimozide: (Major) Concurrent use of tramadol and pimozide should be avoided if possible. Antipsychotics may enhance the seizure risk of tramadol. Additive CNS depression may also be seen with the concomitant use of tramadol and pimozide.
Posaconazole: (Major) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with posaconazole is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of posaconazole, a strong CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Potassium-sparing diuretics: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when potassium-sparing diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Pramipexole: (Major) Concomitant use of opioid agonists with pramipexole may cause excessive sedation and somnolence. Limit the use of opioid pain medications with pramipexole to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. Dopaminergic agents like pramipexole have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment.
Prasugrel: (Moderate) Consider the use of a parenteral anti-platelet agent for patients with acute coronary syndrome who require concomitant opioid agonists, such as tramadol. Coadministration of opioid agonists with prasugrel delays and reduces the absorption of prasugrel's active metabolite due to slowed gastric emptying.
Pregabalin: (Moderate) Concomitant use of opioid agonists with pregabalin may cause excessive sedation and somnolence. Limit the use of opioid pain medications with pregabalin to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Primidone: (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate.
Procarbazine: (Major) Avoid use of tramadol concurrently or within 14 days of discontinuing a drug with monamine oxidase inhibitor (MAOI)-like activity, such as procarbazine. If concomitant treatment is clinically warranted, careful observation of the patient is advised, especially during treatment initiation and dose increases. International recommendations contraindicate the use of tramadol within 14 days of an MAOI. There is an increased risk of seizures and serotonin syndrome in patients receiving these drugs currently. In animal studies, an increased number of deaths was noted with the combination due to interference with detoxification mechanisms.
Prochlorperazine: (Moderate) Concurrent use of tramadol and prochlorperazine should be avoided if possible. Antipsychotics may enhance the seizure risk of tramadol. Additive CNS depression may also be seen with the concomitant use of tramadol and prochlorperazine.
Promethazine: (Moderate) Caution is advisable during concurrent use of tramadol and promethazine. Seizures have been reported in patients receiving monotherapy with both tramadol and promethazine at recommended doses. Concomitant use of tramadol and promethazine may increase the risk of seizures. In addition, due to the primary CNS effects of promethazine, caution is advisable during use of other centrally acting medications such as tramadol. Impairment of metabolism of tramadol by CYP2D6 inhibitors, such as promethazine, may increase the risk of serotonin syndrome. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a

CYP2D6 inhibitor may decrease tramadol analgesic efficacy.
Propafenone: (Moderate) As propafenone is a moderate CYP2D6 inhibitor and tramadol is primarily metabolized by CYP2D6 and CYP3A4, concurrent therapy may decrease tramadol metabolism. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Decreased analgesia might occur. Inhibition of either CYP2D6 and/or CYP3A4 is also expected to reduce the metabolic clearance of tramadol and may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.
Propantheline: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Propoxyphene: (Major) As propoxyphene is a moderate CYP2D6 inhibitor and tramadol is primarily metabolized by CYP2D6 (and CYP3A4), concurrent therapy may decrease tramadol metabolism. This interaction may result in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of either or both CYP2D6 and CYP3A4 is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.
Quazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Quetiapine: (Moderate) Due to the primary CNS effects of quetiapine, caution should be used when given in combination with other centrally acting medications, such as tramadol. Both of these medications can lower the seizure threshold when used alone, therefore there is an even greater risk when they are used concomitantly.
Quinidine: (Moderate) As quinidine is a potent inhibitor of CYP2D6 and tramadol is partially metabolized by CYP2D6, concurrent therapy may decrease tramadol metabolism. This interaction may result in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of CYP2D6 metabolism is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.
Quinine: (Moderate) Quinine inhibits CYP2D6 and may theoretically increase concentrations of other drugs metabolized by this enzyme including tramadol.
Ramelteon: (Moderate) Concomitant use of opioid agonists with ramelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with ramelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Ranolazine: (Moderate) As ranolazine is a weak to moderate CYP2D6 and CYP3A4 inhibitor and tramadol is primarily metabolized by CYP2D6 and CYP3A4, concurrent therapy may decrease tramadol metabolism. This interaction may result in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of either or both CYP2D6 and CYP3A4 is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.
Rasagiline: (Severe) Rasagiline is contraindicated for use with tramadol due to the risk of serotonin syndrome. Serotonin syndrome is characterized by the rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. At least 14 days should elapse between the discontinuation of rasagiline and the initiation of tramadol.
Remifentanil: (Major) Concomitant use of tramadol and remifentanil increases the risk of adverse effects including seizures, serotonin syndrome, and additive opioid toxicity. If concurrent use is necessary, closely monitor the patient, particularly during remifentanil initiation and dosage adjustment. Discontinue remifentanil if serotonin syndrome is suspected or significant adverse events occur.
Ribociclib: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with ribociclib is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of ribociclib, a strong CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Ribociclib; Letrozole: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with ribociclib is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of ribociclib, a strong CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Rifampin: (Moderate) Monitor for reduced efficacy of tramadol and signs of opioid withdrawal if coadministration with rifampin is necessary; consider increasing the dose of tramadol as needed. If rifampin is discontinued, consider a dose reduction of tramadol and frequently monitor for seizures, serotonin syndrome, and signs of respiratory depression and sedation. Tramadol is a CYP3A4 substrate and rifampin is a strong CYP3A4 inducer. Concomitant use with CYP3A4 inducers can decrease tramadol levels; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence.
Risperidone: (Major) Concurrent use of tramadol and risperidone should be avoided if possible due to a possible increased risk of seizures. Seizures have been reported in patients receiving monotherapy with tramadol or antipsychotics at recommended doses. In addition, due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally-acting medications such as tramadol.
Ritonavir: (Major) Tramadol is primarily metabolized by CYP2D6 and CYP3A4; drugs that inhibit these enzymes, such as ritonavir, may decrease the metabolism of tramadol. This may result in a decreased concentration of the active metabolite (O-desmethyltramadol) leading to decreased analgesic effects and possibly increased side effects (seizures and serotonin syndrome) due to higher tramadol concentrations.
Rizatriptan: (Moderate) Caution is advised when tramadol is coadministered with serotonin-receptor agonists because of the potential for serotonin syndrome. If concomitant treatment of tramadol and a serotonin-receptor agonist is clinically warranted, careful observation of the patient is advised, especially during the initial time both drugs are used together and during a dose increase of either tramadol or the serotonin-receptor agonist.
Rolapitant: (Major) Use caution if tramadol and rolapitant are used concurrently, and monitor for tramadol-related adverse effects as well as possible changes to the efficacy of tramadol. Rolapitant is a moderate CYP2D6 inhibitor; the inhibitory effect of rolapitant is expected to persist beyond 28 days for an unknown duration. Exposure to another CYP2D6 substrate, following a single dose of rolapitant increased about 3-fold on Days 8 and Day 22. The inhibition of CYP2D6 persisted on Day 28 with a 2.3-fold increase in the CYP2D6 substrate concentrations, the last time point measured. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6; therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of CYP2D6 is expected to result in reduced metabolic clearance of tramadol, which in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures; serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.

Ropinirole: (Moderate) Ropinirole can cause CNS depression. Tramadol use increases the risk of CNS depression and respiratory depression when used with other agents that are CNS depressants. Extreme caution is needed in using tramadol at the same time as other CNS depressants. A reduced dose of tramadol is recommended when used with another CNS depressant.
Rotigotine: (Major) Concomitant use of opioid agonists with rotigotine may cause excessive sedation and somnolence. Limit the use of opioid pain medications with rotigotine to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression. Dopaminergic agents like rotigotine have also been associated with sudden sleep onset during activities of daily living such as driving, which has resulted in accidents in some cases. Prescribers should re-assess patients for drowsiness or sleepiness regularly throughout treatment, especially since events may occur well after the start of treatment.
Rucaparib: (Moderate) Monitor for an increase in tramadol-related adverse reactions, including serotonin syndrome, seizures, sedation, and respiratory depression, if coadministration with rucaparib is necessary; the risk is greatest if rucaparib is added to a stable dose of tramadol. Consider decreasing the dose of tramadol if necessary. Rucaparib is a weak CYP3A4 inhibitor and tramadol is metabolized by both CYP3A4 and CYP2D6. Coadministration with a CYP3A4 inhibitor may result in a greater amount of tramadol metabolism via CYP2D6, and greater levels of the active metabolite, M1.
Safinamide: (Severe) Safinamide is contraindicated for use with tramadol due to the risk of serotonin syndrome. Serotonin syndrome is characterized by the rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. At least 14 days should elapse between the discontinuation of safinamide and the initiation of tramadol.
Scopolamine: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Secobarbital: (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate.
Serotonin-Receptor Agonists: (Moderate) Caution is advised when tramadol is coadministered with serotonin-receptor agonists because of the potential for serotonin syndrome. If concomitant treatment of tramadol and a serotonin-receptor agonist is clinically warranted, careful observation of the patient is advised, especially during the initial time both drugs are used together and during a dose increase of either tramadol or the serotonin-receptor agonist.
Sertraline: (Moderate) Patients receiving tramadol in combination with an SSRI should be monitored for the emergence of serotonin syndrome, neuroleptic malignant syndrome-like reactions, seizures, and decreased analgesic effect of tramadol. Several cases of serotonin syndrome have been reported after the administration of tramadol with a SSRI. Symptoms may occur hours to days after concomitant use, particularly after dose increases. Serotonin syndrome may occur within recommended dose ranges. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs. Post-marketing reports also implicate the concurrent use of SSRIs with tramadol in some cases of seizures. Sertraline may also inhibit the formation of the active M1 metabolite of tramadol by inhibiting CYP2D6. The inhibition of this metabolite may decrease the analgesic effectiveness of tramadol but increase the level of the parent compound, which has more serotonergic activity than the metabolite.
Sibutramine: (Major) Sibutramine is a serotonin reuptake inhibitor. Because of the potential risk and severity of serotonin syndrome or neuroleptic malignant syndrome-like reactions, caution should be observed when administering sibutramine with drugs that have serotonergic properties such as tramadol. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome. Patients receiving this combination should be monitored for the emergence of serotonin syndrome or neuroleptic malignant syndrome-like reactions.
Simeprevir: (Moderate) Simeprevir, a mild intestinal CYP3A4 inhibitor, may increase the side effects of tramadol, which is partially metabolized by CYP3A4. Monitor patients for adverse effects of tramadol, such as seizures and serotonin syndrome.
Sodium Oxybate: (Major) Sodium oxybate has the potential to induce seizures; it has been speculated that this effect may be mediated through the action of sodium oxybate at GABA receptors. Although convulsant effects occur primarily at high dosages, sodium oxybate should be used cautiously with drugs that are known to lower seizure threshold such as tramadol.
Solifenacin: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug, such as solifenacin. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Spironolactone: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when potassium-sparing diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
St. John's Wort, Hypericum perforatum: (Moderate) Concurrent use of St. John's Wort with other agents that decrease the neuronal uptake of serotonin, such as tramadol, may increase the risk of a serious serotonin syndrome reaction.
Sufentanil: (Major) Concomitant use of tramadol increases the seizure risk in patients taking opiate agonists. Also, tramadol can cause additive CNS depression and respiratory depression when used with opiate agonists; avoid concurrent use whenever possible. If used together, extreme caution is needed, and a reduced tramadol dose is recommended.
Sumatriptan: (Moderate) Caution is advised when tramadol is coadministered with serotonin-receptor agonists because of the potential for serotonin syndrome. If concomitant treatment of tramadol and a serotonin-receptor agonist is clinically warranted, careful observation of the patient is advised, especially during the initial time both drugs are used together and during a dose increase of either tramadol or the serotonin-receptor agonist.
Suvorexant: (Moderate) Concomitant use of opioid agonists with suvorexant may cause excessive sedation and somnolence. Limit the use of opioid pain medications with suvorexant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Tapentadol: (Major) Because of the potential risk and severity of serotonin syndrome and/or seizures, use tramadol with extreme caution, if at all, in patients receiving immediate-release tapentadol; discontinue tramadol prior to initiating and while taking extended-release tapentadol. Cases of life-threatening serotonin syndrome have been reported with the concurrent use of tapentadol and serotonergic drugs. In addition, the risk of seizure is increased in patients receiving tramadol with other opioids. These effects may occur within therapeutic dose ranges. Serotonin syndrome is characterized by the rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Additive CNS depressant effects and respiratory depression are also possible.
Tasimelteon: (Moderate) Concomitant use of opioid agonists with tasimelteon may cause excessive sedation and somnolence. Limit the use of opioid pain medications with tasimelteon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Tedizolid: (Minor) Caution is warranted with the concurrent use of tedizolid and tramadol. Tedizolid is an antibiotic that is also a weak reversible, non-selective inhibitor of MAO. Serious CNS reactions, such as serotonin syndrome, have been reported during the concurrent use of linezolid, which is structurally similar to tedizolid, and psychiatric medications that enhance central serotonergic activity; therefore, caution is warranted with concomitant use of other agents with serotonergic activity, including tramadol.
Telaprevir: (Moderate) Close clinical monitoring is advised when administering tramadol with telaprevir due to an increased potential for tramadol-

related adverse events. If tramadol dose adjustments are made, re-adjust the dose upon completion of telaprevir treatment. Although this interaction has not been studied, predictions about the interaction can be made based on the metabolic pathway of tramadol. Tramadol is partially metabolized by the hepatic isoenzyme CYP3A4; telaprevir inhibits this isoenzyme. Coadministration may result in elevated tramadol plasma concentrations.

Telithromycin: (Moderate) Increased serum concentrations of tramadol would be expected from concurrent use of tramadol and a CYP3A4 inhibitor, such as telithromycin (see tramadol Pharmacokinetics). The risk for serious adverse effects such as seizures and serotonin syndrome may be increased.

Telotristat Ethyl: (Moderate) Use caution if coadministration of telotristat ethyl and tramadol is necessary, as the systemic exposure of tramadol may be decreased resulting in reduced efficacy and in some patients, may result in signs and symptoms of opioid withdrawal. If these drugs are used together, monitor patients for suboptimal efficacy of tramadol; consider increasing the dose of tramadol if necessary. The discontinuation of telotristat ethyl may result in an increase in tramadol plasma concentrations, which could increase or prolong adverse reactions, increase the risk for serious adverse events including seizures and serotonin syndrome, and may cause potentially fatal respiratory depression. Tramadol is a CYP3A4 substrate. The mean Cmax and AUC of another sensitive CYP3A4 substrate was decreased by 25% and 48%, respectively, when coadministered with telotristat ethyl; the mechanism of this interaction appears to be that telotristat ethyl increases the glucuronidation of the CYP3A4 substrate.

Temazepam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Terbinafine: (Moderate) As terbinafine inhibits CYP2D6 and tramadol is partially metabolized by CYP2D6, concurrent therapy may decrease tramadol metabolism. This interaction may result in decreased tramadol efficacy and/or increased tramadol-induced risks of serotonin syndrome or seizures. The analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), and M1 formation is dependent on CYP2D6. Therefore, use of tramadol with a CYP2D6-inhibitor may alter tramadol efficacy. In addition, inhibition of CYP2D6 metabolism is expected to result in reduced metabolic clearance of tramadol. This in turn may increase the risk of tramadol-related adverse events including serotonin syndrome and seizures. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death.

Tetrabenazine: (Moderate) Additive effects are possible when tetrabenazine is combined with other drugs that cause CNS depression. Concurrent use of tetrabenazine and drugs that can cause CNS depression, such as tramadol, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, dizziness, and orthostatic hypotension.

Tezacaftor; Ivacaftor: (Minor) Use caution when administering ivacaftor and tramadol concurrently. Ivacaftor is an inhibitor of CYP3A and tramadol is partially metabolized by CYP3A. Co-administration can theoretically increase tramadol exposure leading to increased or prolonged therapeutic effects and adverse events; however, the clinical impact of this has not yet been determined.

Thalidomide: (Major) Avoid the concomitant use of thalidomide with other central nervous system depressants such as tramadol due to the potential for additive sedative effects.

Thiazide diuretics: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when thiazide diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Thiethylperazine: (Major) Administration of tramadol may enhance the seizure risk in patients taking other medications, such as thiethylperazine, that decrease the seizure threshold. Additive CNS depression may also occur when thiethylperazine is given concurrently with tramadol.

Thiopental: (Major) Concomitant use of tramadol with barbiturates may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with barbiturates to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation. Additionally, concomitant use of tramadol with a barbiturate can decrease tramadol concentrations; this may result in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence. Monitor for reduced efficacy of tramadol and signs of opioid withdrawal. Discontinuation of a barbiturate may increase the risk of seizures, serotonin syndrome, and the risk of opioid-related adverse reactions, such as fatal respiratory depression. Barbiturates induce CYP3A4; tramadol is a CYP3A4 substrate.

Thioridazine: (Major) Concurrent use of tramadol and thioridazine should be avoided if possible. Antipsychotics may enhance the seizure risk of tramadol. In addition, thioridazine has clinically significant CYP2D6 inhibitory effects and has the potential to decrease the metabolism of CYP2D6 substrates such as tramadol. Although the full pharmacologic impact of increased tramadol exposure is unknown, close monitoring for serious adverse effects, such as seizures, is advisable. In addition, serotonin syndrome may occur during use of tramadol with medications that impair its metabolism. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, hyperreflexia, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Because the analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), CYP2D6 inhibition by thioridazine may alter the analgesic response to tramadol. Additive CNS depression may also be seen with the concomitant use of tramadol and thioridazine.

Thiothixene: (Major) Concurrent use of tramadol and thiothixene should be avoided if possible. Antipsychotics may enhance the seizure risk of tramadol. In addition, in vitro data suggest that thiothixene is a weak CYP2D6 inhibitor and has the potential to decrease the metabolism of CYP2D6 substrates such as tramadol. Although the full pharmacologic impact of increased tramadol exposure is unknown, close monitoring for serious adverse effects, such as seizures, is advisable. In addition, serotonin syndrome may occur during use of tramadol with medications that impair its metabolism. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Because the analgesic activity of tramadol is due to the activity of both the parent drug and the O-desmethyltramadol metabolite (M1), CYP2D6 inhibition by thiothixene may alter the analgesic response to tramadol. Additive CNS depression may also be seen with the concomitant use of tramadol and thiothixene.

Ticagrelor: (Moderate) Coadministration of opioid agonists, such as tramadol, may delay and reduce the absorption of ticagrelor resulting in reduced exposure and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Mean ticagrelor exposure decreased up to 36% in ACS patients undergoing PCI when intravenous morphine was administered with a loading dose of ticagrelor; mean platelet aggregation was higher up to 3 hours post loading dose. Similar effects on ticagrelor exposure and platelet inhibition were observed when fentanyl was administered with a ticagrelor loading dose in ACS patients undergoing PCI. Although exposure to ticagrelor was decreased up to 25% in healthy adults administered intravenous morphine with a loading dose of ticagrelor, platelet inhibition was not delayed or decreased in this population.

Tizanidine: (Major) Concomitant use of tramadol with a skeletal muscle relaxant may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opioid pain medications with a skeletal muscle relaxant to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, reduce initial dosage and titrate to clinical response; use the lowest effective doses and minimum treatment durations. Educate patients about the risks and symptoms of respiratory depression and sedation.

Tolterodine: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug, such as tolterodine. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.

Topiramate: (Moderate) Topiramate may contribute to the CNS depression seen with tramadol; tramadol may also decrease the seizure threshold in some patients and thus, potentially, interfere with the ability of anticonvulsants to control seizures.

Torsemide: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when loop diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.

Trazodone: (Major) Concomitant use of opioid agonists with trazodone may cause excessive sedation, somnolence, and increased risk of serotonin syndrome. Limit the use of opioid pain medications with trazodone to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical

effect. Educate patients about the risks and symptoms of excessive CNS depression and serotonin syndrome.
Triamterene: (Moderate) Monitor for decreased diuretic efficacy and additive orthostatic hypotension when potassium-sparing diuretics are administered with tramadol. Adjustments to diuretic therapy may be needed in some patients. The efficacy of diuretics may be reduced due to opioid-induced release of antidiuretic hormone.
Triazolam: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Tricyclic antidepressants: (Major) Concomitant use of tramadol with tricyclic antidepressants may cause excessive sedation, somnolence, and increased risk of seizures and serotonin syndrome. The anticholinergic properties of tricyclic antidepressants may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Limit the use of tramadol with tricyclic antidepressants to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression, serotonin syndrome, and seizures. Monitor for signs of urinary retention and reduced gastric motility.
Trifluoperazine: (Moderate) Concurrent use of tramadol and trifluoperazine should be avoided if possible. Antipsychotics may enhance the seizure risk of tramadol. Additive CNS depression may also be seen with the concomitant use of tramadol and trifluoperazine.
Trihexyphenidyl: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Trimethobenzamide: (Moderate) The concurrent use of trimethobenzamide with other medications that cause CNS depression, like tramadol, may potentiate the effects of either trimethobenzamide or tramadol.
Trospium: (Moderate) Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with an anticholinergic drug, such as trospium. The concomitant use of tramadol and anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Opiates increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.
Valproic Acid, Divalproex Sodium: (Moderate) Concomitant use of opioid agonists with valproic acid may cause excessive sedation and somnolence. Limit the use of opioid pain medications with valproic acid to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Educate patients about the risks and symptoms of excessive CNS depression.
Vemurafenib: (Moderate) Concomitant use of vemurafenib and tramadol may result in altered concentrations of tramadol. Vemurafenib is a weak inhibitor of CYP2D6 and an inducer of CYP3A4. Tramadol is a substrate of CYP2D6 and CYP3A4. Use caution and monitor patients for toxicity and efficacy.
Venlafaxine: (Major) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering serotonin norepinephrine reuptake inhibitors (SNRIs) with other drugs that have serotonergic properties such as tramadol. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome. In one case, the addition of tramadol to extended-release venlafaxine (300 mg/day) and mirtazapine (30 mg/day) likely caused serotonin syndrome. A patient developed agitation, confusion, severe shivering, diaphoresis, myoclonus, hyperreflexia, mydriasis, tachycardia, and fever within 7 weeks of taking tramadol 400 mg daily. He had taken 300 mg tramadol without difficulty. Discontinuation of the 3 drugs and rehydration led to symptom resolution over 36 hours. Reinstitution of the antidepressants 3 days after patient presentation was uneventful. Also, duloxetine and venlafaxine may inhibit the formation of the active M1 metabolite of tramadol by inhibiting CYP2D6. The inhibition of this metabolite may decrease the analgesic effectiveness of tramadol but increase the level of the parent compound, which has more serotonergic activity than the metabolite The risk for serious adverse effects such as seizures and serotonin syndrome may be increased. Patients receiving tramadol in combination with an SNRI should be monitored for the emergence of serotonin syndrome or other adverse effects.
Vigabatrin: (Moderate) Tramadol may decrease the seizure threshold and thus, interfere with the ability of anticonvulsants to control seizures. Vigabatrin may cause somnolence and fatigue. Drugs that can cause CNS depression, if used concomitantly with vigabatrin, may increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness. Caution should be used when vigabatrin is given in combination with tramadol.
Vilazodone: (Major) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering vilazodone with other drugs that have serotonergic properties such as tramadol. Serotonin syndrome is characterized by the rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Patients receiving vilazodone and tramadol should be monitored for the emergence of serotonin syndrome, particularly during treatment initiation and during dosage increases. Vilazodone and tramadol should be discontinued if serotonin syndrome occurs and supportive symptomatic treatment should be initiated. Due to the CNS effects of vilazodone, caution should be used when vilazodone is given in combination with other centrally acting medications such as tramadol.
Voriconazole: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with voriconazole is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of voriconazole, a strong CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Vortioxetine: (Major) Because of the potential risk and severity of serotonin syndrome, caution should be observed when administering vortioxetine with other drugs that have serotonergic properties such as tramadol. Serotonin syndrome is characterized by rapid development of hyperthermia, hypertension, myoclonus, rigidity, autonomic instability, mental status changes (e.g., delirium or coma), and in rare cases, death. Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome. Several cases of serotonin syndrome have been reported after the administration of tramadol with serotonergic antidepressants. Patients receiving tramadol in combination with vortioxetine should be monitored for the emergence of serotonin syndrome or other adverse effects.
Voxelotor: (Moderate) Consider a tramadol dosage reduction until stable drug effects are achieved if coadministration with voxelotor is necessary. Closely monitor for seizures, serotonin syndrome, and signs of sedation and respiratory depression. Respiratory depression from increased tramadol exposure may be fatal. Concurrent use of voxelotor, a weak CYP3A4 inhibitor, may increase tramadol exposure and result in greater CYP2D6 metabolism thereby increasing exposure to the active metabolite M1, which is a more potent mu-opioid agonist.
Warfarin: (Moderate) Monitor prothrombin time and adjust the warfarin dose as needed if administered with tramadol. Advise patients of the increased bleeding risk associated with concomitant use. Alterations in warfarin effect and elevated prothrombin time have been reported rarely following coadministration in postmarketing surveillance.
Zaleplon: (Major) Concomitant use of opioid agonists with zaleplon may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Limit the use of opioid pain medications with zaleplon to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression.
Ziconotide: (Moderate) Tramadol is a CNS depressant medication that may increase drowsiness, dizziness, and confusion that are associated with ziconotide. Due to potentially additive effects, dosage adjustments may be necessary.
Ziprasidone: (Moderate) Concurrent use of tramadol and ziprasidone should be avoided if possible. Antipsychotics may enhance the seizure risk of tramadol. Additive CNS depression may also be seen with the concomitant use of tramadol and ziprasidone.
Zolmitriptan: (Moderate) Caution is advised when tramadol is coadministered with serotonin-receptor agonists because of the potential for serotonin syndrome. If concomitant treatment of tramadol and a serotonin-receptor agonist is clinically warranted, careful observation of the patient is advised, especially during the initial time both drugs are used together and during a dose increase of either tramadol or the serotonin-receptor agonist.

Zolpidem: (Major) Concomitant use of opioid agonists with zolpidem may cause excessive sedation, somnolence, and complex sleep-related behaviors (e.g., driving, talking, eating, or performing other activities while not fully awake). Limit the use of opioid pain medications with zolpidem to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. Instruct patients to contact their provider immediately if sleep-related symptoms or behaviors occur. Educate patients about the risks and symptoms of excessive CNS depression. A dosage reduction of the Intermezzo brand of sublingual zolpidem tablets to 1.75 mg/night is recommended in patients receiving concomitant CNS depressants.

PREGNANCY AND LACTATION

Pregnancy

Breast-feeding is not recommended during treatment with tramadol because of the potential for serious adverse events, including excess sedation and respiratory depression in the breastfed infant. If an infant is exposed to tramadol through breast milk, they should be monitored for excessive sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal use of an opioid is stopped or when breast-feeding is stopped. Alternative analgesics that previous American Academy of Pediatrics recommendations considered as usually compatible with breast-feeding include acetaminophen, ibuprofen, and morphine. There is no information on the effects of tramadol on milk production. Tramadol and its metabolite (M1) are excreted into human milk. An infant nursing from an ultra-rapid metabolizer mother taking tramadol could potentially be exposed to high metabolite concentrations and experience life-threatening respiratory depression. In women with normal tramadol metabolism (normal CYP2D6 activity), the amount of tramadol secreted into human milk is low and dose-dependent. After a single IV dose of tramadol 100 mg, the cumulative excretion in breast milk within 16 hours was 100 mcg of tramadol (0.1% of the maternal dose) and 27 mcg of M1. Samples of breast milk taken from 75 women 2 to 4 days postpartum after receiving at least 4 doses of tramadol indicated that an exclusively breast-fed infant would receive 2.24% of the maternal weight adjusted dose of tramadol and 0.64% of its metabolite. Assessments of the infants of these mothers using the Neurologic and Adaptive Capacity Score found no difference when compared to infants in a control group. Forty-nine percent of mothers in the tramadol group and 100% of mothers in the control group were also receiving other opioids (mostly oxycodone).

MECHANISM OF ACTION

Mechanism of Action: Tramadol has a unique dual mechanism of pain relief. It has central opiate receptor agonist activity and, thus, exerts an analgesic effect from binding of the parent drug and the O-desmethyltramadol metabolite (M1) to mu-receptors. The relative contribution of tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound (see Pharmacokinetics). There are limited data available on the efficacy of tramadol for pain in poor versus extensive CYP2D6 metabolizers. Data from a randomized, double-blind, crossover study suggest that receipt of tramadol 2 mg/kg orally produces a greater analgesic effect, especially after the first 4 hours after dosing in extensive metabolizers whereas the analgesic effect in poor metabolizers is more modest but is sustained up to 10 hours after dosing. The threshold for pressure pain detection, tolerance, nociceptive reflex, and peak pain as compared with placebo was greater in extensive metabolizers as compared with the difference between placebo and tramadol receipt in poor metabolizers. The affinity of tramadol for mu-receptors is 10-fold less than codeine, 60-fold less than propoxyphene, and 6000-fold less than morphine. The M1 metabolite has 4—200 times greater affinity for the μ-receptor than tramadol. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone (see Interactions). Opiate receptors are coupled with G-protein (guanine-nucleotide-binding protein) receptors and function as modulators, both positive and negative, of synaptic transmission via G-proteins that activate effector proteins. Opiate agonists decrease intracellular cAMP by inhibiting adenylate cyclase which modulates the release of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine and norepinephrine. The stimulatory effects of opioids are the result of 'disinhibition' as the release of inhibitory neurotransmitters such as GABA and acetylcholine is blocked. The exact mechanism how opioid agonists cause both inhibitory and stimulatory processes is not well understood.In addition to central opiate receptor agonist activity, tramadol exerts norepinephrine and serotonin reuptake inhibition in the CNS, which inhibits pain transmission in the spinal cord. The monoaminergic reuptake blockade, similar to MAOIs, is an important contribution to the analgesic and adverse event profile of tramadol. The inhibitory reuptake effects of tramadol on norepinephrine and serotonin are 100—1000 times less than those of imipramine.

PHARMACOKINETICS

Tramadol is administered orally, rectally, or intravenously; however, only the oral formulations are available in the United States. Tramadol has a high tissue affinity. Minimum protein binding occurs (about 20%) and appears to be independent of concentration up to 10 mcg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range. The drug volume of distribution ranges from 2.6 to 2.9 L/kg. Tramadol is known to cross the placenta; in 40 women given tramadol during labor, a mean ratio of tramadol serum concentration in umbilical veins as compared to maternal veins was 0.83. Approximately 0.1% of the maternal dose is distributed into breast milk.

Tramadol undergoes significant first-pass metabolism after oral administration. Hepatic metabolism takes place via 2 metabolic, phase I pathways to form N- and O-demethylated tramadol. Of a tramadol dose, 60% is metabolized by the liver. The metabolism is also stereoselective; the (-) enantiomer undergoes O-demethylation selectively, and the (+) enantiomer preferentially undergoes N-demethylation, which is mediated by CYP3A4 and CYP2B6. O-demethylation is mediated by CYP2D6, and the O-demethylated metabolites are further conjugated (phase II reactions). Of 11 identified metabolites, only the O-demethylated metabolite (M1) has analgesic activity, which appears to be critical to the activity of tramadol. The production of M1 depends on CYP2D6. Patients with impaired CYP2D6 activity or those receiving concurrent medications that affect CYP2D6 or CYP3A4 enzymes may experience an altered response to tramadol. Excretion of tramadol and its metabolites is mostly renal. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites. In normal healthy adults, the mean terminal plasma elimination half-lives of racemic tramadol and racemic M1, respectively, are approximately 6.3 and 7.4 hours after administration of immediate-release tramadol (either ODT or regular tablets), 7.9 and 8.8 hours after administration of coated extended-release tablets, 6.5 and 7.5 hours after administration of dual-matrix extended-release tablets, and 10 and 11 hours after administration of extended-release capsules.

Oral Route

Immediate-release tablets (e.g., Ultram): Absorption of immediate-release tablets is rapid and bioavailability is 68% after single doses and approaches 100% after multiple doses; the increase in bioavailability with multiple doses is thought to be due to saturable first-pass metabolism. The rate and extent of oral absorption of the immediate-release tablets is not significantly affected by food. Tramadol is detected in plasma within 15 to 45 minutes of oral dosing, with peak plasma concentrations of tramadol occurring at about 1.5 hours post-dose and peak plasma concentrations of the active metabolite M1 occurring at about 2 hours post-dose. Analgesia onset is within 1 hour of administration of the immediate-release tablets with a peak effect around 2 to 3 hours; analgesia lasts about 6 hours. Similar to the orally disintegrating tablets and the dual-matrix extended-release tablets, steady state concentrations are achieved after 2 days of multiple dosing with the immediate-release tablets.

Orally disintegrating tablets (Rybix ODT): The absolute bioavailability of orally disintegrating tramadol is approximately 75% after the administration of a single 100 mg dose. The rate and extent of oral absorption of the orally disintegrating tablets is not significantly affected by food. There are no studies to indicate that the onset of action of tramadol orally disintegrating tablets (time unstated) is any faster than that of the immediate-release tablets (within 1 hour). After administration of orally disintegrating tablets, peak plasma concentrations of tramadol occur at approximately 2 hours post-administration and peak plasma concentrations of the active metabolite M1 occur at approximately 3 hours post-dose. As with the immediate-release tablet and the dual-matrix extended-release tablets, steady state concentrations are achieved after 2 days

of multiple dosing with the orally disintegrating tablets. At equipotent doses of immediate-release and orally disintegrating tablets, the AUC, Cmax, time to peak exposure, and half-life of tramadol are similar.
Dual-matrix extended-release tablets (Ryzolt): The dual-matrix release tablet has characteristics of both the immediate-release and the coated extended-release formulations. The bioavailability of a 200 mg dual-matrix extended-release tablet, relative to a 50 mg immediate-release tablet every 6 hours, was 95%. The rate and extent of oral absorption of the dual-matrix extended-release tablets is not significantly affected by food. After administration of dual matrix extended-release tablets, peak plasma concentrations of tramadol occur at about 4 hours post-dose and the peak plasma concentrations of the active metabolite M1 occur at about 5 hours post-dose. Steady state concentrations are achieved after 2 days of multiple dosing with the dual-matrix extended-release tablets compared to 2 days of either immediate-release tablet or orally disintegrating tablet therapy and 4 days of coated extended-release tablet use. In healthy patients, pharmacokinetic parameters are approximately dose proportional over a 100 to 300 mg dose range.
Coated extended-release tablets (e.g., Ultram ER): The bioavailability of a 200 mg coated extended-release tablet, relative to a 50 mg immediate-release tablet every 6 hours, was approximately 85 to 90%. Unlike other oral dosage formulations, coated extended-release tablets are recommended to be taken in a consistent manner with or without food, as the Cmax and systemic exposure of tramadol decreased 28% and 16%, respectively, when a single 200 mg dose was taken with a high fat meal as compared with fasting conditions. Further, the mean Tmax increased from 14 hours under fasting conditions to 17 hours under fed conditions. After administration of coated extended-release tablets, peak plasma concentrations of tramadol occur at about 12 hours post-dose and peak plasma concentrations of the active metabolite M1 occur at about 15 hours post-dose. The mean Cmax and systemic exposure at steady state are similar for 200 mg coated extended-release tablets administered once daily and 50 mg immediate-release tablets administered every 6 hours. Steady state concentrations are achieved after 4 days of therapy with the coated extended-release tablets compared to 2 days of therapy with the dual-matrix extended-release tablets. In healthy patients, pharmacokinetic parameters are approximately dose proportional over a 100 to 400 mg dose range. However, systemic exposure after tramadol 400 mg oral dose of coated extended-release tablet was 26% higher than predicted based on systemic exposure after a 200 mg dose.
Extended-release capsules (ConZip): Extended-release tramadol capsules contain both immediate-release (IR) and extended-release (ER) tramadol in the following specific amounts: 100 mg capsules contain 25 mg IR and 75 mg ER, 200 mg capsules contain 50 mg IR and 150 mg ER, and 300 mg capsules contain 50 mg IR and 250 mg ER. The rate and extent of oral absorption is not significantly affected by food. After administration, peak plasma concentrations of tramadol occur at 5.9 hours post-dose and the peak plasma concentrations of the active metabolite M1 occur at 11 hours post-dose. Steady state concentrations of both tramadol and M1 are achieved after 4 days of once-daily dosing. In healthy patients, pharmacokinetic parameters are approximately dose proportional over a 100 to 300 mg dose range.

Intramuscular Route

NOTE: This dosage form is not available in the U.S.

Following IM administration, the bioavailability of tramadol is 100%.

Other Route(s)

Rectal Route
NOTE: This dosage form is not available in the U.S.

Following rectal administration, the bioavailability of tramadol is 78%.

Exhibit 3

Exhibit 3

PDR.net

CLASSES

Anxiolytics, Benzodiazepines

BOXED WARNING

Chronic obstructive pulmonary disease (COPD), coadministration with other CNS depressants, pulmonary disease, respiratory depression, sleep apnea

As with other benzodiazepines, alprazolam should be avoided in patients with pulmonary disease if possible. Additionally, avoid coadministration with other CNS depressants, especially opioids, unless no other alternatives are available as coadministration significantly increases the risk for respiratory depression, low blood pressure, and death. Alprazolam should be avoided if possible in patients with respiratory depression severe chronic obstructive pulmonary disease (COPD), or sleep apnea because the drug can exacerbate ventilatory failure. In rare instances, death has occurred in patients with severe pulmonary disease shortly after the initiation of alprazolam.

DEA CLASS

Rx, schedule IV

DESCRIPTION

Oral benzodiazepine used for the management of anxiety including panic disorder; relatively shorter half-life and absence of active metabolites; potential for significant CYP3A4 interactions.

COMMON BRAND NAMES

Niravam, Xanax, Xanax XR

HOW SUPPLIED

Alprazolam Oral Sol: 1mg, 1mL
Alprazolam/Niravam Oral Tab Orally Dis: 0.25mg, 0.5mg, 1mg, 2mg
Alprazolam/Xanax Oral Tab: 0.25mg, 0.5mg, 1mg, 2mg
Alprazolam/Xanax XR Oral Tab ER: 0.5mg, 1mg, 2mg, 3mg

DOSAGE & INDICATIONS

For the treatment of transient symptoms of anxiety, anxiety associated with depression, or generalized anxiety disorder (GAD).

Oral dosage (immediate-release tablets, orally disintegrating tablets or oral solution)

Adults

Initially, 0.25 mg to 0.5 mg PO 3 times per day. Use the lower dose for debilitated adults initially. If clinically indicated, increase the dose as tolerated at intervals of 3 to 4 days, up to a maximum of 4 mg/day in divided doses. If discontinuation becomes necessary, the manufacturer suggests that the daily dose be decreased by no more than 0.5 mg every 3 days. Some patients may require a more gradual and individualized taper.

Geriatric Adults

Initially, 0.25 mg PO 2 or 3 times daily. Lower initial doses may be appropriate in some patients. If indicated, the dose may be increased gradually as tolerated. The maximum adult dosage is 4 mg/day PO. The elderly may be more sensitive to the effects of benzodiazepines. If discontinuation becomes necessary, the manufacturer suggests that the daily dose be decreased by no more than 0.5 mg every 3 days. Some patients may require a more gradual and individualized taper. The federal Omnibus Budget Reconciliation Act (OBRA) regulates the use of anxiolytics in long-term care facility (LTCF) residents. Max: 0.75 mg/day PO in residents meeting the criteria for treatment, except when documentation is provided showing that higher doses are necessary to maintain or improve the resident's functional status. In addition, the facility should attempt periodic tapering of the medication or provide documentation of medical necessity in accordance with OBRA guidelines.

Children† and Adolescents† 7 years and older

Definitive dosage not established. In a study of children 7 to 16 years old (n = 13), initial doses of 0.005 mg/kg/dose PO or 0.125 mg/dose PO were given 3 times per day for situational anxiety. Doses were increased in 0.125 mg to 0.25 mg increments. Max: 0.02 mg/kg/dose PO or 0.06 mg/kg/day PO. In another study of children with overanxious or avoidant disorder (n = 30), initial doses were 0.25 mg PO per day for children 40 kg or less and 0.5 mg PO per day for those more than 40 kg. Doses were titrated at 2-day intervals to a maximum of 0.04 mg/kg/day. Required doses ranged from 0.5 mg to 3.5 mg/day with a mean dose of 1.6 mg/day.

For the treatment of panic disorder with or without agoraphobia.

Oral dosage (immediate-release tablets, orally disintegrating tablets or oral solution)

Adults

Initially, 0.5 mg PO 3 times per day. In debilitated adults, a lower initial dose of 0.25 mg PO 2 or 3 times daily is recommended. The dose may be increased gradually as tolerated, by no more than 1 mg/day at intervals of 3 to 4 days. Many patients require more than 4 mg/day. It is advisable to slowly titrate to higher doses and divide the doses throughout the waking hours on a 3 to 4 times per day schedule. Periodically reassess for possible dose reduction. During clinical trials, the mean effective dosage was 5 to 6 mg/day, although doses up to 10 mg/day were required in some patients. If discontinuation becomes necessary, decrease the daily dose by no more than 0.5 mg every 3 days. Some patients may require a more gradual and individualized taper.

Geriatric Adults

Initially, 0.25 mg PO 2 or 3 times daily. Lower initial doses may be appropriate in some patients. The dose may be increased gradually as tolerated, at intervals of 3 to 4 days. During clinical trials in younger adults, the mean effective dosage was 5 to 6 mg/day. The geriatric patient is more sensitive to the effects of benzodiazepines; use lowest effective dose. If discontinuation becomes necessary, decrease the daily dose by no more than 0.5 mg every 3 days. Some patients may require a more gradual and individualized taper. The federal Omnibus Budget Reconciliation Act (OBRA) regulates the use of anxiolytics in long-term care facility (LTCF) residents. Max: 0.75 mg/day PO in residents meeting the criteria for treatment, except when documentation is provided showing that higher doses are necessary to maintain or improve the resident's functional status. In addition, the facility should attempt periodic tapering of the medication or provide documentation of medical necessity in accordance with OBRA guidelines.

Oral dosage (extended-release tablets, Xanax XR)

Adults

Initially, 0.5 mg to 1 mg PO once a day, preferably in the morning. Use the lower initial dose in debilitated adult patients. Increase by no more than 1 mg/day, at intervals of every 3 to 4 days, as needed and tolerated. 3 to 6 mg PO once daily was the effective dose in most patients during clinical trials. Up to 10 mg/day has been required in occasional patients. To switch from immediate-release alprazolam, calculate the total daily dose and administer once daily using the XR formulation. If discontinuation becomes necessary, decrease the daily dose by no more than 0.5 mg every 3 days. Some patients may require a more gradual and individualized taper.

Geriatric Adults

Initially, 0.5 mg PO once daily, preferably in the morning. Gradually increase as needed and tolerated. In younger patients, doses were increased in increments of 1 mg/day or less, at intervals of every 3 to 4 days. Doses as high as 10 mg/day have been used in adults. However, the elderly are more sensitive to the effects of benzodiazepines; use the lowest effective dose. To switch from immediate-release alprazolam, calculate the total daily dose and administer once daily using the XR formulation. The federal Omnibus Budget Reconciliation Act (OBRA) regulates the use of anxiolytics in long-term care facility (LTCF) residents. Max: 0.75 mg/day PO in residents meeting criteria for treatment, except when documentation is provided showing that higher doses are necessary to maintain or improve the resident's functional status. In addition, the facility should attempt periodic tapering of the medication or provide documentation of medical necessity in accordance with OBRA guidelines.

For the treatment of anxiety and mood-symptoms associated with premenstrual syndrome (PMS)† or premenstrual dysphoric disorder (PMDD)† that are unresponsive to non-pharmacologic therapy.

Oral dosage (immediate-release tablets or oral solution)

Adult females

0.25 mg PO three times daily administered during the luteal phase through the second day of menses has been studied and was found to be superior to placebo in treating the emotional symptoms associated with PMS. A maximum dose up to 4 mg/day is recommended. Dose should be tapered by 25% per day through menses. In a placebo-controlled, comparative study with oral progesterone of 138 subjects, after 3 months, alprazolam was superior to progesterone or placebo overall but progesterone was better than alprazolam for physical symptoms while alprazolam was better than progesterone for controlling mood and mental function. Alprazolam was initially dosed at 0.25 mg PO four times per day administered from day 18 of the menstrual cycle to the first day of menses with a taper on the first 2 menstrual days, however, dosing was flexible; patients could receive up to twelve 0.25 mg capsules/day if necessary. The actual alprazolam dose taken during the third treatment cycle was 1.5 mg/day PO.

†Indicates off-label use

MAXIMUM DOSAGE

Adults

10 mg/day PO.

Geriatric

10 mg/day PO.

Adolescents

Safety and efficacy have not been established; 0.06 mg/kg/day PO (immediate-release tablets or oral solution) has been suggested for the treatment of anxiety.

Children

7 years and older: Safety and efficacy have not been established; 0.06 mg/kg/day PO (immediate-release tablets or oral solution) has been suggested for the treatment of anxiety.
Less than 7 years: Safety and efficacy have not been established.

DOSING CONSIDERATIONS

Hepatic Impairment

Quantitative guidelines are not available for the immediate-release product; consider initial dose reduction in those with hepatic impairment. A lower initial adult dose of extended-release alprazolam (e.g., 0.5 mg PO once daily) is suggested. Titrate as needed and tolerated to attain clinical goals.

Renal Impairment

Guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

ADMINISTRATION

Oral Administration

Oral Solid Formulations

Immediate-release tablets
May be administered without regard to meals.

Orally disintegrating tablets (ODT)
Do not remove ODT from the package until just prior to administration.
With dry hands, place the tablet on top of the tongue where it will disintegrate and be swallowed with saliva.
Administration with liquid is not necessary.

Extended-release tablets
Do not chew, break or crush. Patient should swallow whole with a drink of water.
Extended-release tablets should be taken preferably in the morning.

Oral Liquid Formulations

Oral solution
May be administered without regard to meals.
Measure with a calibrated oral liquid medicine measuring device to give an accurate dose.

STORAGE

Generic:
- Discard opened bottle after 90 days
- Protect from light
- Store at room temperature (between 59 to 86 degrees F)

Niravam:
- Store between 68 to 77 degrees F, excursions permitted 59 to 86 degrees F

Xanax:
- Protect from light
- Store at controlled room temperature (between 68 and 77 degrees F)

Xanax XR:
- Store between 68 to 77 degrees F, excursions permitted 59 to 86 degrees F

CONTRAINDICATIONS / PRECAUTIONS

Benzodiazepine hypersensitivity

Alprazolam is contraindicated in any patient with a known alprazolam or other benzodiazepine hypersensitivity or known allergies to any component of the formulation.

Abrupt discontinuation, benzodiazepine dependence, seizure disorder, seizures, status epilepticus, substance abuse

Alprazolam can cause physical and psychological dependence, and should be used with caution in patients with known, suspected, or a history of substance abuse. The risk of dependence with alprazolam appears to be most probable with daily dosages greater than 4 mg and with a treatment period of more than 12 weeks. Abrupt discontinuation of alprazolam after prolonged use should be avoided. Abrupt discontinuation of benzodiazepine therapy has been reported to cause a withdrawal syndrome (see Adverse Effects), especially following high dose or prolonged benzodiazepine therapy. However, benzodiazepine dependence can occur with therapeutic doses administered for as few as 1—2 weeks and withdrawal symptoms may be seen following the discontinuance of therapy. Benzodiazepine withdrawal also can be more intense if the benzodiazepine involved possesses a relatively short duration of action such as alprazolam. Panic rebound may be particularly problematic for patients receiving higher doses for panic disorder. Patients with a history of a seizure disorder or who are taking other drugs that lower the seizure threshold (i.e., TCAs, phenothiazines) should not be withdrawn abruptly from alprazolam due to the risk of precipitating seizures; status epilepticus has also been reported during therapy with immediate-release alprazolam. During withdrawal, the greatest risk of seizure appears to be during the first 24 to 72 hours. Seizures have also been reported with the use of the extended-release formulation of alprazolam, due to abrupt withdrawal and/or concomitant alcohol intake. Alprazolam (immediate-release or extended-release formulations) should be withdrawn slowly, using a gradual tapering schedule. Flumazenil, a benzodiazepine receptor antagonist, is indicated for partial or complete reversal of the depressive effects of benzodiazepines, and may be useful in overdose situations (see Flumazenil monograph). The prescriber should be aware of the risk for seizure activity with flumazenil use, particularly in long-term users of benzodiazepines or patients presenting with a cyclic antidepressant overdose.

Anxiety

Worsening of daytime anxiety has been reported with the use of some hypnotic benzodiazepines, such as alprazolam, as few as 10 days after continuous use. In some patients this may be due to interdose withdrawal. If increased daytime anxiety is observed, it may be advisable to discontinue treatment gradually.

Bipolar disorder, depression, mania, psychosis, suicidal ideation

Although alprazolam is occasionally beneficial for patients with major depression, the drug should be administered to these patients with careful monitoring. According to the manufacturer, alprazolam typically has no use in the treatment of psychosis; use with extreme caution if at all in patients with suicidal ideation. Alprazolam should be used cautiously in patients with bipolar disorder because mania and hypomania have been reported in conjunction with the use of alprazolam in depressive disorders.

Chronic obstructive pulmonary disease (COPD), coadministration with other CNS depressants, pulmonary disease, respiratory depression, sleep apnea

As with other benzodiazepines, alprazolam should be avoided in patients with pulmonary disease if possible. Additionally, avoid coadministration with other CNS depressants, especially opioids, unless no other alternatives are available as coadministration significantly increases the risk for respiratory depression, low blood pressure, and death. Alprazolam should be avoided if possible in patients with respiratory depression severe chronic obstructive pulmonary disease (COPD), or sleep apnea because the drug can exacerbate ventilatory failure. In rare instances, death has occurred in patients with severe pulmonary disease shortly after the initiation of alprazolam.

CNS depression, coma, driving or operating machinery, ethanol ingestion, ethanol intoxication, shock

Due to CNS depression, patients should be cautioned against driving or operating machinery until they know how alprazolam may affect them. Some patients may experience excessive sedation and an impaired ability to perform tasks. Anterograde amnesia may occur with any short-acting benzodiazepine if given in sufficient doses. Because alprazolam can cause drowsiness and a decreased level of consciousness, there is a higher risk of falls, particularly in the elderly, with the potential for subsequent severe injuries. Increased CNS and respiratory effects may be seen with concurrent use of alprazolam and other CNS depressant agents, including alcohol. Ethanol ingestion should be avoided during treatment with alprazolam. Patients with ethanol intoxication who have also consumed alprazolam have an increased risk of respiratory depression and coma. Benzodiazepines should be used cautiously in patients in shock or coma due to the increased risk of further CNS and respiratory depression.

Closed-angle glaucoma

Alprazolam is contraindicated in patients with acute closed-angle glaucoma. However, the benzodiazepine may be used in patients with open-angle glaucoma who are receiving appropriate therapy. The mechanistic rational for this contraindication has been questioned, as benzodiazepines do not have antimuscarinic activity and do not raise intraocular pressure; few cases have been reported.

Myasthenia gravis

Alprazolam should be used with extreme caution in patients with myasthenia gravis because the drug can exacerbate this condition.

Parkinson's disease

Patients with late stage Parkinson's disease may experience worsening of their psychosis or impaired cognition with administration of benzodiazepines, such as alprazolam. Benzodiazepines may also cause incoordination or paradoxical reactions that may worsen symptoms of Parkinson's disease.

Porphyria

The administration of alprazolam can exacerbate acute intermittent porphyria, so the drug should be used with caution in patients with this condition.

Labor, neonates, obstetric delivery, pregnancy

Alprazolam, like other benzodiazepines, poses a risk of harm to the fetus when administered to pregnant women. Positive evidence of human fetal risk exists based on investigational, marketing, or human studies. In general, the use of benzodiazepines is not life-saving and thus should be avoided in pregnancy whenever possible. An increased risk of congenital malformations and other developmental abnormalities is associated with benzodiazepine use during the first trimester. If alprazolam is to be used during pregnancy or the patient becomes pregnant while taking alprazolam, the patient should be apprised of the potential hazard to the fetus. The possibility that a woman of childbearing age may be pregnant when initiating therapy with alprazolam should be considered. Patients who become pregnant or intend to become pregnant while taking alprazolam should be advised to discuss the possibility of discontinuing the drug with their physician. It should be anticipated that neonates may experience withdrawal symptoms if the mother has been using benzodiazepines during pregnancy. Neonatal flaccidity has been reported in an infant whose mother was using benzodiazepines during pregnancy. Alprazolam has no established use in labor or obstetric delivery.

Breast-feeding

Many benzodiazepines distribute into breast milk. Because of the potential for adverse effects in the nursing infant, such as sedation, feeding difficulties, and weight loss, alprazolam generally is not recommended during breast-feeding. The estimated dose that a breast-feeding infant would receive based on breat milk concentrations after single oral doses of 0.5 mg has been reported to be 0.5—5 mcg/kg/day or approximately 3% of the maternal weight-adjusted dose. Irritability and withdrawal symptoms have been reported in babies exposed to alprazolam through breast milk upon discontinuation of either breast-feeing or alprazolam. Alprazolam is listed by the American Academy of Pediatrics as a drug whose effect on the nursing infant is not known but may be of concern, particularly with prolonged exposure. If occasional maternal therapy with a benzodiazepine is required, a shorter-acting agent such as lorazepam may be considered. Some experts have concluded that occasional maternal treatment with usual doses of lorazepam would pose little risk to a nursing infant. If any benzodiazepine is used by a breast-feeding mother, monitor the infant for adverse effects, such as sedation. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding baby experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

Hepatic disease, obesity

Alprazolam should be administered cautiously to patients with severe hepatic disease because the elimination half-life of the drug can be prolonged, possibly resulting in toxicity. Patients with hepatic disease are more likely to experience adverse CNS reactions and should receive reduced initial dosages. Additionally, alprazolam is significantly metabolized via the hepatic microsomal P450 isoenzyme CYP3A4. Concomitant administration of alprazolam and potent inhibitors of CYP3A4 is contraindicated. Medications considered to be potent CYP3A4 inhibitors which should not be used concurrently with alprazolam include systemically-administered azole antifungals, some macrolide antibiotics, and anti-retroviral protease inhibitors (see Drug Interactions). Other CYP3A4 inhibitors could potentially cause alprazolam toxicity (see Drug Interactions). This list is not inclusive of all agents that may potently inhibit CYP3A4. Reduced elimination of alprazolam has also been reported in obesity.

Renal failure, renal impairment

Patients with renal impairment, including renal failure, should be carefully monitored during prolonged treatment with benzodiazepines, such as alprazolam, in order to avoid the adverse reactions that may occur from drug accumulation.

Dementia, geriatric

Use alprazolam with caution in geriatric adults as the clearance and/or elimination of alprazolam are reduced. The mean half-life of alprazolam is prolonged to 16.3 hours in the geriatric population compared to 11.2 hours in healthy adult subjects. Delayed elimination can either intensify or prolong the actions of adverse reactions of the drug. It is recommended that the dosage be limited to the smallest effective dose to preclude the development of ataxia or oversedation which may be a particular problem in debilitated or geriatric patients. The impairment of cognitive and motor function may be more marked in this patient group and a lower dosage is recommended together with close monitoring. Because alprazolam can cause drowsiness and a decreased level of consciousness, there is a higher risk of falls, particularly in the elderly, with the potential for subsequent severe injuries. According to the Beers Criteria, benzodiazepines are considered potentially inappropriate medications (PIMs) in geriatric patients and avoidance is generally recommended, although some agents may be appropriate for conditions such as seizure disorders, rapid eye movement sleep disorders, benzodiazepine or ethanol withdrawal, severe generalized anxiety disorder, or peri-procedural anesthesia. Older adults have an increased sensitivity to benzodiazepines. In general, all benzodiazepines increase the risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents in older adults. The Panel recommends avoiding benzodiazepines in geriatric patients with the following due to the potential for symptom exacerbation or adverse effects: delirium (new-onset or worsening delirium), dementia (adverse CNS effects), and history of falls/fractures (ataxia, impaired psychomotor function, syncope, and additional falls). If a benzodiazepine must be used in a patient with a history of falls or fractures, consider reducing use of other CNS-active medications that increase the risk of falls and fractures and implement other strategies to reduce fall risk. The federal Omnibus Budget Reconciliation Act (OBRA) regulates medication use in residents of long-term care facilities (LTCFs). Specific criteria for anxiolytics must be met, including 1) limiting use to indications specified in the OBRA guidelines (e.g., generalized anxiety disorder, panic disorder, significant anxiety to a situational trigger, alcohol withdrawal) which meet the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for the indication, and 2) evidence exists that other possible reasons for the individual's distress have been considered, and 3) use results in maintenance or improvement in mental, physical, and psychosocial well-being as reflected on the Minimum

Data Set (MDS) or other assessment tool. Anxiolytics should be used for delirium, dementia, or other cognitive disorders only when there are associated behaviors that are 1) quantitatively and objectively documented, and 2) are persistent, and 3) are not due to preventable or correctable reasons, and 4) constitute clinically significant distress or dysfunction to the LTCF resident or represent a danger to the resident or others. There are exceptions that may warrant the use of an anxiolytic such as a long-acting benzodiazepine for withdrawal from a short-acting benzodiazepine, use for neuromuscular syndromes (e.g., tardive dyskinesia, restless legs syndrome, seizure disorder, cerebral palsy), or end of life care. Benzodiazepines may increase the risk of confusion, sedation, and falls. OBRA provides dosing guidance for alprazolam as an anxiolytic. When a medication is being used to manage behavior, stabilize mood, or treat a psychiatric disorder, the facility should attempt periodic tapering of the medication or provide documentation of medical necessity in accordance with OBRA guidelines.

Children, infants

The safe and effective use of alprazolam in neonates, infants, children and adolescents less than 18 years old has not been established. Children are generally more sensitive to the CNS effects of benzodiazepines.

ADVERSE REACTIONS

Severe

seizures / Delayed / 0.1-0.9
angioedema / Rapid / Incidence not known
Stevens-Johnson syndrome / Delayed / Incidence not known
hepatic failure / Delayed / Incidence not known
teratogenesis / Delayed / Incidence not known

Moderate

withdrawal / Early / 10.0-35.0
memory impairment / Delayed / 5.5-33.1
impaired cognition / Early / 7.2-28.8
constipation / Delayed / 8.1-26.2
dysarthria / Delayed / 10.9-23.3
sinus tachycardia / Rapid / 0.1-15.4
depression / Delayed / 1.3-13.9
confusion / Early / 1.5-10.4
ataxia / Delayed / 7.2-7.2
edema / Delayed / 0.1-4.9
hypotension / Rapid / 0.1-4.7
akathisia / Delayed / 1.6-3.0
dyskinesia / Delayed / 1.7-1.7
hot flashes / Early / 1.5-1.5
amnesia / Delayed / 0.1-0.9
euphoria / Early / 0.1-0.9
mania / Early / 0.1-0.9
impulse control symptoms / Delayed / 0.1-0.9
dysphonia / Delayed / 0.1-0.9
hypotonia / Delayed / 0.1-0.9
urinary incontinence / Early / 0.1-0.9
dysuria / Early / 0.1-0.9
photophobia / Early / 0.1-0.9
dyspnea / Early / 0.1-0.9
hallucinations / Early / 0.1-0.9
blurred vision / Early / 1.0
palpitations / Early / 1.0
chest pain (unspecified) / Early / 1.0
tolerance / Delayed / Incidence not known
psychological dependence / Delayed / Incidence not known
physiological dependence / Delayed / Incidence not known
hostility / Early / Incidence not known
peripheral edema / Delayed / Incidence not known
jaundice / Delayed / Incidence not known
hyperbilirubinemia / Delayed / Incidence not known
elevated hepatic enzymes / Delayed / Incidence not known
hyperprolactinemia / Delayed / Incidence not known
hepatitis / Delayed / Incidence not known
galactorrhea / Delayed / Incidence not known

Mild

drowsiness / Early / 23.0-76.8
fatigue / Early / 13.9-48.6
appetite stimulation / Delayed / 7.0-32.7
dizziness / Early / 1.8-29.8
weight gain / Delayed / 2.7-27.2
weight loss / Delayed / 2.3-22.6
nausea / Early / 6.0-22.0
anxiety / Delayed / 1.1-16.6
xerostomia / Early / 10.2-14.7
libido decrease / Delayed / 6.0-14.4
menstrual irregularity / Delayed / 10.4-10.4
libido increase / Delayed / 1.0-7.7
hypersalivation / Early / 0.1-5.6
infection / Delayed / 1.9-4.3
syncope / Early / 0.1-3.8
dysmenorrhea / Delayed / 3.6-3.6
paresthesias / Delayed / 2.4-2.4
arthralgia / Delayed / 2.4-2.4
influenza / Delayed / 2.4-2.4
abnormal dreams / Early / 1.8-1.8

lethargy / Early / 1.7-1.7
myalgia / Early / 1.5-1.5
anorexia / Delayed / 1.5-1.5
pruritus / Rapid / 1.1-1.1
psychomotor impairment / Early / 0.1-0.9
asthenia / Delayed / 0.1-0.9
tinnitus / Delayed / 0.1-0.9
epistaxis / Delayed / 0.1-0.9
rhinorrhea / Early / 0.1-0.9
rash / Early / 0.1-0.9
mydriasis / Early / 0.1-0.9
urticaria / Rapid / 0.1-0.9
fever / Early / 0.1-0.9
agitation / Early / 1.0
nightmares / Early / 1.0
irritability / Delayed / 1.0
tremor / Early / 1.0
malaise / Early / 1.0
back pain / Delayed / 1.0
vertigo / Early / 1.0
muscle cramps / Delayed / 1.0
insomnia / Early / 1.0
weakness / Early / 1.0
headache / Early / 1.0
hyperventilation / Early / 1.0
diaphoresis / Early / 1.0
nasal congestion / Early / 1.0
rhinitis / Early / 1.0
diarrhea / Early / 1.0
dyspepsia / Early / 1.0
abdominal pain / Early / 1.0
vomiting / Early / 1.0
diplopia / Early / Incidence not known
gynecomastia / Delayed / Incidence not known

DRUG INTERACTIONS

Acetaminophen; Aspirin, ASA; Caffeine: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Acetaminophen; Butalbital: (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers.
Acetaminophen; Butalbital; Caffeine: (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Acetaminophen; Butalbital; Caffeine; Codeine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Acetaminophen; Caffeine: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Acetaminophen; Caffeine; Dihydrocodeine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Acetaminophen; Caffeine; Magnesium Salicylate; Phenyltoloxamine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Acetaminophen; Caffeine; Phenyltoloxamine; Salicylamide: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of

phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Acetaminophen; Codeine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines.
Acetaminophen; Dextromethorphan; Doxylamine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Acetaminophen; Dextromethorphan; Guaifenesin; Phenylephrine: (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Acetaminophen; Dextromethorphan; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Acetaminophen; Dichloralphenazone; Isometheptene: (Moderate) The CNS depressant effects of dichloralphenazone can be potentiated by benzodiazepines.
Acetaminophen; Diphenhydramine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Acetaminophen; Guaifenesin; Phenylephrine: (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Acetaminophen; Hydrocodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.
Acetaminophen; Oxycodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at one-third to one-half the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Acetaminophen; Pentazocine: (Major) Concomitant use of mixed opiate agonists/antagonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of mixed opiate agonists/antagonists with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If a mixed opiate agonist/antagonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the mixed opiate agonist/antagonist and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking a mixed opiate agonist/antagonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Acetaminophen; Propoxyphene: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. The dose of any opiate agonist administered with parenteral diazepam should be reduced by at least one-third.
Acetaminophen; Tramadol: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Acetazolamide: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs, including anticonvulsants, can potentiate the CNS effects of either agent.
Acrivastine; Pseudoephedrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Aldesleukin, IL-2: (Moderate) Aldesleukin, IL-2 may affect CNS function significantly. Therefore, psychotropic pharmacodynamic interactions could occur following concomitant administration of drugs with significant CNS activity. Use with caution.
Alfentanil: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Amiodarone: (Moderate) Amiodarone is a CYP3A4 inhibitors and may theoretically inhibit CYP3A4 metabolism of alprazolam.
Amitriptyline; Chlordiazepoxide: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs can potentiate the CNS effects of either agent.
Amobarbital: (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers.
Amoxapine: (Moderate) Amoxapine may enhance the response to the effects of benzodiazepines and other CNS depressants. Patients should be warned of the possibility of drowsiness that may impair performance of potentially hazardous tasks such as driving an automobile or operating machinery.
Amoxicillin; Clarithromycin; Lansoprazole: (Moderate) Clarithromycin inhibits CYP3A4 and may profoundly decrease alprazolam clearance. Use this combination with caution and consider a dose reduction of alprazolam of up to 50%.
Amoxicillin; Clarithromycin; Omeprazole: (Moderate) Clarithromycin inhibits CYP3A4 and may profoundly decrease alprazolam clearance. Use this combination with caution and consider a dose reduction of alprazolam of up to 50%. (Moderate) Omeprazole inhibits CYP2C19. There have been some case reports describing an interaction between omeprazole and benzodiazepines metabolized via the cytochrome P450 system, such as alprazolam. Patients should be monitored to determine if it is necessary to adjust the dosage of the benzodiazepine when taken concomitantly with omeprazole.
Amprenavir: (Major) Due to potent inhibition of alprazolam metabolism, it is recommended that alprazolam be avoided or reduced doses given when co-administered with anti-retroviral protease inhibitors.
Apalutamide: (Moderate) Monitor for withdrawal symptoms or lack of alprazolam efficacy if coadministration with apalutamide is necessary. Alprazolam is a CYP3A4 substrate and apalutamide is a strong CYP3A4 inducer.
Apomorphine: (Moderate) Apomorphine causes significant somnolence. Concomitant administration of apomorphine and CNS depressants could result in additive depressant effects.
Apraclonidine: (Minor) No specific drug interactions were identified with systemic agents and apraclonidine during clinical trials. Theoretically,

apraclonidine might potentiate the effects of CNS depressant drugs such as the anxiolytics, sedatives, and hypnotics, including barbiturates or benzodiazepines.

Aprepitant, Fosaprepitant: (Major) Use caution if alprazolam and aprepitant, fosaprepitant are used concurrently and monitor for an increase in alprazolam-related adverse effects for several days after administration of a multi-day aprepitant regimen. If a benzodiazepine is necessary, a dosage adjustment of the multi-day regimen may be necessary depending on the clinical situation (e.g., elderly patients) and degree of monitoring available; no dosage adjustment is needed for a single dose of aprepitant (40 mg) or fosaprepitant (150 mg). Consider selection of an agent that is not metabolized via CYP3A4 isoenzymes (e.g., lorazepam, oxazepam, temazepam). Alprazolam is a CYP3A4 substrate. Aprepitant, when administered as a 3-day oral regimen (125 mg/80 mg/80 mg), is a moderate CYP3A4 inhibitor and inducer and may increase plasma concentrations of alprazolam. For example, a 5-day oral aprepitant regimen increased the AUC of another CYP3A4 substrate, midazolam (single dose), by 2.3-fold on day 1 and by 3.3-fold on day 5. After a 3-day oral aprepitant regimen, the AUC of midazolam (given on days 1, 4, 8, and 15) increased by 25% on day 4, and then decreased by 19% and 4% on days 8 and 15, respectively. As a single 125 mg or 40 mg oral dose, the inhibitory effect of aprepitant on CYP3A4 is weak, with the AUC of midazolam increased by 1.5-fold and 1.2-fold, respectively. After administration, fosaprepitant is rapidly converted to aprepitant and shares many of the same drug interactions. However, as a single 150 mg intravenous dose, fosaprepitant only weakly inhibits CYP3A4 for a duration of 2 days; there is no evidence of CYP3A4 induction. Fosaprepitant 150 mg IV as a single dose increased the AUC of midazolam (given on days 1 and 4) by approximately 1.8-fold on day 1; there was no effect on day 4. Less than a 2-fold increase in the midazolam AUC is not considered clinically important.

Aripiprazole: (Moderate) Due to the primary CNS effects of aripiprazole, caution should be used when aripiprazole is given in combination with other centrally-acting medications including benzodiazepines and other anxiolytics, sedatives, and hypnotics. The intensity of sedation and orthostatic hypotension is greater during concurrent use of lorazepam and oral aripiprazole and during use of a parenteral benzodiazepine and intramuscular (IM) aripiprazole compared to aripiprazole alone; therefore, patients receiving a benzodiazepine with oral or parenteral aripiprazole should be monitored for sedation and blood pressure and the dose should be adjusted accordingly. Data from the manufacturer indicate there are no clinically significant pharmacokinetic changes when aripiprazole is given with lorazepam.

Asenapine: (Moderate) Drugs that can cause CNS depression, if used concomitantly with asenapine, may increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness. Caution should be used when asenapine is given in combination with other centrally-acting medications including anxiolytics, sedatives, and hypnotics (including barbiturates), buprenorphine, buprenorphine; naloxone, butorphanol, dronabinol, THC, nabilone, nalbuphine, opiate agonists, pentazocine, acetaminophen; pentazocine, aspirin, ASA; pentazocine, and pentazocine; naloxone.

Aspirin, ASA; Butalbital; Caffeine: (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.

Aspirin, ASA; Butalbital; Caffeine; Codeine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.

Aspirin, ASA; Caffeine; Dihydrocodeine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.

Aspirin, ASA; Caffeine; Orphenadrine: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.

Aspirin, ASA; Carisoprodol; Codeine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines.

Aspirin, ASA; Omeprazole: (Moderate) Omeprazole inhibits CYP2C19. There have been some case reports describing an interaction between omeprazole and benzodiazepines metabolized via the cytochrome P450 system, such as alprazolam. Patients should be monitored to determine if it is necessary to adjust the dosage of the benzodiazepine when taken concomitantly with omeprazole.

Aspirin, ASA; Oxycodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at one-third to one-half the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Atazanavir: (Major) Coadministration of alprazolam and atazanavir is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Atazanavir is a potent CYP3A4 inhibitor. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.

Atazanavir; Cobicistat: (Major) Avoid coadministration of alprazolam and cobicistat due to the potential for elevated alprazolam concentrations, which may cause prolonged sedation and respiratory depression. Lorazepam, oxazepam, or temazepam may be safer alternatives if a benzodiazepine must be administered in combination with cobicistat, as these benzodiazepines are not oxidatively metabolized. Alprazolam is a CYP3A4 substrate and cobicistat is a strong CYP3A4 inhibitor. Coadministration with other strong CYP3A4 inhibitors increased alprazolam exposure by 2.7- to 3.98-fold. (Major) Coadministration of alprazolam and atazanavir is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Atazanavir is a potent CYP3A4 inhibitor. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.

Atracurium: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when

additional CNS depressants are given.
Atropine; Difenoxin: (Moderate) Concomitant administration of benzodiazepines with CNS-depressant drugs, such as diphenoxylate/difenoxin, can potentiate the CNS effects of either agent.
Atropine; Diphenoxylate: (Moderate) Concomitant administration of benzodiazepines with CNS-depressant drugs, such as diphenoxylate/difenoxin, can potentiate the CNS effects of either agent.
Atropine; Hyoscyamine; Phenobarbital; Scopolamine: (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers. (Moderate) Scopolamine may cause dizziness and drowsiness. Concurrent use of scopolamine and CNS depressants can adversely increase the risk of CNS depression.
Azelastine: (Moderate) An enhanced CNS depressant effect may occur when azelastine is combined with CNS depressants including benzodiazepines.
Azelastine; Fluticasone: (Moderate) An enhanced CNS depressant effect may occur when azelastine is combined with CNS depressants including benzodiazepines.
Barbiturates: (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers.
Belladonna Alkaloids; Ergotamine; Phenobarbital: (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers. (Moderate) Drugs that may inhibit CYP3A4, such as ergotamine, may reduce the metabolism of alprazolam. Use alprazolam and ergotamine with caution and consider alprazolam dose reduction of up to 50%.
Belladonna; Opium: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Benzhydrocodone; Acetaminophen: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If benzhydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Benztropine: (Moderate) CNS depressants, such as anxiolytics, sedatives, and hypnotics, can increase the sedative effects of benztropine.
Boceprevir: (Major) Coadministration of alprazolam and boceprevir is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Boceprevir is a potent CYP3A4 inhibitor. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.
Bosentan: (Moderate) Bosentan is an inducer of cytochrome P450 enzymes, specifically the CYP2C9 and CYP3A4 isoenzymes, and may decrease concentrations of drugs metabolized by these enzymes, including alprazolam.
Brexpiprazole: (Moderate) Due to the CNS effects of brexpiprazole, caution should be used when brexpiprazole is given in combination with other centrally-acting medications including benzodiazepines and other anxiolytics, sedatives, and hypnotics.
Brimonidine: (Moderate) Based on the sedative effects of brimonidine in individual patients, brimonidine administration has potential to enhance the CNS depressants effects of the anxiolytics, sedatives, and hypnotics including benzodiazepines.
Brimonidine; Brinzolamide: (Moderate) Based on the sedative effects of brimonidine in individual patients, brimonidine administration has potential to enhance the CNS depressants effects of the anxiolytics, sedatives, and hypnotics including benzodiazepines.
Brimonidine; Timolol: (Moderate) Based on the sedative effects of brimonidine in individual patients, brimonidine administration has potential to enhance the CNS depressants effects of the anxiolytics, sedatives, and hypnotics including benzodiazepines.
Brompheniramine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Brompheniramine; Carbetapentane; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Brompheniramine; Dextromethorphan; Guaifenesin: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Brompheniramine; Guaifenesin; Hydrocodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Brompheniramine; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Brompheniramine; Pseudoephedrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Buprenorphine: (Major) Concomitant use of mixed opiate agonists/antagonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of mixed opiate agonists/antagonists with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If a mixed opiate agonist/antagonist is initiated for pain in a patient taking a benzodiazepine, use a lower initial dose of the mixed opiate agonist/antagonist and titrate to clinical response. Reduce injectable buprenorphine dose by 1/2, and for the buprenorphine transdermal patch, start therapy with the 5 mcg/hour patch. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking a mixed opiate agonist/antagonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. In patients treated with buprenorphine for opioid use disorder, cessation of benzodiazepines or other CNS depressants is preferred in most cases. Consider alternatives to benzodiazepines for conditions such as anxiety or insomnia in patients receiving buprenorphine maintenance treatment. Educate

patients about the risks and symptoms of respiratory depression and sedation.
Buprenorphine; Naloxone: (Major) Concomitant use of mixed opiate agonists/antagonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of mixed opiate agonists/antagonists with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If a mixed opiate agonist/antagonist is initiated for pain in a patient taking a benzodiazepine, use a lower initial dose of the mixed opiate agonist/antagonist and titrate to clinical response. Reduce injectable buprenorphine dose by 1/2, and for the buprenorphine transdermal patch, start therapy with the 5 mcg/hour patch. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking a mixed opiate agonist/antagonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. In patients treated with buprenorphine for opioid use disorder, cessation of benzodiazepines or other CNS depressants is preferred in most cases. Consider alternatives to benzodiazepines for conditions such as anxiety or insomnia in patients receiving buprenorphine maintenance treatment. Educate patients about the risks and symptoms of respiratory depression and sedation.
Buspirone: (Moderate) It is common for patients to overlap anxiety treatment when switching from benzodiazepines to buspirone. Buspirone has a slow onset of action and the drug will not block the withdrawal syndrome often seen with cessation of benzodiazepine therapy in those with benzodiazepine dependence. Therefore, before starting therapy with buspirone, withdraw patients gradually from the benzodiazepine. Alternatively, conversion to buspirone therapy may require treatment overlap to allow for the downward titration of the benzodiazepine while buspirone takes effect. It should be noted that the combination of buspirone and benzodiazepines can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Butabarbital: (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers.
Butorphanol: (Major) Concomitant use of mixed opiate agonists/antagonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of mixed opiate agonists/antagonists with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If a mixed opiate agonist/antagonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the mixed opiate agonist/antagonist and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking a mixed opiate agonist/antagonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Caffeine: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Caffeine; Ergotamine: (Moderate) Drugs that may inhibit CYP3A4, such as ergotamine, may reduce the metabolism of alprazolam. Use alprazolam and ergotamine with caution and consider alprazolam dose reduction of up to 50%. (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Cannabidiol: (Moderate) Monitor for excessive sedation and somnolence during coadministration of cannabidiol and alprazolam. CNS depressants can potentiate the effects of cannabidiol.
Carbamazepine: (Moderate) Carbamazepine is a hepatic enzyme inducer and may potentially accelerate the hepatic metabolism of alprazolam leading to lower alprazolam serum concentrations. Concomitant administration of alprazolam with CNS-depressant drugs, including anticonvulsants, can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Carbetapentane; Chlorpheniramine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines.
Carbetapentane; Chlorpheniramine; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Carbetapentane; Diphenhydramine; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Carbetapentane; Guaifenesin: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines.
Carbetapentane; Guaifenesin; Phenylephrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Carbetapentane; Phenylephrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Carbetapentane; Phenylephrine; Pyrilamine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Carbetapentane; Pseudoephedrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines.
Carbetapentane; Pyrilamine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane is combined with other CNS depressants including benzodiazepines.
Carbinoxamine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Carbinoxamine; Dextromethorphan; Pseudoephedrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Carbinoxamine; Hydrocodone; Phenylephrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Carbinoxamine; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations

needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.

Carbinoxamine; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.

Carbinoxamine; Pseudoephedrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.

Cariprazine: (Moderate) Due to the CNS effects of cariprazine, caution should be used when cariprazine is given in combination with other centrally-acting medications including benzodiazepines and other anxiolytics, sedatives, and hypnotics.

Ceritinib: (Major) Avoid coadministration of alprazolam and ceritinib due to the potential for elevated alprazolam concentrations, which may cause prolonged sedation and respiratory depression. Lorazepam, oxazepam, or temazepam may be safer alternatives if a benzodiazepine must be administered in combination with ceritinib, as these benzodiazepines are not oxidatively metabolized. Alprazolam is a CYP3A4 substrate and ceritinib is a strong CYP3A4 inhibitor. Coadministration with other strong CYP3A4 inhibitors increased alprazolam exposure by 2.7- to 3.98-fold.

Cetirizine: (Moderate) Concurrent use of cetirizine/levocetirizine with benzodiazepines should generally be avoided. Coadministration may increase the risk of CNS depressant-related side effects. If concurrent use is necessary, monitor for excessive sedation and somnolence.

Cetirizine; Pseudoephedrine: (Moderate) Concurrent use of cetirizine/levocetirizine with benzodiazepines should generally be avoided. Coadministration may increase the risk of CNS depressant-related side effects. If concurrent use is necessary, monitor for excessive sedation and somnolence.

Chlophedianol; Dexbrompheniramine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.

Chlophedianol; Dexchlorpheniramine; Pseudoephedrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.

Chlophedianol; Guaifenesin; Phenylephrine: (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.

Chloramphenicol: (Major) Coadministration of alprazolam and chloramphenicol is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Chloramphenicol is a potent CYP3A4 inhibitor. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.

Chlorcyclizine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.

Chlordiazepoxide: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs can potentiate the CNS effects of either agent.

Chlordiazepoxide; Clidinium: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs can potentiate the CNS effects of either agent.

Chlorpheniramine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.

Chlorpheniramine; Codeine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.

Chlorpheniramine; Dextromethorphan: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.

Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.

Chlorpheniramine; Dihydrocodeine; Phenylephrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.

Chlorpheniramine; Dihydrocodeine; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.

Chlorpheniramine; Guaifenesin; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.

Chlorpheniramine; Hydrocodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients

taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Chlorpheniramine; Hydrocodone; Phenylephrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Chlorpheniramine; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Chlorpheniramine; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Chlorpheniramine; Pseudoephedrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Chlorthalidone; Clonidine: (Moderate) Clonidine has CNS depressive effects and can potentiate the actions of other CNS depressants including benzodiazepines.
Cimetidine: (Moderate) Coadministration of alprazolam should be avoided with potent CYP3A4 inhibitors such as cimetidine. In patients taking drugs that inhibit CYP3A isoenzymes to a significant but lesser degree, use alprazolam with caution and consider alprazolam dose reduction (up to 50% dose reduction).
Ciprofloxacin: (Moderate) A decrease in the alprazolam dose may be needed. Ciprofloxacin is a CYP3A4 inhibitor and may reduce the metabolism of alprazolam and increase the potential for benzodiazepine toxicity.
Cisapride: (Moderate) Cisapride may enhance the sedative effects of benzodiazepines. Patients should not drive or operate heavy machinery until they know how the combination affects them. Patient counseling is important, as cisapride alone does not cause drowsiness or affect psychomotor function.
Cisatracurium: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.
Clarithromycin: (Moderate) Clarithromycin inhibits CYP3A4 and may profoundly decrease alprazolam clearance. Use this combination with caution and consider a dose reduction of alprazolam of up to 50%.
Clemastine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Clobazam: (Moderate) Use clobazam with other benzodiazepines with caution due to the potential for increased risk of drowsiness and sedation.
Clonazepam: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs can potentiate the CNS effects of either agent.
Clonidine: (Moderate) Clonidine has CNS depressive effects and can potentiate the actions of other CNS depressants including benzodiazepines.
Clorazepate: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs can potentiate the CNS effects of either agent.
Clozapine: (Moderate) If concurrent therapy with clozapine and a benzodiazepine is necessary, it is advisable to begin with the lowest possible benzodiazepine dose and closely monitor the patient, particularly at initiation of treatment and following dose increases. Although the combination has been used safely, adverse reactions such as confusion, ataxia, somnolence, delirium, collapse, cardiac arrest, respiratory arrest, and death have occurred rarely in patients receiving clozapine concurrently or following benzodiazepine therapy. Several benzodiazepines, including clonazepam, oxazepam, flurazepam, diazepam, clobazam, flunitrazepam, and lorazepam have been implicated in these reactions. At least one case of sudden death was reported following intravenous administration of lorazepam to a patient receiving clozapine.
Cobicistat: (Major) Avoid coadministration of alprazolam and cobicistat due to the potential for elevated alprazolam concentrations, which may cause prolonged sedation and respiratory depression. Lorazepam, oxazepam, or temazepam may be safer alternatives if a benzodiazepine must be administered in combination with cobicistat, as these benzodiazepines are not oxidatively metabolized. Alprazolam is a CYP3A4 substrate and cobicistat is a strong CYP3A4 inhibitor. Coadministration with other strong CYP3A4 inhibitors increased alprazolam exposure by 2.7- to 3.98-fold.
Codeine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines.
Codeine; Guaifenesin: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines.
Codeine; Phenylephrine; Promethazine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Codeine; Promethazine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines.
Colchicine; Probenecid: (Moderate) Probenecid may inhibit the metabolism of the benzodiazepines, including those which are metabolized by conjugation (e.g., lorazepam) or oxidation (e.g., midazolam). Probenecid has been shown to decrease lorazepam clearance by about 50% and

increase its elimination half-life. In addition, pretreatment with probenecid shortened the induction time (85 vs. 109 seconds) of midazolam in presurgical patients. Patients receiving alprazolam therapy should be monitored for signs of altered benzodiazepine response when probenecid is initiated or discontinued.

COMT inhibitors: (Moderate) Concomitant administration of benzodiazepines with CNS-depressant drugs, including COMT inhibitors, can potentiate the CNS effects of either agent.

Conivaptan: (Major) Coadministration of alprazolam and conivaptan is not recommended. Subsequent treatment with CYP3A substrates, such as alprazolam, may be initiated no sooner than 1 week after completion of conivaptan therapy. Conivaptan is a potent CYP3A4 inhibitor. Intravenous conivaptan 40 mg/day increases the mean AUC values by approximately 2-fold and 3-fold when coadministered with midazolam 1 mg IV or 2 mg PO, respectively. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.

Crizotinib: (Moderate) Monitor for an increase in alprazolam-related adverse reactions including sedation and respiratory depression if coadministration with crizotinib is necessary; consider reducing the dose of alprazolam as clinically appropriate. Crizotinib is a moderate CYP3A substrate and alprazolam is a CYP3A substrate. Drugs inhibiting this metabolic pathway may have a profound effect on the clearance of alprazolam.

Cyclizine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.

Cyclosporine: (Moderate) In patients taking drugs that inhibit CYP3A isoenzymes, use alprazolam with caution and consider alprazolam dose reduction (up to 50% dose reduction may be needed). Other drugs that may theoretically inhibit CYP3A4 metabolism of alprazolam include cyclosporine.

Cyproheptadine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.

Dalfopristin; Quinupristin: (Major) Coadministration of alprazolam and dalfopristin; quinupristin is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Dalfopristin; quinupristin is a potent CYP3A4 inhibitor. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.

Danazol: (Moderate) Danazol is a CYP3A4 inhibitor and can decrease the hepatic metabolism of CYP3A4 substrates, including alprazolam.

Darunavir: (Major) Coadministration of alprazolam and darunavir is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Darunavir is a potent CYP3A4 inhibitor. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.

Darunavir; Cobicistat: (Major) Avoid coadministration of alprazolam and cobicistat due to the potential for elevated alprazolam concentrations, which may cause prolonged sedation and respiratory depression. Lorazepam, oxazepam, or temazepam may be safer alternatives if a benzodiazepine must be administered in combination with cobicistat, as these benzodiazepines are not oxidatively metabolized. Alprazolam is a CYP3A4 substrate and cobicistat is a strong CYP3A4 inhibitor. Coadministration with other strong CYP3A4 inhibitors increased alprazolam exposure by 2.7- to 3.98-fold. (Major) Coadministration of alprazolam and darunavir is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Darunavir is a potent CYP3A4 inhibitor. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.

Darunavir; Cobicistat; Emtricitabine; Tenofovir alafenamide: (Major) Avoid coadministration of alprazolam and cobicistat due to the potential for elevated alprazolam concentrations, which may cause prolonged sedation and respiratory depression. Lorazepam, oxazepam, or temazepam may be safer alternatives if a benzodiazepine must be administered in combination with cobicistat, as these benzodiazepines are not oxidatively metabolized. Alprazolam is a CYP3A4 substrate and cobicistat is a strong CYP3A4 inhibitor. Coadministration with other strong CYP3A4 inhibitors increased alprazolam exposure by 2.7- to 3.98-fold. (Major) Coadministration of alprazolam and darunavir is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Darunavir is a potent CYP3A4 inhibitor. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.

Dasabuvir; Ombitasvir; Paritaprevir; Ritonavir: (Major) Coadministration of alprazolam and ritonavir or lopinavir; ritonavir is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Lopinavir and ritonavir are potent CYP3A4 inhibitors. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.

Delavirdine: (Severe) According to the manufacturer of delavirdine, coadministration of alprazolam and delavirdine is contraindicated. Delavirdine is a potent CYP3A4 inhibitor. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation.

Desflurane: (Moderate) Concurrent use with benzodiazepines can decrease the minimum alveolar concentration (MAC) of desflurane needed to produce anesthesia.

Deutetrabenazine: (Moderate) Advise patients that concurrent use of deutetrabenazine and drugs that can cause CNS depression, such as alprazolam, may have additive effects and worsen drowsiness or sedation.

Dexchlorpheniramine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.

Dexchlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.

Dexmedetomidine: (Moderate) Co-administration of dexmedetomidine with benzodiazepines is likely to lead to an enhancement of CNS depression.

Dextromethorphan; Diphenhydramine; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.

Dextromethorphan; Guaifenesin; Phenylephrine: (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.

Diazepam: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs can potentiate the CNS effects of either agent.

Dicyclomine: (Moderate) Dicyclomine can cause drowsiness, so it should be used cautiously in patients receiving CNS depressants like benzodiazepines.

Digoxin: (Moderate) Digoxin toxicity may occur in patients receiving alprazolam and digoxin. This interaction may be the result of increased plasma protein binding of digoxin and/or an effect of the benzodiazepine at the renal tubules that results in decreased digoxin elimination. Patients receiving alprazolam or diazepam and digoxin concurrently should be monitored for increased serum digoxin levels.

Dihydrocodeine; Guaifenesin; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist,

use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid prescribing opiate cough medications in patients taking benzodiazepines.
Diltiazem: (Moderate) Consider a reduced dose of alprazolam is concurrent use of diltiazem is necessary. Coadministration of alprazolam, a CYP3A4 substrate, with diltiazem, a moderate CYP3A4 inhibitor, may result in increased alprazolam exposure.
Dimenhydrinate: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Diphenhydramine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Diphenhydramine; Hydrocodone; Phenylephrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Diphenhydramine; Ibuprofen: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Diphenhydramine; Naproxen: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Diphenhydramine; Phenylephrine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Disulfiram: (Moderate) Disulfiram can decrease the hepatic oxidative metabolism of alprazolam if administered concomitantly. Patients receiving alprazolam therapy should be monitored for signs of altered benzodiazepine response when disulfiram is initiated or discontinued.
Doxacurium: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.
Doxylamine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Doxylamine; Pyridoxine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Dronabinol: (Moderate) Use caution if the use of benzodiazepines are necessary with dronabinol, and monitor for additive dizziness, confusion, somnolence, and other CNS effects.
Dronedarone: (Moderate) Dronedarone is metabolized by and is an inhibitor of CYP3A. Alprazolam is a substrate for CYP3A4. The concomitant administration of dronedarone and CYP3A substrates may result in increased exposure of the substrate and should, therefore, be undertaken with caution.
Droperidol: (Major) Droperidol administration is associated with an established risk for QT prolongation and torsades de pointes. In December 2001, the FDA issued a black box warning regarding the use of droperidol and its association with QT prolongation and potential for cardiac arrhythmias based on post-marketing surveillance data. Risk factors for the development of prolonged QT syndrome may include the use of benzodiazepines. Also, droperidol and benzodiazepines can both cause CNS depression. If used with a benzodiazepine, droperidol should be initiated at a low dose and adjusted upward, with caution, as needed to achieve the desired effect.
Drospirenone; Ethinyl Estradiol: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Drospirenone; Ethinyl Estradiol; Levomefolate: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Efavirenz: (Moderate) In vivo, efavirenz has been shown to induce hepatic enzymes CYP3A4 and CYP2B6. Patients receiving benzodiazepines that are metabolized by these isoenzymes may experience decreased benzodiazepine serum concentrations if administered concurrently with efavirenz. Efavirenz should be used with caution with oxidized benzodiazepines including alprazolam. Monitor patients closely for excessive side effects.
Efavirenz; Emtricitabine; Tenofovir: (Moderate) In vivo, efavirenz has been shown to induce hepatic enzymes CYP3A4 and CYP2B6. Patients receiving benzodiazepines that are metabolized by these isoenzymes may experience decreased benzodiazepine serum concentrations if administered concurrently with efavirenz. Efavirenz should be used with caution with oxidized benzodiazepines including alprazolam. Monitor patients closely for excessive side effects.
Efavirenz; Lamivudine; Tenofovir Disoproxil Fumarate: (Moderate) In vivo, efavirenz has been shown to induce hepatic enzymes CYP3A4 and CYP2B6. Patients receiving benzodiazepines that are metabolized by these isoenzymes may experience decreased benzodiazepine serum concentrations if administered concurrently with efavirenz. Efavirenz should be used with caution with oxidized benzodiazepines including alprazolam. Monitor patients closely for excessive side effects.
Elagolix: (Moderate) Monitor for withdrawal symptoms or lack of alprazolam efficacy if coadministration with elagolix is necessary. Alprazolam is a CYP3A4 substrate and elagolix is a weak to moderate CYP3A4 inducer.
Elbasvir; Grazoprevir: (Moderate) Administering alprazolam with elbasvir; grazoprevir may result in elevated alprazolam plasma concentrations. Alprazolam is a substrate of CYP3A; grazoprevir is a weak CYP3A inhibitor. If these drugs are used together, closely monitor for signs of adverse events.
Elexacaftor; tezacaftor; ivacaftor: (Moderate) Use caution when administering ivacaftor and alprazolam concurrently because patients are at increased risk for adverse effects from alprazolam. Ivacaftor is a CYP3A inhibitor, and alprazolam is a CYP3A substrate. Co-administration of ivacaftor with midazolam, another CYP3A substrate, increased midazolam exposure by 1.5-fold.
Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Alafenamide: (Major) Avoid coadministration of alprazolam and cobicistat due to the potential for elevated alprazolam concentrations, which may cause prolonged sedation and respiratory depression. Lorazepam, oxazepam, or temazepam may be safer alternatives if a benzodiazepine must be administered in combination with cobicistat, as these benzodiazepines are not oxidatively metabolized. Alprazolam is a CYP3A4 substrate and cobicistat is a strong CYP3A4 inhibitor. Coadministration with other strong CYP3A4 inhibitors increased alprazolam exposure by 2.7- to 3.98-fold.
Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Disoproxil Fumarate: (Major) Avoid coadministration of alprazolam and cobicistat due to the potential for elevated alprazolam concentrations, which may cause prolonged sedation and respiratory depression. Lorazepam, oxazepam, or temazepam may be safer alternatives if a benzodiazepine must be administered in combination with cobicistat, as these benzodiazepines are not oxidatively metabolized. Alprazolam is a CYP3A4 substrate and cobicistat is a strong CYP3A4 inhibitor. Coadministration with other strong CYP3A4 inhibitors increased alprazolam exposure by 2.7- to 3.98-fold.
Enflurane: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Enzalutamide: (Moderate) Monitor for withdrawal symptoms or lack of alprazolam efficacy if coadministration with enzalutamide is necessary. Alprazolam is a CYP3A4 substrate and enzalutamide is a strong CYP3A4 inducer.
Ergotamine: (Moderate) Drugs that may inhibit CYP3A4, such as ergotamine, may reduce the metabolism of alprazolam. Use alprazolam and ergotamine with caution and consider alprazolam dose reduction of up to 50%.
Erythromycin: (Moderate) Drugs that may inhibit CYP3A4, such as erythromycin, may inhibit the metabolism of alprazolam. Use alprazolam and erythromycin with caution and consider alprazolam dose reduction.

Erythromycin; Sulfisoxazole: (Moderate) Drugs that may inhibit CYP3A4, such as erythromycin, may inhibit the metabolism of alprazolam. Use alprazolam and erythromycin with caution and consider alprazolam dose reduction.
Esketamine: (Major) Closely monitor patients receiving esketamine and benzodiazepines for sedation and other CNS depressant effects. Instruct patients who receive a dose of esketamine not to drive or engage in other activities requiring alertness until the next day after a restful sleep.
Eslicarbazepine: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs, including anticonvulsants, can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Additionally, eslicarbazepine is an inducer of the hepatic CYP3A4 isoenzyme thereby having the potential to lower the plasma levels of medications metabolized through these pathways. The effectiveness of medications such as alprazolam could theoretically be decreased.
Estazolam: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs can potentiate the CNS effects of either agent.
Eszopiclone: (Moderate) Concomitant administration of benzodiazepines with eszopiclone can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. The concurrent use of eszopiclone with other anxiolytics, sedatives, and hypnotics at bedtime or in the middle of the night is not recommended. In addition, the risk of next-day psychomotor impairment is increased during co-administration of eszopiclone and other CNS depressants, which may decrease the ability to perform tasks requiring full mental alertness such as driving. If used together, a reduction in the dose of one or both drugs may be needed.
Ethanol: (Major) Alcohol is associated with CNS depression. The combined use of alcohol and CNS depressants can lead to additive CNS depression, which could be dangerous in tasks requiring mental alertness and fatal in overdose. Alcohol taken with other CNS depressants can lead to additive respiratory depression, hypotension, profound sedation, or coma. Consider the patient's use of alcohol or illicit drugs when prescribing CNS depressant medications. In many cases, the patient should receive a lower dose of the CNS depressant initially if the patient is not likely to be compliant with avoiding alcohol.
Ethinyl Estradiol: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Ethinyl Estradiol; Desogestrel: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Ethinyl Estradiol; Ethynodiol Diacetate: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Ethinyl Estradiol; Etonogestrel: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Ethinyl Estradiol; Levonorgestrel: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Ethinyl Estradiol; Levonorgestrel; Ferrous bisglycinate: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Ethinyl Estradiol; Levonorgestrel; Folic Acid; Levomefolate: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Ethinyl Estradiol; Norelgestromin: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Ethinyl Estradiol; Norethindrone Acetate: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Ethinyl Estradiol; Norethindrone Acetate; Ferrous fumarate: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Ethinyl Estradiol; Norethindrone: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Ethinyl Estradiol; Norethindrone; Ferrous fumarate: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Ethinyl Estradiol; Norgestimate: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Ethinyl Estradiol; Norgestrel: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Ethosuximide: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs, including anticonvulsants, can potentiate the CNS effects of either agent.
Etomidate: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Fedratinib: (Moderate) Monitor for an increase in alprazolam-related adverse reactions including sedation and respiratory depression if coadministration with fedratinib is necessary; consider reducing the dose of alprazolam as clinically appropriate. Fedratinib is a moderate CYP3A inhibitor and alprazolam is a CYP3A substrate. Drugs inhibiting this metabolic pathway may have a profound effect on the clearance of alprazolam.
Felbamate: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs, including anticonvulsants, can potentiate the CNS effects of either agent.
Fentanyl: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Fluconazole: (Moderate) Drugs that inhibit the CYP3A metabolic pathway, such as fluconazole, may profoundly decrease alprazolam clearance. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes. In patients taking drugs that inhibit CYP3A isoenzymes to a significant but lesser degree, use alprazolam with caution and consider alprazolam dose reduction (up to 50% dosage reduction).
Flumazenil: (Major) Flumazenil competes with benzodiazepines for binding at the GABA/benzodiazepine-receptor complex, the specific binding site of benzodiazepines. Because binding at the receptor is competitive and flumazenil has a much shorter duration of action than do most benzodiazepines, it is possible for the effects of flumazenil to dissipate sooner than the effects of the benzodiazepine. Flumazenil does not affect the pharmacokinetics of the benzodiazepines. Abrupt awakening can cause dysphoria, agitation, and possibly increased adverse effects. If administered to patients who have received a benzodiazepine chronically, abrupt interruption of benzodiazepine agonism by flumazenil can induce benzodiazepine withdrawal including seizures. Flumazenil has minimal effects on benzodiazepine-induced respiratory depression; suitable ventilatory support should be available, especially in treating acute benzodiazepine overdose. Flumazenil does not reverse the actions of barbiturates, opiate agonists, or tricyclic antidepressants.

Fluoxetine: (Moderate) Clinical study results suggest that the interaction between alprazolam, a CYP3A4 substrate fluoxetine, a CYP3A4 inhibitor may be of clinical significance, and caution is recommended during co-administration. Concurrent use of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased the half-life by 17%, and decreased measured psychomotor performance. Monitor patients closely for excessive alprazolam-related side effects.
Fluoxetine; Olanzapine: (Moderate) Although oral formulations of olanzapine and benzodiazepines may be used together, additive effects on respiratory depression and/or CNS depression are possible. Drugs that can cause CNS depression, if used concomitantly with olanzapine, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, dizziness, and orthostatic hypotension. Besides ethanol, clinicians should use other anxiolytics, sedatives, and hypnotics cautiously with olanzapine. (Moderate) Clinical study results suggest that the interaction between alprazolam, a CYP3A4 substrate fluoxetine, a CYP3A4 inhibitor may be of clinical significance, and caution is recommended during co-administration. Concurrent use of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased the half-life by 17%, and decreased measured psychomotor performance. Monitor patients closely for excessive alprazolam-related side effects.
Flurazepam: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs can potentiate the CNS effects of either agent.
Fluvoxamine: (Moderate) Caution is advisable during co-administration of alprazolam, a CYP3A4 substrate, and fluvoxamine, a moderate CYP3A4 inhibitor. Monitor patients closely for excessive alprazolam-related side effects. A reduction in alprazolam dose may be needed in some patients. In vivo study results indicate that fluvoxamine approximately doubled the maximum plasma concentration of alprazolam, decreased clearance by 49%, increased half-life by 71%, and decreased measured psychomotor performance.
Food: (Major) Coadministration of marijuana with benzodiazepines may result in an exaggerated sedative effect. Instruct patients receiving these medications concurrently not to drive or operate machinery.
Fosamprenavir: (Major) Coadministration of alprazolam and fosamprenavir is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Fosamprenavir is a potent CYP3A4 inhibitor. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.
Fospropofol: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Gabapentin: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs, including anticonvulsants, can potentiate the CNS effects of either agent.
General anesthetics: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Grapefruit juice: (Major) Grapefruit juice has been shown to significantly increase peak serum concentrations and AUC of triazolam and oral midazolam. According to the manufacturer, a similar interaction may theoretically occur with alprazolam; however, one in-vivo pharmacokinetic study demonstrated that the bioavailability of alprazolam is unlikely to be effected by coadministration with grapefruit juice. Use with caution.
Green Tea: (Minor) Patients taking benzodiazepines for insomnia should not use caffeine-containing products, such as green tea, prior to going to bed as these products may antagonize the sedative effects of the benzodiazepine.
Guaifenesin; Hydrocodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.
Guaifenesin; Hydrocodone; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.
Guaifenesin; Phenylephrine: (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Guanabenz: (Moderate) Guanabenz is associated with sedative effects. Guanabenz can potentiate the effects of CNS depressants such as benzodiazepines, when administered concomitantly.
Guanfacine: (Moderate) Guanfacine has been associated with sedative effects and can potentiate the actions of other CNS depressants including benzodiazepines.
Haloperidol: (Moderate) Mild to moderate increases in haloperidol plasma concentrations have been reported during concurrent use of haloperidol and CYP3A4 substrates such as alprazolam. Until more data are available, it is advisable to closely monitor for adverse events when alprazolam is coadministered with haloperidol. Concomitant administration of alprazolam with CNS-depressant drugs including antipsychotics can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Halothane: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Homatropine; Hydrocodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.
Hydantoins: (Moderate) Hydantoin anticonvulsants can theoretically add to the CNS-depressant effects of other CNS depressants including the benzodiazepines. In addition, potential hepatic enzyme inducers such as hydantoins can theoretically increase the clearance of benzodiazepines metabolized by oxidative metabolism, leading to lower benzodiazepine concentrations.
Hydrochlorothiazide, HCTZ; Methyldopa: (Moderate) Methyldopa is associated with sedative effects. Methyldopa can potentiate the effects of CNS depressants such as barbiturates, benzodiazepines, opiate agonists, or phenothiazines when administered concomitantly.
Hydrocodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.
Hydrocodone; Ibuprofen: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an

indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.

Hydrocodone; Phenylephrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines. (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.

Hydrocodone; Potassium Guaiacolsulfonate: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.

Hydrocodone; Potassium Guaiacolsulfonate; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.

Hydrocodone; Pseudoephedrine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydrocodone is initiated in a patient taking a benzodiazepine, reduce initial dosage and titrate to clinical response; for hydrocodone extended-release products, initiate hydrocodone at 20% to 30% of the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation. Avoid opiate cough medications in patients taking benzodiazepines.

Hydromorphone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If hydromorphone is initiated in a patient taking a benzodiazepine, reduce the initial dosage of hydromorphone and titrate to clinical response; for hydromorphone extended-release tablets, use 1/3 to 1/2 of the estimated hydromorphone starting dose. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Hydroxyzine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.

Ibuprofen; Oxycodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at one-third to one-half the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Idelalisib: (Major) Coadministration of alprazolam and idelalisib is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Idealalisib is a potent CYP3A4 inhibitor. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.

Iloperidone: (Moderate) Drugs that can cause CNS depression, if used concomitantly with iloperidone, may increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness. Caution should be used when iloperidone is given in combination with other centrally-acting medications including anxiolytics, sedatives, and hypnotics.

Imatinib: (Major) In patients taking CYP3A inhibitors such as imatinib, STI-571 use alprazolam with caution and consider alprazolam dose reduction (up to 50% dose reduction may be needed).

Indinavir: (Severe) Coadministration of indinavir with alprazolam is contraindicated. Indinavir is expected to significantly inhibit the CYP3A4 metabolism of alprazolam, producing large increases in the plasma concentrations which may lead to excessive sedation and potentially respiratory depression. Consider an alternative benzodiazepine that does not undergo oxidative metabolism, such as lorazepam, oxazepam, or temazepam.

Isavuconazonium: (Moderate) Concomitant use of isavuconazonium with alprazolam may result in increased serum concentrations of alprazolam. Alprazolam is primarily metabolized by the hepatic isoenzyme CYP3A4; isavuconazole, the active moiety of isavuconazonium, is a moderate inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are used together.

Isoflurane: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.

Isoniazid, INH: (Moderate) Isoniazid can decrease the hepatic oxidative metabolism of benzodiazepines if administered concomitantly. Patients receiving alprazolam therapy should be monitored for signs of altered benzodiazepine response when isoniazid is initiated or discontinued.

Isoniazid, INH; Pyrazinamide, PZA; Rifampin: (Moderate) Isoniazid can decrease the hepatic oxidative metabolism of benzodiazepines if administered concomitantly. Patients receiving alprazolam therapy should be monitored for signs of altered benzodiazepine response when isoniazid is initiated or discontinued. (Moderate) Rifampin is a potent inducer of the cytochrome P-450 hepatic enzyme system. Rifampin could induce the CYP3A4-mediated metabolism of oxidized benzodiazepines, such as alprazolam.

Isoniazid, INH; Rifampin: (Moderate) Isoniazid can decrease the hepatic oxidative metabolism of benzodiazepines if administered concomitantly. Patients receiving alprazolam therapy should be monitored for signs of altered benzodiazepine response when isoniazid is initiated or discontinued. (Moderate) Rifampin is a potent inducer of the cytochrome P-450 hepatic enzyme system. Rifampin could induce the CYP3A4-mediated metabolism of oxidized benzodiazepines, such as alprazolam.

Itraconazole: (Severe) Coadministration of itraconazole and alprazolam is contraindicated. Itraconazole significantly impairs the CYP3A4 metabolism of alprazolam, resulting in elevated alprazolam concentrations, which may cause prolonged sedation and respiratory depression. When a single dose of alprazolam was administered to healthy patients receiving itraconazole, the mean AUC and half-live of alprazolam were increased 2.7 fold. Lorazepam, oxazepam, or temazepam may be safer alternatives if a benzodiazepine must be administered in combination with itraconazole, as these benzodiazepines are not oxidatively metabolized.

Ivacaftor: (Moderate) Use caution when administering ivacaftor and alprazolam concurrently because patients are at increased risk for adverse

effects from alprazolam. Ivacaftor is a CYP3A inhibitor, and alprazolam is a CYP3A substrate. Co-administration of ivacaftor with midazolam, another CYP3A substrate, increased midazolam exposure by 1.5-fold.
Kava Kava, Piper methysticum: (Major) Kava kava should be avoided when possible in patients taking benzodiazepines. Additive sedation or other CNS-related side effects are possible. Kava may inhibit CYP enzymes, increasing benzodiazepine exposure, which may increase the risk for CNS depression and respiratory compromise. Patients should discuss the use of herbal supplements with their health care professional prior to consuming kava kava and should not abruptly stop taking their prescribed medications.
Ketamine: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Ketoconazole: (Severe) Coadministration of ketoconazole and alprazolam is contraindicated. Ketoconazole significantly impairs the CYP3A4 metabolism of alprazolam, resulting in elevated alprazolam concentrations. Lorazepam, oxazepam, or temazepam may be safer alternatives if a benzodiazepine must be administered in combination with ketoconazole, as these benzodiazepines are not oxidatively metabolized.
Lacosamide: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs, including anticonvulsants, can potentiate the CNS effects of either agent.
Lamotrigine: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs, including anticonvulsants, can potentiate the CNS effects of either agent.
Lefamulin: (Moderate) Monitor for an increase in alprazolam-related adverse reactions including sedation and respiratory depression if coadministration with oral lefamulin is necessary; consider reducing the dose of alprazolam as clinically appropriate. Alprazolam is a CYP3A4 substrate and oral lefamulin is a moderate CYP3A4 inhibitor; an interaction is not expected with intravenous lefamulin. Drugs inhibiting this metabolic pathway may have a profound effect on the clearance of alprazolam.
Letermovir: (Moderate) A clinically relevant increase in the plasma concentration of alprazolam may occur if given with letermovir. Coadministration is not recommended if the patient is also receiving cyclosporine, because the magnitude of the interaction may be increased. If coadministration of all 3 drugs cannot be avoided, a dosage reduction of alprazolam should be considered. Alprazolam is primarily metabolized by CYP3A4. Letermovir is a moderate CYP3A4 inhibitor; however, when given with cyclosporine, the combined effect CYP3A4 substrates is similar to a strong CYP3A4 inhibitor. Concurrent administration with other moderate to strong inhibitors increased alprazolam exposure by 1.61- to 3.98-fold.
Levetiracetam: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs, including anticonvulsants, can potentiate the CNS effects of either agent.
Levocetirizine: (Moderate) Concurrent use of cetirizine/levocetirizine with benzodiazepines should generally be avoided. Coadministration may increase the risk of CNS depressant-related side effects. If concurrent use is necessary, monitor for excessive sedation and somnolence.
Levomethadyl: (Moderate) Concomitant administration of benzodiazepines with CNS-depressant drugs, including opiate agonists, can potentiate the CNS effects of either agent.
Levomilnacipran: (Moderate) Concurrent use of many CNS active drugs, including benzodiazepines, with levomilnacipran has not been evaluated by the manufacturer. Therefore, caution is advisable when combining anxiolytics, sedatives, and hypnotics or other psychoactive medications with levomilnacipran.
Levorphanol: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If levorphanol is initiated in a patient taking a benzodiazepine, reduce the initial dose of levorphanol by approximately 50% or more. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Lithium: (Moderate) Because lithium has the potential to impair cognitive and motor skills, caution is advisable during concurrent use of other medications with centrally-acting effects including anxiolytics, sedatives, and hypnotics.
Lofexidine: (Moderate) Monitor for excessive hypotension and sedation during coadministration of lofexidine and benzodiazepines. Lofexidine can potentiate the effects of CNS depressants such as benzodiazepines.
Lomitapide: (Major) Concomitant use of lomitapide and alprazolam may significantly increase the serum concentration of lomitapide. Therefore, the lomitapide dose should not exceed 30 mg/day PO during concurrent use. Alprazolam is a weak CYP3A4 inhibitor; the exposure to lomitapide is increased by approximately 2-fold in the presence of weak CYP3A4 inhibitors.
Lopinavir; Ritonavir: (Major) Coadministration of alprazolam and lopinavir; ritonavir is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Lopinavir and ritonavir are potent CYP3A4 inhibitors. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes. (Major) Coadministration of alprazolam and ritonavir or lopinavir; ritonavir is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Lopinavir and ritonavir are potent CYP3A4 inhibitors. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.
Lorazepam: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs can potentiate the CNS effects of either agent.
Loxapine: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs, including antipsychotics, can potentiate the CNS effects of either agent.
Lumacaftor; Ivacaftor: (Moderate) Lumacaftor; ivacaftor may decrease the systemic exposure and therapeutic efficacy of alprazolam. If used together, alprazolam dosages may need to be adjusted. Alprazolam is a CYP3A substrate. Lumacaftor is a strong CYP3A inducer. When alprazolam (0.8 mg as a single dose) was given with carbamazepine (300 mg/day for 10 days), another strong CYP3A inducer, alprazolam clearance more than doubled and elimination half-life decreased from 17.1 +/- 4.9 hours to 7.7 +/- 1.7 hours.
Lumacaftor; Ivacaftor: (Moderate) Use caution when administering ivacaftor and alprazolam concurrently because patients are at increased risk for adverse effects from alprazolam. Ivacaftor is a CYP3A inhibitor, and alprazolam is a CYP3A substrate. Co-administration of ivacaftor with midazolam, another CYP3A substrate, increased midazolam exposure by 1.5-fold.
Lurasidone: (Moderate) Due to the CNS effects of lurasidone, caution should be used when lurasidone is given in combination with other centrally acting medications such as anxiolytics, sedatives, and hypnotics, including benzodiazepines. In one study, co-administration of lurasidone and midazolam increased the Cmax and AUC of midazolam by about 21% and 44%, respectively, compared to midazolam alone; however, dosage adjustment of midazolam based upon pharmacokinetic parameters is not required during concurrent use of lurasidone.
Magnesium Salts: (Minor) Because of the CNS-depressant effects of magnesium sulfate, additive central-depressant effects can occur following concurrent administration with CNS depressants such as benzodiazepines. Caution should be exercised when using these agents concurrently.
Maprotiline: (Moderate) Benzodiazepines or other CNS depressants should be combined cautiously with maprotiline because they could cause additive depressant effects and possible respiratory depression or hypotension. The combination of benzodiazepines and maprotiline is commonly used clinically and is considered to be safe as long as patients are monitored for excessive adverse effects from either agent. Maprotiline may lower the seizure threshold, so when benzodiazepines are used for anticonvulsant effects the patient should be monitored for desired clinical outcomes.
Meclizine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Melatonin: (Major) Use caution when combining melatonin with the benzodiazepines; when the benzodiazepine is used for sleep, co-use of melatonin should be avoided. In animal studies, melatonin has been shown to increase benzodiazepine binding to receptor sites. In one case report, a benzodiazepine-dependent woman with an 11 year history of insomnia weaned and discontinued her benzodiazepine prescription within a few days without rebound insomnia or apparent benzodiazepine withdrawal when melatonin was given. In another case report, the ingestion of excessive melatonin along with normal doses of chlordiazepoxide and an antidepressant resulted in lethargy and short-term amnestic responses. Both cases suggest additive pharmacodynamic effects. In a clinical trial, there was clear evidence for a transitory pharmacodynamic interaction between melatonin and another hypnotic agent one hour following co-dosing. Concomitant administration resulted in increased impairment of attention, memory and coordination compared to the hypnotic agent alone. Use of more than one agent for hypnotic purposes may increase the risk for over-sedation, CNS effects, or sleep-related behaviors. Be alert for unusual changes in moods or behaviors.Patients reporting unusual

sleep-related behaviors likely should discontinue melatonin use.
Meperidine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Meperidine; Promethazine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Mephobarbital: (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers.
Meprobamate: (Moderate) Concomitant administration of benzodiazepines with meprobamate can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. If used together, a reduction in the dose of one or both drugs may be needed.
Mestranol; Norethindrone: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Methadone: (Major) Concurrent use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective dose and minimum duration possible. If methadone is initiated for pain in an opioid-naive patient taking a benzodiazepine, use an initial methadone dose of 2.5 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial benzodiazepine dose and titrate to response. In patients treated with methadone for opioid use disorder, cessation of benzodiazepines or other CNS depressants is preferred in most cases. Consider alternatives to benzodiazepines for conditions such as anxiety or insomnia during methadone maintenance treatment. Educate patients about the risks and symptoms of respiratory depression and sedation.
Methocarbamol: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including skeletal muscle relaxants, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.
Methohexital: (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers.
Methscopolamine: (Moderate) CNS depression can be increased when methscopolamine is combined with other CNS depressants such as any anxiolytics, sedatives, and hypnotics.
Methsuximide: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs, including anticonvulsants, can potentiate the CNS effects of either agent.
Methyldopa: (Moderate) Methyldopa is associated with sedative effects. Methyldopa can potentiate the effects of CNS depressants such as barbiturates, benzodiazepines, opiate agonists, or phenothiazines when administered concomitantly.
Metoclopramide: (Minor) Combined use of metoclopramide and other CNS depressants, such as anxiolytics, sedatives, and hypnotics, can increase possible sedation.
Metyrapone: (Moderate) Metyrapone may cause dizziness and/or drowsiness. Other drugs that may also cause drowsiness, such as benzodiazepines, should be used with caution. Additive drowsiness and/or dizziness is possible.
Metyrosine: (Moderate) The concomitant administration of metyrosine with benzodiazepines can result in additive sedative effects.
Midazolam: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs can potentiate the CNS effects of either agent.
Mifepristone: (Moderate) Mifepristone inhibits CYP3A4. Coadministration of mifepristone may lead to an increase in serum levels of drugs that are CYP3A4 substrates, such as alprazolam. Due to the slow elimination of mifepristone from the body, such interactions may be observed for a prolonged period after mifepristone administration.
Milnacipran: (Moderate) Concurrent use of many CNS-active drugs with milnacipran or levomilnacipran has not been evaluated by the manufacturer. Therefore, caution is advisable when combining anxiolytics, sedatives, and hypnotics or other psychoactive medications with these medications.
Minocycline: (Minor) Injectable minocycline contains magnesium sulfate heptahydrate. Because of the CNS-depressant effects of magnesium sulfate, additive central-depressant effects can occur following concurrent administration with CNS depressants such as benzodiazepines. Caution should be exercised when using these agents concurrently.
Mirtazapine: (Moderate) Consistent with the pharmacology of mirtazapine and the drug's side effect profile, additive effects may occur with other CNS-active agents, including benzodiazepines.
Mitotane: (Moderate) Avoid the concomitant use of mitotane with alprazolam; if coadministration cannot be avoided, monitor for decreased efficacy of alprazolam. Mitotane is a strong CYP3A4 inducer and alprazolam is a CYP3A4 substrate; coadministration may result in decreased plasma concentrations of alprazolam. Additionally, mitotane can cause sedation, lethargy, vertigo, and other CNS adverse reactions; additive CNS effects may occur initially when mitotane is given concurrently with alprazolam.
Mivacurium: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.
Molindone: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs, including antipsychotics, can potentiate the CNS effects of either agent.
Monoamine oxidase inhibitors: (Moderate) The CNS-depressant effects of MAOIs can be potentiated with concomitant administration of other drugs known to cause CNS depression including benzodiazepines. MAOIs can cause a variable change in seizure patterns, so careful monitoring of the patient with epilepsy is required when benzodiazepines are used in the treatment of epilepsy.
Morphine: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If morphine is initiated in a patient taking a benzodiazepine, reduce initial dosages and titrate to clinical response. For extended-release tablets, start with morphine 15 mg PO every 12 hours, and for extended-release capsules, start with 30 mg PO every 24 hours or less. Use an initial morphine; naltrexone dose of 20 mg/0.8 mg PO every 24 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Morphine; Naltrexone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If morphine is initiated in a patient taking a benzodiazepine, reduce initial dosages and titrate to clinical response. For extended-release tablets, start with morphine 15 mg PO every 12 hours, and for extended-release capsules, start with 30 mg PO every 24 hours or less. Use an initial morphine; naltrexone dose of 20 mg/0.8 mg PO every 24 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Nabilone: (Moderate) Concomitant use of nabilone with other CNS depressants can potentiate the effects of nabilone on respiratory depression.
Nalbuphine: (Major) Concomitant use of mixed opiate agonists/antagonists with benzodiazepines may cause respiratory depression, hypotension,

profound sedation, and death. Limit the use of mixed opiate agonists/antagonists with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If a mixed opiate agonist/antagonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the mixed opiate agonist/antagonist and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking a mixed opiate agonist/antagonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Nefazodone: (Major) In general, nefazodone is not recommended for use with alprazolam in most patients. The initial dose of alprazolam should be reduced by 50% when concurrent use cannot be avoided. Nefazodone inhibits the hepatic CYP3A4 isoenzyme and substantially increases the plasma concentrations of alprazolam. Alprazolam AUC and half-life are increased 2-fold by the addition of nefazodone.

Nelfinavir: (Major) Coadministration of alprazolam and nelfinavir is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Nelfinavir is a potent CYP3A4 inhibitor. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.

Netupitant, Fosnetupitant; Palonosetron: (Major) Netupitant is a moderate inhibitor of CYP3A4 and should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4, such as alprazolam. The plasma concentrations of CYP3A4 substrates can increase when co-administered with netupitant. The inhibitory effect on CYP3A4 can last for multiple days. When midazolam, another benzodiazepine metabolized via CYP3A4, was administered with netupitant, the systemic exposure to midazolam was significantly increased. Increased benzodiazepine exposure may lead to increased sedation or respiratory depression. Monitor patients closely who receive concurrent therapy.

Neuromuscular blockers: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.

Nevirapine: (Moderate) Nevirapine may induce the metabolism of certain benzodiazepines that are metabolized through the cytochrome P450 system including alprazolam. Patients should be monitored closely for loss of clinical effects.

Nicardipine: (Moderate) Nicardipine is an inhibitor of CYP3A4 isoenzymes. Co-administration with nicardipine may lead to an increase in serum levels of drugs that are CYP3A4 substrates including alprazolam.

Nifedipine: (Moderate) In patients taking drugs that inhibit CYP3A isoenzymes, use alprazolam with caution and consider alprazolam dose reduction (up to 50% dose reduction may be needed). Niifedipine may theoretically inhibit CYP3A4 metabolism of alprazolam.

Nilotinib: (Major) Nilotinib is a competitive inhibitor of CYP3A4. Alprazolam is a CYP3A4 substrate. Coadminister these drugs with caution. Increased alprazolam serum concentrations may occur, leading to an increased risk of alprazolam-related adverse reactions. Monitor patients carefully, as the alprazolam dosage may need to be decreased.

Nitroglycerin: (Minor) Nitroglycerin can cause hypotension. This action may be additive with other agents that can cause hypotension such as benzodiazepines. Patients should be monitored more closely for hypotension if nitroglycerin is used concurrently with benzodiazepines.

Obeticholic Acid: (Moderate) Obeticholic acid may increase the exposure to concomitant drugs that are CYP1A2 substrates, such as alprazolam. Therapeutic monitoring is recommended with coadministration.

Olanzapine: (Moderate) Although oral formulations of olanzapine and benzodiazepines may be used together, additive effects on respiratory depression and/or CNS depression are possible. Drugs that can cause CNS depression, if used concomitantly with olanzapine, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, dizziness, and orthostatic hypotension. Besides ethanol, clinicians should use other anxiolytics, sedatives, and hypnotics cautiously with olanzapine.

Ombitasvir; Paritaprevir; Ritonavir: (Major) Coadministration of alprazolam and ritonavir or lopinavir; ritonavir is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Lopinavir and ritonavir are potent CYP3A4 inhibitors. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.

Omeprazole: (Moderate) Omeprazole inhibits CYP2C19. There have been some case reports describing an interaction between omeprazole and benzodiazepines metabolized via the cytochrome P450 system, such as alprazolam. Patients should be monitored to determine if it is necessary to adjust the dosage of the benzodiazepine when taken concomitantly with omeprazole.

Omeprazole; Sodium Bicarbonate: (Moderate) Omeprazole inhibits CYP2C19. There have been some case reports describing an interaction between omeprazole and benzodiazepines metabolized via the cytochrome P450 system, such as alprazolam. Patients should be monitored to determine if it is necessary to adjust the dosage of the benzodiazepine when taken concomitantly with omeprazole.

Oritavancin: (Moderate) Alprazolam is metabolized by CYP3A4; oritavancin is a weak CYP3A4 inducer. Plasma concentrations and efficacy of alprazolam may be reduced if these drugs are administered concurrently.

Oxazepam: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs can potentiate the CNS effects of either agent.

Oxcarbazepine: (Moderate) Oxcarbazepine and its active metabolite, MHD, are dose-dependent inducers of the hepatic CYP3A4/5 isoenzymes thereby having the potential to lower the plasma levels of medications metabolized through these pathways. The effectiveness of medications such as alprazolam could theoretically be decreased. In addition, concomitant administration of alprazolam with CNS-depressant drugs, including anticonvulsants, can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.

Oxybutynin: (Moderate) Additive CNS depression may occur when oxybutynin is used concomitantly with other CNS-depressant drugs, including anxiolytics, sedatives, and hypnotics.

Oxycodone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxycodone is initiated in a patient taking a benzodiazepine, reduce dosages and titrate to clinical response. For acetaminophen; oxycodone extended-release tablets, start with 1 tablet PO every 12 hours, and for other oxycodone products, use an initial dose of oxycodone at one-third to one-half the usual dosage. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Oxymorphone: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If oxymorphone is initiated in a patient taking a benzodiazepine, use an initial dose of oxymorphone at 1/3 to 1/2 the usual dosage and titrate to clinical response. If the extended-release oxymorphone tablets are used concurrently with a CNS depressant, use an initial dosage of 5 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.

Paliperidone: (Moderate) Drugs that can cause CNS depression, such as benzodiazepines, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness when coadministered with paliperidone. Monitor for signs and symptoms of CNS depression and advise patients to avoid driving or engaging in other activities requiring mental alertness until they know how this combination affects them.

Pancuronium: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.

Papaverine: (Moderate) Concurrent use of papaverine with potent CNS depressants such as benzodiazepines could lead to enhanced sedation.

Paroxetine: (Minor) The manufacturer of alprazolam states that in vitro studies suggest paroxetine may inhibit the metabolism of alprazolam via inhibition of CYP3A4. However, paroxetine is typically considered a major inhibitor of CYP2D6, for which alprazolam is not a substrate. The potential for clinical interaction is uncertain. Be alert for any change in psychomotor performance or other benzodiazepine-related side effects when paroxetine is combined with alprazolam.

Pazopanib: (Moderate) Pazopanib is a weak inhibitor of CYP3A4. Coadministration of pazopanib and alprazolam, a CYP3A4 substrate, may cause an increase in systemic concentrations of alprazolam. Use caution when administering these drugs concomitantly.
Pentazocine: (Major) Concomitant use of mixed opiate agonists/antagonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of mixed opiate agonists/antagonists with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If a mixed opiate agonist/antagonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the mixed opiate agonist/antagonist and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking a mixed opiate agonist/antagonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Pentazocine; Naloxone: (Major) Concomitant use of mixed opiate agonists/antagonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of mixed opiate agonists/antagonists with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If a mixed opiate agonist/antagonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the mixed opiate agonist/antagonist and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking a mixed opiate agonist/antagonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Pentobarbital: (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers.
Perampanel: (Moderate) Patients taking benzodiazepines with perampanel may experience increased CNS depression. Monitor patients for adverse effects; dose adjustment of either drug may be necessary. Use of midazolam in healthy subjects who received perampanel 6 mg once daily for 20 days decreased the AUC and Cmax of midazolam by 13% and 15%, respectively, possibly due to weak induction of CYP3A4 by perampanel; the specific clinical significance of this interaction is unknown.
Phenobarbital: (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers.
Phenothiazines: (Moderate) Phenothiazines are CNS depressant drugs that may have cumulative effects when administered concurrently and they should be used cautiously with anxiolytic, sedative, and hypnotic type drugs, such as the benzodiazepines. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension. Additionally, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of other CNS depressants than with sedatives alone. Monitor for additive effects, unusual moods or behaviors, and warn about the potential effects to driving and other activities.
Phentermine; Topiramate: (Moderate) Topiramate has the potential to cause CNS depression as well as other cognitive and/or neuropsychiatric adverse reactions. The CNS depressant effects of topiramate can be potentiated pharmacodynamically by concurrent use of CNS depressant agents such as the benzodiazepines. Concurrent use of topiramate and benzodiazepines associated with thrombocytopenia (e.g., clonazepam, lorazepam, and clobazam), may also increase the risk of bleeding; monitor patients appropriately during benzodiazepine therapy.
Phenylephrine: (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Phenylephrine; Promethazine: (Moderate) The therapeutic effect of phenylephrine may be decreased in patients receiving benzodiazepines. Monitor patients for decreased pressor effect if these agents are administered concomitantly.
Pimozide: (Moderate) Due to the effects of pimozide on cognition, it should be used cautiously with other CNS depressants including benzodiazepines.
Posaconazole: (Major) Coadministration of posaconazole and alprazolam is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Posaconazole is a potent inhibitor of CYP3A4. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.
Pramipexole: (Major) Concomitant administration of benzodiazepines with CNS-depressant drugs, including pramipexole, can potentiate the CNS effects.
Prasterone, Dehydroepiandrosterone, DHEA (Dietary Supplements): (Major) Prasterone, dehydroepiandrosterone, DHEA may inhibit the metabolism of benzodiazepines (e.g., alprazolam, estazolam, midazolam) which undergo CYP3A4-mediated metabolism. In one study of elderly volunteers, half of the patients received DHEA 200 mg/day PO for 2 weeks, followed by a single dose of triazolam 0.25 mg. Triazolam clearance was reduced by close to 30% in the DHEA-pretreated patients vs. the control group; however, the effect of DHEA on CYP3A4 metabolism appeared to vary widely among subjects. While more study is needed, benzodiazepine-induced CNS sedation and other adverse effects might be increased in some individuals if DHEA is co-administered.
Prasterone, Dehydroepiandrosterone, DHEA (FDA-approved): (Major) Prasterone, dehydroepiandrosterone, DHEA may inhibit the metabolism of benzodiazepines (e.g., alprazolam, estazolam, midazolam) which undergo CYP3A4-mediated metabolism. In one study of elderly volunteers, half of the patients received DHEA 200 mg/day PO for 2 weeks, followed by a single dose of triazolam 0.25 mg. Triazolam clearance was reduced by close to 30% in the DHEA-pretreated patients vs. the control group; however, the effect of DHEA on CYP3A4 metabolism appeared to vary widely among subjects. While more study is needed, benzodiazepine-induced CNS sedation and other adverse effects might be increased in some individuals if DHEA is co-administered.
Pregabalin: (Moderate) Pregabalin can potentiate the CNS-depressant action of other drugs such as benzodiazepines. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension.
Primidone: (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers.
Probenecid: (Moderate) Probenecid may inhibit the metabolism of the benzodiazepines, including those which are metabolized by conjugation (e.g., lorazepam) or oxidation (e.g., midazolam). Probenecid has been shown to decrease lorazepam clearance by about 50% and increase its elimination half-life. In addition, pretreatment with probenecid shortened the induction time (85 vs. 109 seconds) of midazolam in presurgical patients. Patients receiving alprazolam therapy should be monitored for signs of altered benzodiazepine response when probenecid is initiated or discontinued.
Procarbazine: (Minor) CNS depressants benzodiazepines can potentiate the CNS depression caused by procarbazine therapy, so these drugs should be used together cautiously.
Propofol: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Propoxyphene: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. The dose of any opiate agonist administered with parenteral diazepam should be reduced by at least one-third.
Quazepam: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs can potentiate the CNS effects of either agent.
Quetiapine: (Moderate) Somnolence is a commonly reported adverse effect of quetiapine; coadministration of quetiapine with anxiolytics, sedatives, and hypnotics, or other CNS depressants may result in additive sedative effects.
Ramelteon: (Moderate) Ramelteon is a sleep-promoting agent; therefore, additive pharmacodynamic effects are possible when combining ramelteon with benzodiazepines or other miscellaneous anxiolytics, sedatives, and hypnotics. Pharmacokinetic interactions have been observed with the use of zolpidem. Use of ramelteon 8 mg/day for 11 days and a single dose of zolpidem 10 mg resulted in an increase in the median Tmax of zolpidem of about 20 minutes; exposure to zolpidem was unchanged. Ramelteon use with hypnotics of any kind is considered duplicative therapy and these drugs are generally not co-administered.
Ranolazine: (Moderate) In patients taking drugs that inhibit CYP3A isoenzymes, use alprazolam with caution and consider alprazolam dose reduction (up to 50% dose reduction may be needed). Ranolazine may theoretically inhibit CYP3A4 metabolism of alprazolam.
Rapacuronium: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.

Rasagiline: (Moderate) The CNS-depressant effects of MAOIs can be potentiated with concomitant administration of other drugs known to cause CNS depression including buprenorphine, butorphanol, dronabinol, THC, nabilone, nalbuphine, and anxiolytics, sedatives, and hypnotics. Use these drugs cautiously with MAOIs; warn patients to not drive or perform other hazardous activities until they know how a particular drug combination affects them. In some cases, the dosages of the CNS depressants may need to be reduced.
Remifentanil: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Benzodiazepine doses may need to be reduced up to 75% during coadministration with remifentanil. Educate patients about the risks and symptoms of respiratory depression and sedation.
Ribociclib: (Major) Avoid coadministration of alprazolam and ribociclib due to the potential for elevated alprazolam concentrations, which may cause prolonged sedation and respiratory depression. Lorazepam, oxazepam, or temazepam may be safer alternatives if a benzodiazepine must be administered in combination with ribociclib, as these benzodiazepines are not oxidatively metabolized. Alprazolam is a CYP3A4 substrate and ribociclib is a strong CYP3A4 inhibitor. Coadministration with other strong CYP3A4 inhibitors increased alprazolam exposure by 2.7- to 3.98-fold.
Ribociclib; Letrozole: (Major) Avoid coadministration of alprazolam and ribociclib due to the potential for elevated alprazolam concentrations, which may cause prolonged sedation and respiratory depression. Lorazepam, oxazepam, or temazepam may be safer alternatives if a benzodiazepine must be administered in combination with ribociclib, as these benzodiazepines are not oxidatively metabolized. Alprazolam is a CYP3A4 substrate and ribociclib is a strong CYP3A4 inhibitor. Coadministration with other strong CYP3A4 inhibitors increased alprazolam exposure by 2.7- to 3.98-fold.
Rifabutin: (Moderate) Rifabutin could induce the CYP3A4-mediated metabolism of oxidized benzodiazepines, such as alprazolam.
Rifampin: (Moderate) Rifampin is a potent inducer of the cytochrome P-450 hepatic enzyme system. Rifampin could induce the CYP3A4-mediated metabolism of oxidized benzodiazepines, such as alprazolam.
Rifapentine: (Moderate) Rifapentine could induce the CYP3A4-mediated metabolism of oxidized benzodiazepines, such as alprazolam.
Risperidone: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.
Ritonavir: (Major) Coadministration of alprazolam and ritonavir or lopinavir; ritonavir is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Lopinavir and ritonavir are potent CYP3A4 inhibitors. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.
Rocuronium: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.
Ropinirole: (Moderate) Concomitant use of ropinirole with other CNS depressants, such as alprazolam, can potentiate the sedation effects of ropinirole.
Rotigotine: (Major) Concomitant use of rotigotine with other CNS depressants, such as benzodiazepines, can potentiate the sedative effects of rotigotine.
Rufinamide: (Minor) Rufinamide is not metabolized through hepatic CYP isozymes; however, it is a weak inducer of CYP3A4. In theory, decreased exposure of drugs that are extensively metabolized by CYP3A4, such as alprazolam, may occur during concurrent use with rufinamide.
Safinamide: (Moderate) Dopaminergic medications, including safinamide, may cause a sudden onset of somnolence which sometimes has resulted in motor vehicle accidents. Patients may not perceive warning signs, such as excessive drowsiness, or they may report feeling alert immediately prior to the event. Because of possible additive effects, advise patients about the potential for increased somnolence during concurrent use of safinamide with other sedating medications, such as benzodiazepines.
Saquinavir: (Major) Coadministration of alprazolam and saquinavir boosted with ritonavir is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Saquinavir boosted with ritonavir is a potent CYP3A4 inhibitor. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.
Scopolamine: (Moderate) Scopolamine may cause dizziness and drowsiness. Concurrent use of scopolamine and CNS depressants can adversely increase the risk of CNS depression.
Secobarbital: (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers.
Sedating H1-blockers: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Segesterone Acetate; Ethinyl Estradiol: (Minor) Oral contraceptives can increase the effects of alprazolam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased response to alprazolam.
Sertraline: (Minor) The manufacturer of alprazolam states that in vitro studies suggest sertraline may inhibit the metabolism of alprazolam via inhibition of CYP3A4. The potential for clinical interaction is uncertain. Be alert for any change in psychomotor performance or other benzodiazepine-related side effects when sertraline is combined with alprazolam.
Sevoflurane: (Moderate) Concomitant administration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Simeprevir: (Moderate) Simeprevir, a mild intestinal CYP3A4 inhibitor, may increase the side effects of alprazolam, which is a CYP3A4 substrate. Monitor patients for adverse effects of alprazolam, such as sedation.
Sincalide: (Moderate) Sincalide-induced gallbladder ejection fraction may be affected by benzodiazepines. False study results are possible in patients with drug-induced hyper- or hypo-responsiveness; thorough patient history is important in the interpretation of procedure results.
Skeletal Muscle Relaxants: (Moderate) Concomitant use of skeletal muscle relaxants with benzodiazepines can result in additive CNS depression. The severity of this interaction may be increased when additional CNS depressants are given.
Sodium Oxybate: (Severe) Sodium oxybate should not be used in combination with CNS depressant anxiolytics, sedatives, and hypnotics or other sedative CNS depressant drugs. Specifically, sodium oxybate use is contraindicated in patients being treated with sedative hypnotic drugs. Sodium oxybate (GHB) has the potential to impair cognitive and motor skills. For example, the concomitant use of barbiturates and benzodiazepines increases sleep duration and may contribute to rapid onset, pronounced CNS depression, respiratory depression, or coma when combined with sodium oxybate.
St. John's Wort, Hypericum perforatum: (Major) St. John's Wort may induce the hepatic CYP3A4 metabolism of alprazolam which is metabolized by oxidation. It would be prudent to avoid coadministration of St. John's Wort with alprazolam. Benzodiazepines that are not metabolized by CYP3A4 such as oxazepam or lorazepam may be alternatives if a benzodiazepine is required in combination with St. John's Wort.
Streptogramins: (Major) Coadministration of alprazolam and dalfopristin; quinupristin is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Dalfopristin; quinupristin is a potent CYP3A4 inhibitor. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.
Succinimides: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs, including anticonvulsants, can potentiate the CNS effects of either agent.
Succinylcholine: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.

Sufentanil: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Suvorexant: (Moderate) CNS depressant drugs may have cumulative effects when administered concurrently and they should be used cautiously with suvorexant. A reduction in dose of the CNS depressant may be needed in some cases. These agents include the benzodiazepines.
Tapentadol: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If tapentadol is initiated in a patient taking a benzodiazepine, a reduced initial dosage of tapentadol is recommended. If the extended-release tapentadol tablets are used concurrently with a benzodiazepine, use an initial tapentadol dose of 50 mg PO every 12 hours. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Tasimelteon: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs can potentiate the CNS effects of either agent.
Teduglutide: (Moderate) Teduglutide may increase absorption of benzodiazepines or other psychotropic agents because of it's pharmacodynamic effect of improving intestinal absorption. In studies with teduglutide, one of the subjects was receiving concomitant treatment with prazepam and experienced dramatic deterioration in mental status progressing to coma during her first week of teduglutide therapy. Upon admission to the ICU, her benzodiazepine level was reported as >300 mcg/L. Both drugs were discontinued, and the coma resolved 5 days later. Careful monitoring and possible dose adjustment of the psychotropic agent is recommended.
Telaprevir: (Moderate) Close clinical monitoring is advised when administering alprazolam with telaprevir due to an increased potential for serious alprazolam-related adverse events. If alprazolam dose adjustments are made, re-adjust the dose upon completion of telaprevir treatment. Predictions about the interaction can be made based on the metabolic pathway of alprazolam. Alprazolam is metabolized by the hepatic isoenzyme CYP3A4; telaprevir inhibits this isoenzyme. Coadministration may result in elevated alprazolam plasma concentrations.
Telithromycin: (Major) Coadministration of alprazolam and telithromycin is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Telithromycin is a potent CYP3A4 inhibitor. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.
Telotristat Ethyl: (Moderate) Use caution if coadministration of telotristat ethyl and alprazolam is necessary, as the systemic exposure of alprazolam may be decreased resulting in reduced efficacy. If these drugs are used together, monitor patients for suboptimal efficacy of alprazolam; consider increasing the dose of alprazolam if necessary. Alprazolam is a CYP3A4 substrate. The mean Cmax and AUC of another sensitive CYP3A4 substrate was decreased by 25% and 48%, respectively, when coadministered with telotristat ethyl; the mechanism of this interaction appears to be that telotristat ethyl increases the glucuronidation of the CYP3A4 substrate.
Temazepam: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs can potentiate the CNS effects of either agent.
Tetrabenazine: (Moderate) Concurrent use of tetrabenazine and drugs that can cause CNS depression, such as benzodiazepines, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, dizziness, and orthostatic hypotension.
Tezacaftor; Ivacaftor: (Moderate) Use caution when administering ivacaftor and alprazolam concurrently because patients are at increased risk for adverse effects from alprazolam. Ivacaftor is a CYP3A inhibitor, and alprazolam is a CYP3A substrate. Co-administration of ivacaftor with midazolam, another CYP3A substrate, increased midazolam exposure by 1.5-fold.
Thalidomide: (Major) The use of benzodiazepine anxiolytics, sedatives, or hypnotics with thalidomide may cause an additive sedative effect and should be avoided. Thalidomide frequently causes drowsiness and somnolence. Dose reductions may be required. Patients should be instructed to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness without adequate medical advice. Advise patients as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex or dangerous machinery.
Theophylline, Aminophylline: (Moderate) Aminophylline has been reported to counteract the pharmacodynamic effects of diazepam. A proposed mechanism is competitive binding of aminophylline to adenosine receptors in the brain. Whether a similar interaction occurs with other benzodiazepines is not known. If aminophylline therapy is initiated or discontinued, monitor the clinical response to benzodiazepines. (Moderate) Theophylline has been reported to counteract the pharmacodynamic effects of diazepam. A proposed mechanism is competitive binding of theophylline to adenosine receptors in the brain. Whether a similar interaction occurs with other benzodiazepines is not known. If theophylline therapy is initiated or discontinued, monitor the clinical response to benzodiazepines.
Thiopental: (Moderate) Additive CNS and/or respiratory depression may occur. Additionally, the oral clearance of alprazolam (0.8 mg single dose) was increased in the presence of another CYP3A4 inducer for 10 days from 0.9 +/- 0.21 mL/minute/kg to 2.13 +/- 0.54 mL/minute/kg and the elimination half-life was shortened from 17.1 +/- 4.9 to 7.7 +/- 1.7 hours. Alprazolam is a CYP3A4 substrate. Barbiturates are CYP3A4 inducers.
Thiothixene: (Moderate) Thiothixene can potentiate the CNS-depressant action of other drugs such as benzodiazepines. Caution should be exercised during simultaneous use of these agents due to potential excessive CNS effects or additive hypotension.
Tiagabine: (Moderate) Because of the possible additive effects of drugs that depress the central nervous system, benzodiazepines should be used with caution in patients receiving tiagabine.
Tipranavir: (Major) Coadministration of alprazolam and tipranavir is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Tipranavir is a potent CYP3A4 inhibitor. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes.
Tizanidine: (Moderate) Concurrent use of tizanidine and CNS depressants like the benzodiazepines can cause additive CNS depression. The severity of this interaction may be increased when additional CNS depressants are given.
Tobacco: (Moderate) The clinical significance of the pharmacokinetic effect of tobacco smoking on alprazolam clearance is unclear. According to the manufacturer, alprazolam concentrations may be reduced by up to 50% in tobacco smokers vs. non-smokers. In one small study (n = 10), the mean half-life of alprazolam was significantly shorter in smokers (more than 10 cigarettes/day) than in nonsmokers. No significant differences between groups were found in the Cmax or AUC. A bioavailability study (n = 17) evaluating the immediate-release and controlled-release formulations of alprazolam found that cigarette smokers had a 100% increase in clearance of alprazolam compared with nonsmokers. Polycyclic aromatic hydrocarbons (PAHs) found in tobacco smoke are potent inducers of CYP1A1, CYP1A2, and possibly CYP2E1. Because alprazolam is a primary substrate of CYP3A4, further evaluation of this potential interaction is needed in order to determine its clinical impact to patients.
Topiramate: (Moderate) Topiramate has the potential to cause CNS depression as well as other cognitive and/or neuropsychiatric adverse reactions. The CNS depressant effects of topiramate can be potentiated pharmacodynamically by concurrent use of CNS depressant agents such as the benzodiazepines. Concurrent use of topiramate and benzodiazepines associated with thrombocytopenia (e.g., clonazepam, lorazepam, and clobazam), may also increase the risk of bleeding; monitor patients appropriately during benzodiazepine therapy.
Tramadol: (Major) Concomitant use of opiate agonists with benzodiazepines may cause respiratory depression, hypotension, profound sedation, and death. Limit the use of opiate pain medications with benzodiazepines to only patients for whom alternative treatment options are inadequate. If concurrent use is necessary, use the lowest effective doses and minimum treatment durations needed to achieve the desired clinical effect. If an opiate agonist is initiated in a patient taking a benzodiazepine, use a lower initial dose of the opiate and titrate to clinical response. If a benzodiazepine is prescribed for an indication other than epilepsy in a patient taking an opiate agonist, use a lower initial dose of the benzodiazepine and titrate to clinical response. Educate patients about the risks and symptoms of respiratory depression and sedation.
Trandolapril; Verapamil: (Moderate) Consider a reduced dose of alprazolam is concurrent use of verapamil is necessary. Coadministration of alprazolam, a CYP3A4 substrate, with verapamil, a moderate CYP3A4 inhibitor, may result in increased alprazolam exposure.
Trazodone: (Major) Monitor for excessive sedation and somnolence during coadministration of trazodone and benzodiazepines. Concurrent use may result in additive CNS depression.
Triazolam: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs can potentiate the CNS effects of either agent.

Tricyclic antidepressants: (Moderate) Concomitant administration of benzodiazepines with CNS-depressant drugs, such as tricyclic antidepressants, can potentiate the CNS effects of either agent. Tricyclic antidepressants may also lower the seizure threshold leading to pharmacodynamic interactions with anticonvulsant benzodiazepines (i.e., clobazam, clonazepam, diazepam, and lorazepam). The plasma concentrations of imipramine and desipramine may increase an average of 31% and 20%, respectively, when administered concurrently with alprazolam. The significance of this interaction has not been described; therefore, patients should be monitored closely for symptoms of tricyclic toxicity during coadministration of these agents with alprazolam.
Trihexyphenidyl: (Moderate) CNS depressants, such as anxiolytics, sedatives, and hypnotics, can increase the sedative effects of trihexyphenidyl.
Trimethobenzamide: (Moderate) The concurrent use of trimethobenzamide with other medications that cause CNS depression, like the benzodiazepines, may potentiate the effects of either trimethobenzamide or the benzodiazepine.
Triprolidine: (Moderate) Coadministration can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. Use caution with this combination.
Tubocurarine: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.
Valerian, Valeriana officinalis: (Major) Any substances that act on the CNS, including psychoactive drugs and drugs used as anesthetic adjuvants (e.g., barbiturates, benzodiazepines), may theoretically interact with valerian, Valeriana officinalis. The valerian derivative, dihydrovaltrate, binds at barbiturate binding sites; valerenic acid has been shown to inhibit enzyme-induced breakdown of GABA in the brain; the non-volatile monoterpenes (valepotriates) have sedative activity. These interactions are probably pharmacodynamic in nature. There is a possibility of interaction with valerian at normal prescription dosages of anxiolytics, sedatives, and hypnotics (including barbiturates and benzodiazepines). Patients who are taking barbiturates or other sedative/hypnotic drugs should avoid concomitant administration of valerian. Patients taking medications such as tricyclic antidepressants, lithium, MAOIs, skeletal muscle relaxants, SSRIs and serotonin norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine) should discuss the use of herbal supplements with their health care professional prior to consuming valerian; combinations should be approached with caution in the absence of clinical data. Patients should not abruptly stop taking their prescribed psychoactive medications.
Valproic Acid, Divalproex Sodium: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs, including anticonvulsants, can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent.
Vecuronium: (Moderate) Concurrent use of benzodiazepines and other CNS active medications including neuromuscular blockers, can potentiate the CNS effects of either agent. Lower doses of one or both agents may be required. The severity of this interaction may be increased when additional CNS depressants are given.
Verapamil: (Moderate) Consider a reduced dose of alprazolam is concurrent use of verapamil is necessary. Coadministration of alprazolam, a CYP3A4 substrate, with verapamil, a moderate CYP3A4 inhibitor, may result in increased alprazolam exposure.
Vigabatrin: (Moderate) Vigabatrin may cause somnolence and fatigue. Drugs that can cause CNS depression, if used concomitantly with vigabatrin, may increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness. Caution should be used when vigabatrin is given in combination with benzodiazepines.
Vilazodone: (Moderate) Due to the CNS effects of vilazodone, caution should be used when vilazodone is given in combination with other centrally acting medications such as the benzodiazepines.
Voriconazole: (Severe) Coadministration of voriconazole and alprazolam is contraindicated. Voriconazole is a strong CYP3A4 inhibitor and significantly impairs the CYP3A4 metabolism of alprazolam, resulting in elevated alprazolam concentrations. Lorazepam, oxazepam, or temazepam may be safer alternatives if a benzodiazepine must be administered in combination with voriconazole, as these benzodiazepines are not oxidatively metabolized.
Zafirlukast: (Moderate) Alprazolam is metabolized by cytochrome CYP3A. Zafirlukast inhibits CYP3A isoenzymes to a significant but lesser degree, and use with alprazolam should be done with caution and consider alprazolam dose reduction up to 50%.
Zaleplon: (Moderate) In premarketing studies, zaleplon potentiated the CNS effects of ethanol, imipramine, and thioridazine for at least 2 to 4 hours. Other drugs that may have additive CNS effects with zaleplon but have not been studied include benzodiazepines. If used together, a reduction in the dose of one or both drugs may be needed.
Zileuton: (Moderate) Zileuton may inhbit the CYP3A isoenzymes and reduce the metabolism of alprazolam, potentially increasing the risk for benzodiazepine toxicity. Consider alprazolam dose reduction of up to 50%. Monitor for an increase in CNS and/or respiratory depression.
Ziprasidone: (Moderate) Ziprasidone has the potential to impair cognitive and motor skills. Additive CNS depressant effects are possible when ziprasidone is used concurrently with any CNS depressant.
Zolpidem: (Moderate) Concomitant administration of benzodiazepines with zolpidem can potentiate the CNS effects (e.g., increased sedation or respiratory depression) of either agent. If used together, a reduction in the dose of one or both drugs may be needed. For Intermezzo brand of sublingual zolpidem tablets, reduce the dose to 1.75 mg/night. Concurrent use of zolpidem with other sedative-hypnotics, including other zolpidem products, at bedtime or the middle of the night is not recommended. In addition, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of zolpidem and other CNS depressants than with zolpidem alone.
Zonisamide: (Moderate) Concomitant administration of alprazolam with CNS-depressant drugs, including anticonvulsants, can potentiate the CNS effects of either agent.

PREGNANCY AND LACTATION

Pregnancy

Alprazolam, like other benzodiazepines, poses a risk of harm to the fetus when administered to pregnant women. Positive evidence of human fetal risk exists based on investigational, marketing, or human studies. In general, the use of benzodiazepines is not life-saving and thus should be avoided in pregnancy whenever possible. An increased risk of congenital malformations and other developmental abnormalities is associated with benzodiazepine use during the first trimester. If alprazolam is to be used during pregnancy or the patient becomes pregnant while taking alprazolam, the patient should be apprised of the potential hazard to the fetus. The possibility that a woman of childbearing age may be pregnant when initiating therapy with alprazolam should be considered. Patients who become pregnant or intend to become pregnant while taking alprazolam should be advised to discuss the possibility of discontinuing the drug with their physician. It should be anticipated that neonates may experience withdrawal symptoms if the mother has been using benzodiazepines during pregnancy. Neonatal flaccidity has been reported in an infant whose mother was using benzodiazepines during pregnancy. Alprazolam has no established use in labor or obstetric delivery.

MECHANISM OF ACTION

Benzodiazepines act at the level of the limbic, thalamic, and hypothalamic regions of the CNS and can produce any level of CNS depression required including sedation, hypnosis, skeletal muscle relaxation, and anticonvulsant activity. Recent evidence indicates that benzodiazepines exert their effects through enhancement of the gamma-aminobutyric acid (GABA)-benzodiazepine receptor complex. GABA is an inhibitory neurotransmitter that exerts its effects at specific receptor subtypes designated GABA-A and GABA-B. GABA-A is the primary receptor subtype in the CNS and is thought to be involved in the actions of anxiolytics and sedatives.

Specific benzodiazepine receptor subtypes are thought to be coupled to GABA-A receptors. Three types of BNZ receptors are located in the CNS and other tissues; the BNZ-1 receptors are located in the cerebellum and cerebral cortex, the BNZ-2 receptors in the cerebral cortex and spinal cord, and the BNZ-3 receptors in peripheral tissues. Activation of the BNZ-1 receptor is thought to mediate sleep while the BNZ-2 receptor affects muscle relaxation, anticonvulsant activity, motor coordination, and memory. Benzodiazepines bind nonspecifically to BNZ-1 and BNZ-2 which ultimately enhances the effects of GABA. Unlike barbiturates which augment GABA responses by increasing the length of time that chloride channels are open, benzodiazepines enhance the effects of GABA by increasing GABA affinity for the GABA receptor. Binding of GABA to the site

opens the chloride channel resulting in a hyperpolarized cell membrane that prevents further excitation of the cell.

Benzodiazepines alleviate insomnia by decreasing the latency to sleep and increasing sleep continuity and total sleep time through their effects on GABA. Preliminary evidence suggests that alprazolam decreases cerebral blood flow and plasma epinephrine concentrations.

PHARMACOKINETICS

Alprazolam is administered orally.

Alprazolam is widely distributed and is 90% plasma protein-bound, primarily to serum albumin. Alprazolam may cross the placenta and distributes into breast milk (see Contraindications). Alprazolam undergoes oxidative metabolism in the liver through CYP3A4, producing metabolites with little or no activity. The alpha-hydroxy-alprazolam metabolite is approximately one half as potent as the parent compound while the benzophenone derivative is inactive. Both metabolites are excreted primarily in the urine. The half-life of alprazolam immediate-release tablets is 11.2 hours (range 6.3—26.9 hours). The half-life of alprazolam extended-release ranges from roughly 11 to 16 hours.

Oral Route

Alprazolam is rapidly absorbed following oral administration. Peak plasma concentrations are attained within 1—2 hours of administration of the immediate-release tablets. The onset of action usually occurs within 15—30 minutes. The pharmacokinetics of alprazolam extended-release tablets are similar to the immediate-release tablets, except that the extended-release tablets have a slower rate of absorption and yield a constant concentration maintained between 5 and 11 hours after dosing. Although elevations up to 25% in the Cmax have been observed when extended-release tablets were given following a high-fat meal, the AUC and T1/2 were not affected by consumption of food. Additionally, alprazolam extended-release given at night (vs. the morning) results in a 30% higher Cmax and a reduction in Tmax by 1 hour. The rate of metabolism of alprazolam extended-release is not effected by the slower rate of absorption.

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DISTRICT COURT
FAMILY DIVISION
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THOMAS A. PICKENS, Individually and as Trustee of the LV Blue Trust, Plaintiff/Counterdefendant. vs. DANKA K. MICHAELS, Individually and as Trustee of the Mich-Mich Trust, Defendant/Counterclaimant; and related Counterclaims.	CASE NO.: D-17-560737-D DEPT. J **Dates of Trial: February 14, 2020 & February 21, 2020** **Time of Trial: 9:00 a.m.**

PLAINTIFF'S REQUEST FOR THE COURT TO TAKE JUDICIAL NOTICE PURSUANT TO NRS 47.130

Plaintiff, Thomas A. Pickens ("Tom"), by and through his attorneys of record, Michele Touby LoBello, John D. Jones and the law firm of Black & LoBello hereby requests this Court take judicial notice of the following documents:

BLACK & LOBELLO
10777 W. Twain Avenue, 3rd Floor
Las Vegas, Nevada 89135
(702) 869-8801 FAX: (702) 869-2669

1. AMA Code of Medical Ethics Opinion 9.1.1

2. AMA Code of Medical Ethics Opinion 1.2.8

3. NRS 630.301

Pursuant to NRS 47.130, this Court may take judicial notice of facts generally known within the territorial jurisdiction of the trial court or capable of accurate and ready determination by resort to sources whose accuracy cannot reasonably be questioned, so that the fact is not subject to reasonable dispute.

Neither party hereto can reasonably dispute the existence of AMA regulations which are designed to control and regulate the medical profession. The Defendant has already recognized the AMA as one of the governing bodies of her profession. The Court should take note of these Ethics Opinions as they relate to sexual or romantic relationships with patients and the reasons for the prohibition thereof and the receipt by a physician of a gift from a patient.

Likewise, neither party can dispute the existence of NRS 630.301 which sets forth the actions of Physician which constitute grounds for initiating disciplinary action. Specifically, the Court should take notice of NRS 630.301 (5) pertaining to sexual relations with a patient, and (7) pertaining to conduct exploiting a patient for the physician's financial or personal gain.

NRS 47.150 provides that a judge or court may take judicial notice, whether requested or not, and a judge or court shall take judicial notice if requested by a party and supplied with the necessary information. NRS 47.160 provides, "A party is

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entitled upon timely request to an opportunity to be heard as to the propriety of taking judicial notice and the tenor of the matter to be noticed." As to timing, NRS 47.170 provides: "Judicial notice may be taken at any stage of the proceeding prior to submission to the court or jury."

RESPECTFULLY SUBMITTED this 20 day of February, 2020.

BLACK & LOBELLO

Michele Touby DoBello
Nevada Bar No. 5527
10777 West Twain Avenue, Suite 300
Las Vegas, Nevada 89135
Attorneys for Plaintiff,
THOMAS PICKENS

BLACK & LOBELLO
10777 W. Twain Avenue, 3rd Floor
Las Vegas, Nevada 89135
(702) 869-8801 FAX: (702) 869-2669

CERTIFICATE OF SERVICE

Pursuant to NRCP 5(b), I certify that I am an employee of BLACK & LOBELLO and that on the 20th day of February, 2020, I caused the above and foregoing document entitled foregoing PLAINTIFF'S REQUEST FOR THE COURT TO TAKE JUDICIAL NOTICE PURSUANT TO NRS 47.130 to be served as follows:

☐ by placing same to be deposited for mailing in the United States Mail, in a sealed envelope upon which first class postage was prepaid in Las Vegas, Nevada; and

☒ pursuant to N.E.F.C.R. 9, to be sent via electronic service;

☐ pursuant to EDCR 7.26, to be sent via facsimile;

☒ by email to JVAGroup@TheAbramsLawFirm.com

☐ hand delivered

to the party or their attorney(s) listed below at the address and/or facsimile number indicated below:

Jennifer V. Abrams, Esq.
The Abrams & Mayo Law Firm
6252 South Rainbow Blvd., #100
Las Vegas, NV 89118
Email: JVAGroup@TheAbramsLawFirm.com
Attorney for Defendant

and that there is regular communication by mail between the place of mailing and the place(s) so addressed.

An Employee of Black & LoBello

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Exhibit 1

Exhibit 1

Join / Renew

ETHICS

Romantic or Sexual Relationships With Patients

Code of Medical Ethics Opinion 9.1.1

Romantic or sexual interactions between physicians and patients that occur concurrently with the patient physician relationship are unethical. Such interactions detract from the goals of the patient-physician relationship and may exploit the vulnerability of the patient, compromise the physician's ability to make objective judgments about the patient's health care, and ultimately be detrimental to the patient's well-being.

CME course: Boundaries for physicians

This e-learning module will help physicians identify and understand how to maintain boundaries with their patients as well as boundaries for treating family, self and colleagues.

Go to course

A physician must terminate the patient-physician relationship before initiating a dating, romantic, or sexual relationship with a patient.

Likewise, sexual or romantic relationships between a physician and a former patient may be unduly influenced by the previous physician-patient relationship. Sexual or romantic relationships with former patients are unethical if the physician uses or exploits trust, knowledge, emotions, or influence derived from the previous professional relationship, or if a romantic relationship would otherwise foreseeably harm the individual.

In keeping with a physician's ethical obligations to avoid inappropriate behavior, a physician who has reason to believe that nonsexual, nonclinical contact with a patient may be perceived as or may lead to romantic or sexual contact should avoid such contact.

AMA Principles of Medical Ethics: I, II, IV

Read more opinions about this topic

Code of Medical Ethics: Sexual boundaries

Visit the Ethics main page to access additional Opinions, the Principles of Medical Ethics and more information about the Code of Medical Ethics.

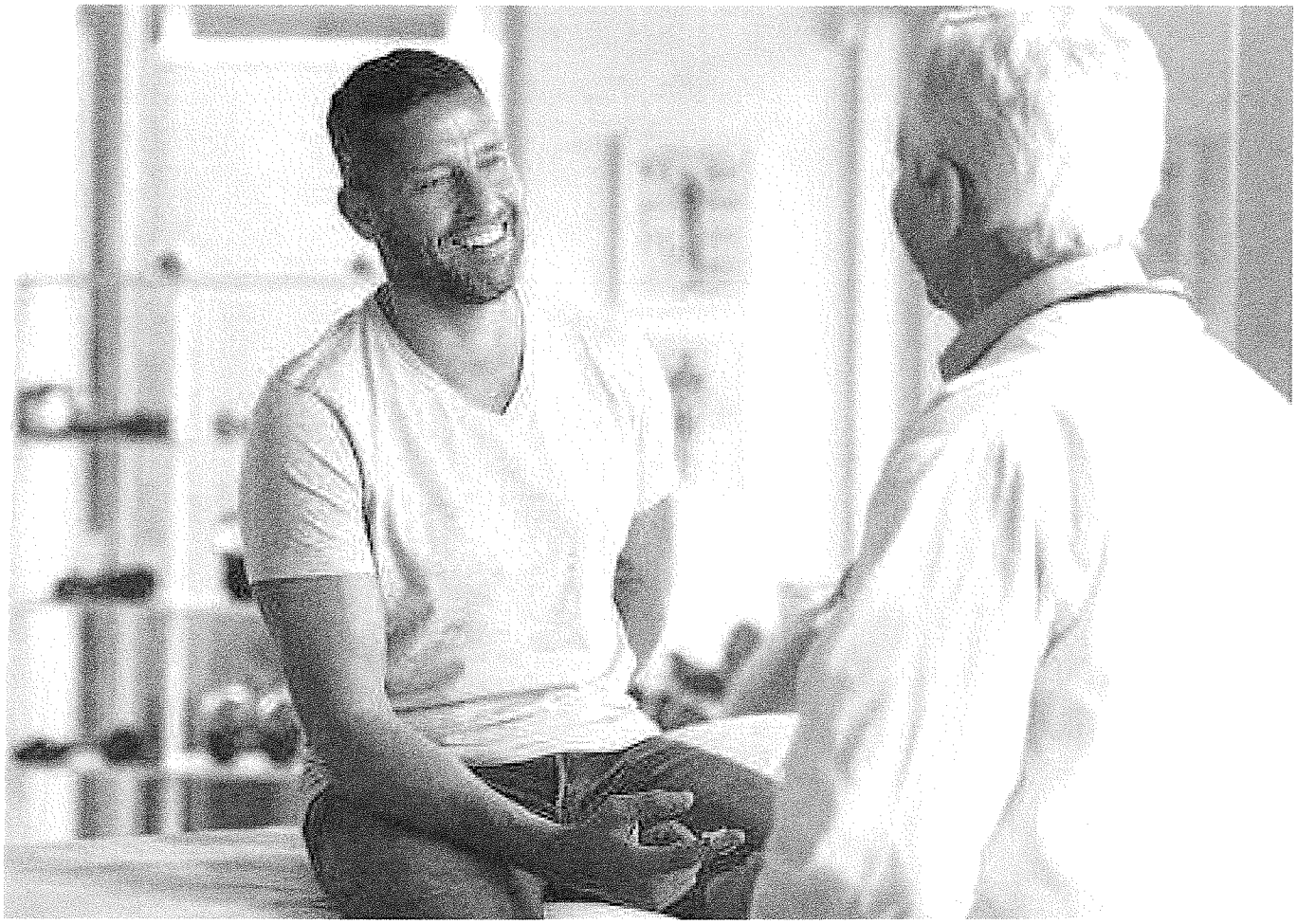
Ethics of Professional Self-Regulation AMA Code of Medical Ethics

PUBLIC HEALTH

8 ways to protect doctors caring for patients with COVID-19

PHYSICIAN HEALTH

4 personal reasons why some doctors have a lower risk of burnout



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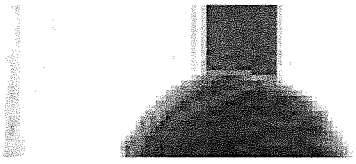
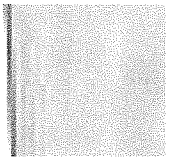
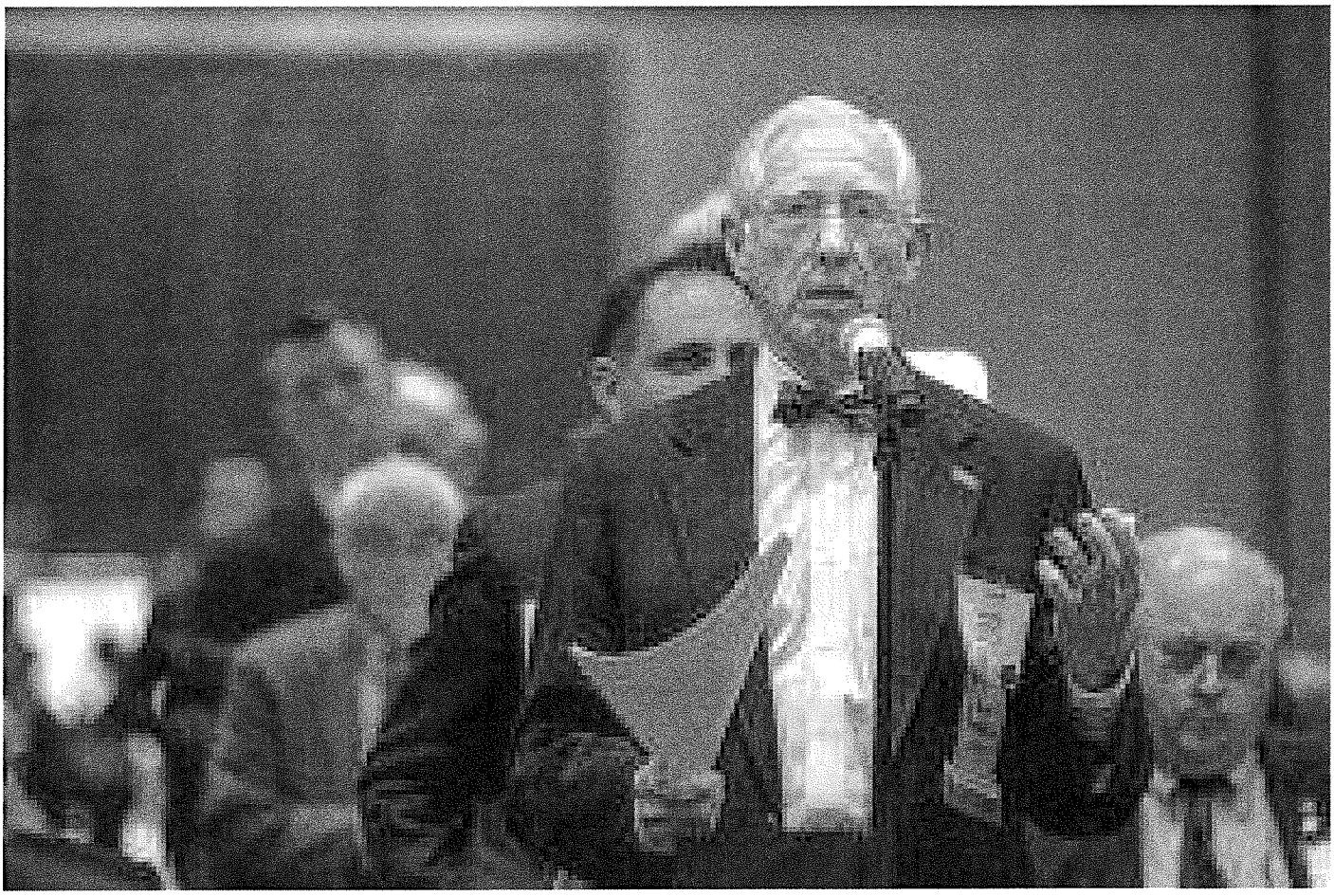




AA07213
Docket 83491 Document 2022-05932

The top 10 ethical issues medical students should be taught



Physicians have duty to monitor their own competence

A medical resident's guide to gifts from industry

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Exhibit 2

Exhibit 2

ETHICS

Gifts From Patients

Code of Medical Ethics Opinion 1.2.8

Patients offer gifts to a physician for many reasons. Some gifts are offered as an expression of gratitude or a reflection of the patient's cultural tradition. Accepting gifts offered for these reasons can enhance the patient-physician relationship.

CME course: Boundaries for physicians

This e-learning module will help physicians identify and understand how to maintain boundaries with their patients as well as boundaries for treating family, self and colleagues.

Go to course

Other gifts may signal psychological needs that require the physician's attention. Some patients may offer gifts or cash to secure or influence care or to secure preferential treatment. Such gifts can undermine physicians' obligation to provide services fairly to all patients; accepting them is likely to damage the patient-physician relationship.

The interaction of these factors is complex and physicians should consider them sensitively before accepting or declining a gift.

Physicians to whom a patient offers a gift should:

(a) Be sensitive to the gift's value relative to the patient's or physician's means. Physicians should decline gifts that are disproportionately or inappropriately large, or when the physician would be uncomfortable to have colleagues know the gift had been accepted.

(b) Not allow the gift or offer of a gift to influence the patient's medical care.

(c) Decline a bequest from a patient if the physician has reason to believe accepting the gift would present an emotional or financial hardship to the patient's family.

(d) Physicians may wish to suggest that the patient or family make a charitable contribution in lieu of the bequest, in keeping with ethics guidance.

AMA Principles of Medical Ethics: I, II

Read more opinions about this topic

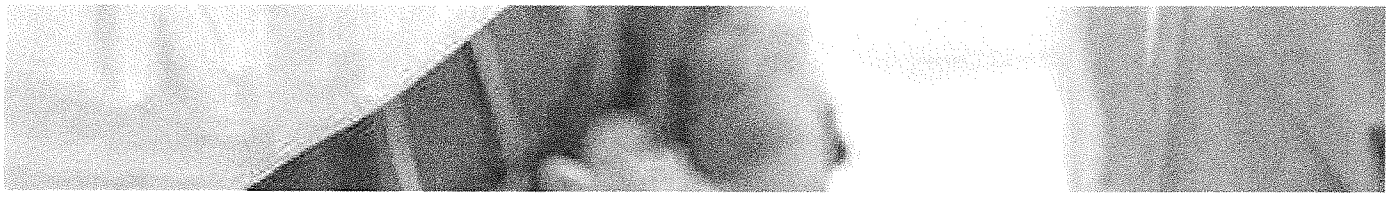
Code of Medical Ethics: Patient-Physician Relationships

Visit the Ethics main page to access additional Opinions, the Principles of Medical Ethics and more information about the Code of Medical Ethics.

Ethics of Patient-Physician Relationships AMA Code of Medical Ethics

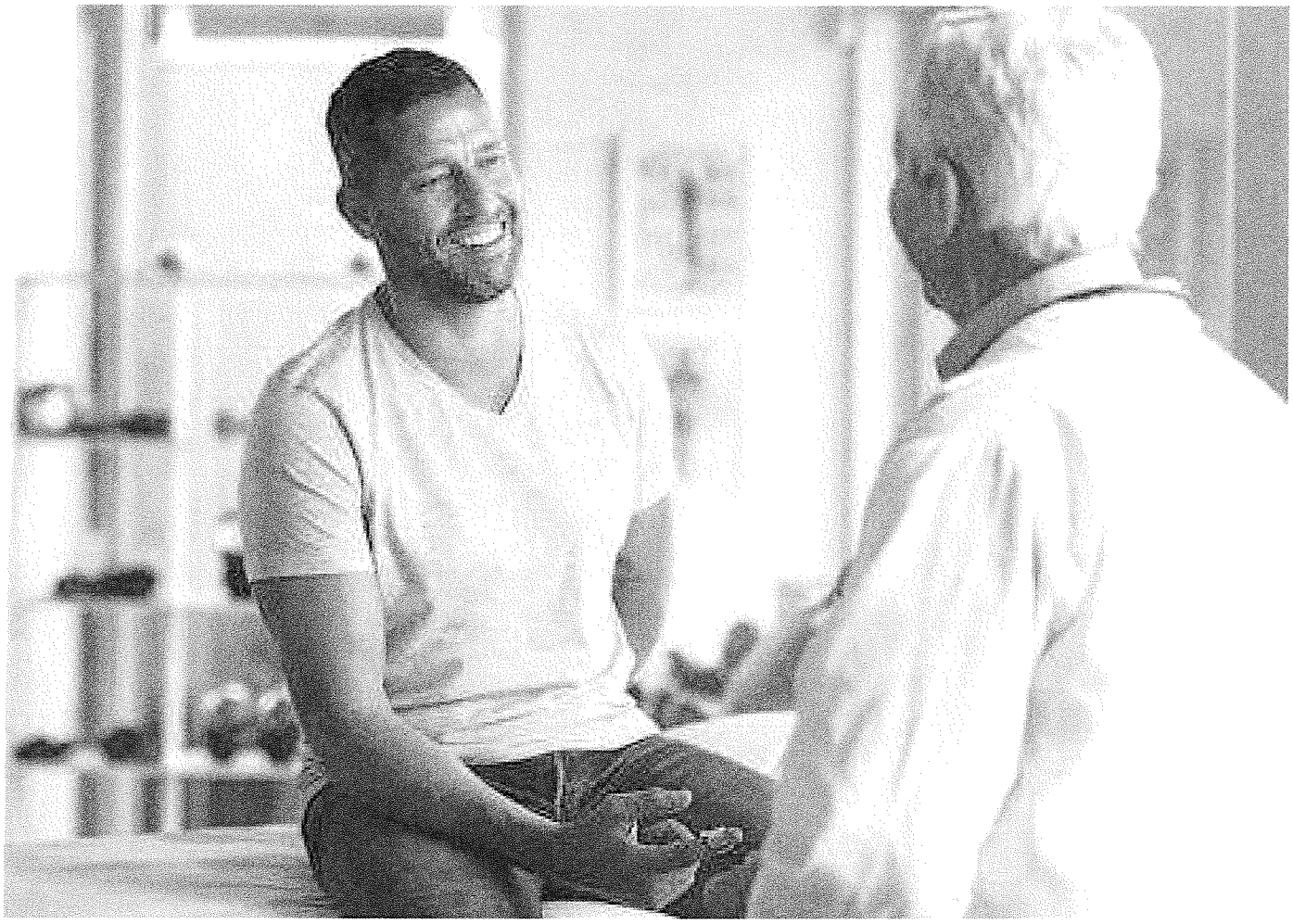
PUBLIC HEALTH

8 ways to protect doctors caring for patients with COVID-19



PHYSICIAN HEALTH

4 personal reasons why some doctors have a lower risk of burnout



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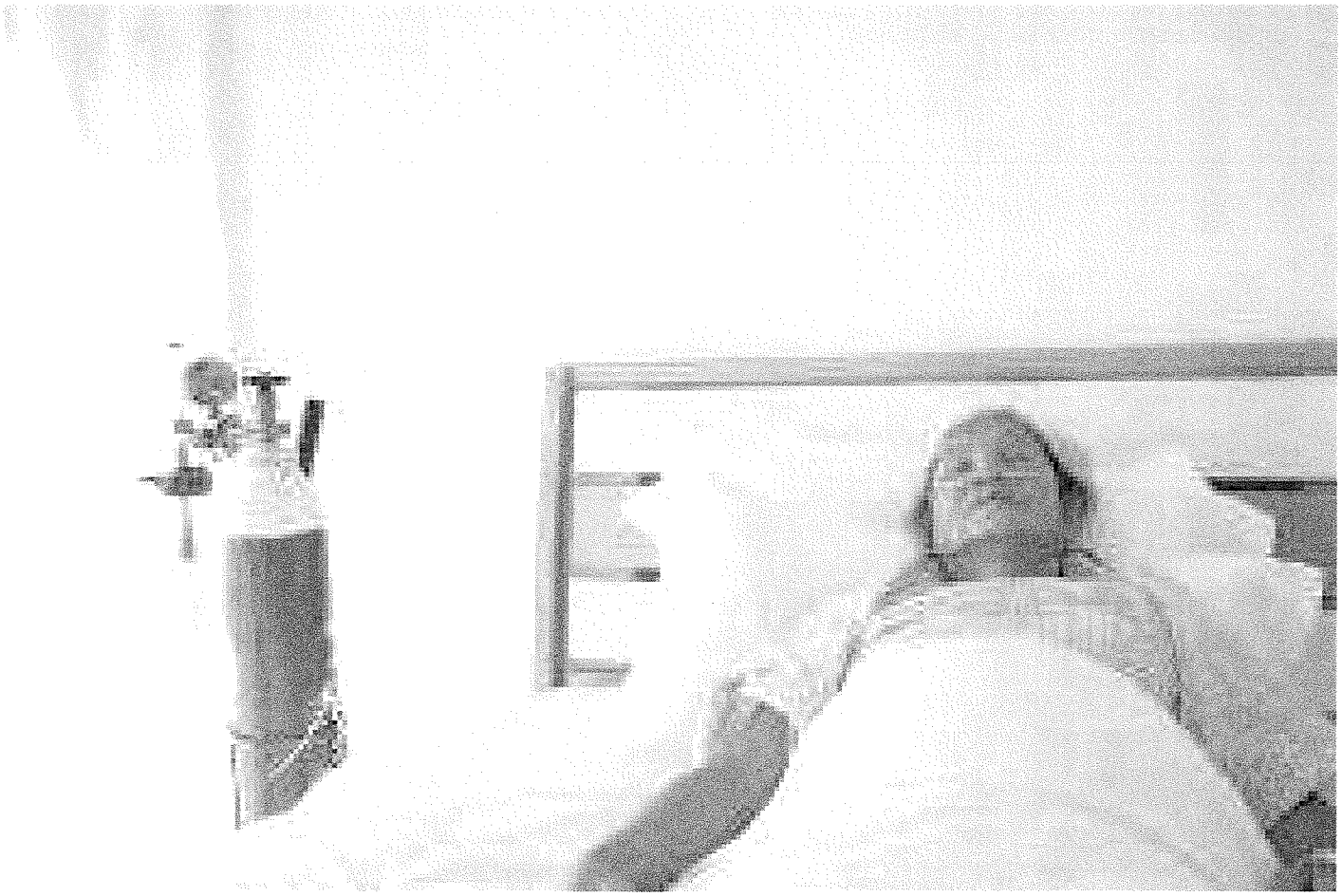
The top 10 ethical issues medical students should be taught



Caring for "unrepresented" patients: 5 things to keep in mind

Inside Mayo Clinic's 5-step process for handling biased patients

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Exhibit 3

Exhibit 3

West's Nevada Revised Statutes Annotated
Title 54. Professions, Occupations and Businesses (Chapters 622-656a)
Chapter 630. Physicians, Physician Assistants, Medical Assistants, Perfusionists and Practitioners of Respiratory Care
Regulation; Disciplinary and Other Actions
Grounds for Initiating Disciplinary Action or Denying Licensure (Refs & Annos)

N.R.S. 630.301

630.301. Criminal offenses; disciplinary action taken by other jurisdiction; surrender of previous license while under investigation; malpractice; engaging in sexual activity with patient; disruptive behavior; violating or exploiting trust of patient for financial or personal gain; failure to offer appropriate care with intent to positively influence financial well-being; engaging in disreputable conduct; engaging in sexual contact with surrogate of patient or relatives of patient

Effective: October 1, 2011

Currentness

The following acts, among others, constitute grounds for initiating disciplinary action or denying licensure:

1. Conviction of a felony relating to the practice of medicine or the ability to practice medicine. A plea of nolo contendere is a conviction for the purposes of this subsection.

2. Conviction of violating any of the provisions of NRS 616D.200, 616D.220, 616D.240, 616D.300, 616D.310, or 616D.350 to 616D.440, inclusive.

3. Any disciplinary action, including, without limitation, the revocation, suspension, modification or limitation of a license to practice any type of medicine, taken by another state, the Federal Government, a foreign country or any other jurisdiction or the surrender of the license or discontinuing the practice of medicine while under investigation by any licensing authority, a medical facility, a branch of the Armed Services of the United States, an insurance company, an agency of the Federal Government or an employer.

4. Malpractice, which may be evidenced by claims settled against a practitioner, but only if the malpractice is established by a preponderance of the evidence.

5. The engaging by a practitioner in any sexual activity with a patient who is currently being treated by the practitioner.

6. Disruptive behavior with physicians, hospital personnel, patients, members of the families of patients or any other persons if the behavior interferes with patient care or has an adverse impact on the quality of care rendered to a patient.

7. The engaging in conduct that violates the trust of a patient and exploits the relationship between the physician and the patient for financial or other personal gain.

8. The failure to offer appropriate procedures or studies, to protest inappropriate denials by organizations for managed care, to provide necessary services or to refer a patient to an appropriate provider, when the failure occurs with the intent of positively influencing the financial well-being of the practitioner or an insurer.

9. The engaging in conduct that brings the medical profession into disrepute, including, without limitation, conduct that violates any provision of a code of ethics adopted by the Board by regulation based on a national code of ethics.

10. The engaging in sexual contact with the surrogate of a patient or other key persons related to a patient, including, without limitation, a spouse, parent or legal guardian, which exploits the relationship between the physician and the patient in a sexual manner.

11. Conviction of:

(a) Murder, voluntary manslaughter or mayhem;

(b) Any felony involving the use of a firearm or other deadly weapon;

(c) Assault with intent to kill or to commit sexual assault or mayhem;

(d) Sexual assault, statutory sexual seduction, incest, lewdness, indecent exposure or any other sexually related crime;

(e) Abuse or neglect of a child or contributory delinquency;

(f) A violation of any federal or state law regulating the possession, distribution or use of any controlled substance or any dangerous drug as defined in chapter 454 of NRS; or

(g) Any offense involving moral turpitude.

Credits

Added by Laws 1977, p. 824. Amended by Laws 1981, p. 590; Laws 1983, p. 305; Laws 1985, p. 2236; Laws 1987, p. 197; Laws 1991, p. 1070; Laws 1993, p. 782; Laws 1997, c. 207, § 16; Laws 2001, c. 152, § 28, eff. July 1, 2001; Laws 2003, c. 447, § 32, eff. July 1, 2003; Laws 2003, c. 508, § 52, eff. July 1, 2003; Laws 2003 (20th ss), c. 6, §§ 15, 16, eff. July 22, 2003; Laws 2005, c. 489, § 4, eff. July 1, 2005; Laws 2007, c. 514, § 13; Laws 2011, c. 187, § 10.

Notes of Decisions (6)

N. R. S. 630.301, NV ST 630.301
Current through the end of the 80th Regular Session (2019)

End of Document

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DISTRICT COURT
CLARK COUNTY, NEVADA

Divorce - Complaint **COURT MINUTES** February 21, 2020

D-17-560737-D Thomas A. Pickens, Plaintiff
vs.
Danka K. Michaels, Defendant.

February 21, 2020 8:00 AM Non-Jury Trial

HEARD BY: Steel, Dianne **COURTROOM:** Courtroom 04

COURT CLERK: Antoria Pickens

PARTIES:

Danka Michaels, Defendant, Counter Claimant, present	Jennifer Abrams, Attorney, present
Thomas Pickens, Plaintiff, Counter Defendant, present	John Jones, Attorney, present

JOURNAL ENTRIES

- NON-JURY TRIAL: DAY 2

The Court reviewed the case history and the pleadings on file.

Attorney Abrams stated the Defendant received a call prior to the hearing informing her that her mother passed away.

Court noted the Defendant stated she would like to proceed with the trial.

The Court and Counsel engaged in a discussion regarding Attorney Jones's housekeeping matter of the Defendant's, untimely notice, and request to call a witness by Skype.

Attorney Abrams stated she would be pursuing Attorney Fees, and she would not be pursuing the additional counterclaims filed with the Court.

Plaintiff and Defendant were SWORN and TESTIFIED.
Testimony resumed with the Plaintiff's direct witness Shannon Evans.

Court noted anything after bates number 1157 shall be labeled as 1157. (1, 2, 3, 4).

Witnesses and Exhibits presented. (see worksheets)

Shannon Evans's deposition was published in OPEN COURT.

Attorney Jones rests his case in chief.

Matter Trailed for lunch.
Matter Recalled.

Testimony resumed with Danka Michaels/Defendant.

Prior to the trial resuming, Attorney Abrams requested the matter be continued as she felt her client was not at her best.

Based on the Defendant's family emergency, the Court is inclined to continue the matter to a new date.

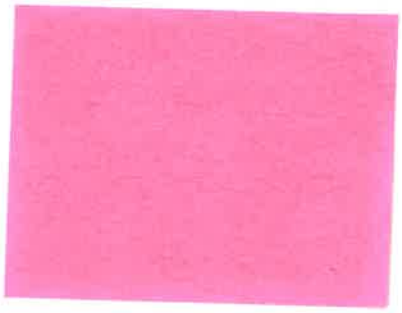
There being insufficient time to conclude, COURT ORDERED, Evidentiary Hearing shall be CONTINUED. The Honorable Steel shall coordinate a new date and time for the matter to be heard and notify the parties.

INTERIM CONDITIONS:

FUTURE HEARINGS:

Canceled: February 21, 2020 9:00 AM Non-Jury Trial
Reason: Canceled as the result of a hearing cancel, Hearing Canceled Reason:
Courtroom 04
Pickens, Antoria
Steel, Dianne

Canceled: February 26, 2020 3:00 PM Further Proceedings
Reason: Canceled as the result of a hearing cancel, Hearing Canceled Reason: Vacated - per Judge
Courtroom 04
Hughes, Rena G.
Skaggs, Tiffany



Subject: Re: P1 loan documents

From: ROBERT SEMONIAN (semon@prodigy.net)

To: dankashen@icloud.com;

Cc: jmichalecko@BLUEPOINTMEDICALGROUPLV.COM;

Date: Wednesday, May 10, 2017 4:47 PM

There were no changes, just an abusive loan monitoring process. They make you the loan but you have to continue to prove that you qualify
It's a lousy system

I still need the details of how Tom gave up his interest. I know, its sensitive, I'm sorry to intrude

Bob

From: danka michaels <dankashen@icloud.com>
To: ROBERT SEMONIAN <semon@prodigy.net>
Cc: Jakub Michalecko <jmichalecko@BLUEPOINTMEDICALGROUPLV.COM>
Sent: Wednesday, May 10, 2017 4:38 PM
Subject: Re: P1 loan documents

Oh, there was change to our loan rules? They didn't notify us about anything.

I am representing P1. Tom gave up his position. I will ask Jakub to forward the updated document from the atty's office.

Danka K. Michaels MD
BluePoint Medical Group
3320 N. Buffalo dr #106
LV NV 89129
702.869.6190

On May 10, 2017, at 3:02 PM, ROBERT SEMONIAN <semon@prodigy.net> wrote:

> Danka,
>
> Yes, I know, I getting it from them as well
>
> So, Patience One is going to be the problem entity so I want to complete it first.
>
> Is it possible for you to email me your agreement with Tom. I know he was a partner for part of the year, but I need to see how he gave up his interest and the date he transferred it to you
>
> By the way, the Bank knows they are being abusive with their requests. It came out of the changes to the Mortgage Loan Rules

MARKED CASE # PROPOSED

Nevada PRESCRIPTION MONITORING PROGRAM

For help using the application please contact:

775-687-5694

Report Prepared: 02/14/2020

Patient Report

Date Range: 01/01/2000 – 02/14/2020

thomas pickens

Linked Records

Name	DOB	ID	Gender	Address
THOMAS PICKENS	10/05/1956	2	male	9517 QUEEN CHARLOTTE DR LAS VEGAS NV 89145
THOMAS A PICKENS	10/05/1956	1	male	9517 QUEEN CHARLOTTE DR LAS VEGAS NV 89145

Report Criteria

First Name: thomas, **Last Name:** pickens, **DOB:** 10/05/1956

Summary

Summary		Opioids* (excluding buprenorphine)		Buprenorphine*	
Total Prescriptions	65	Current Qty	0.0	Current Qty	0.0
Total Private Pay	37	Current MME/day	0.0	Curre	
Total Prescribers	6	30 Day Avg MME/day	0.0	30 Da	
Total Pharmacies	4				

MARKED FO
CASE # D
PROPOSED

PLAINTIFF'S EXHIBIT 155 D510357 2-27-20
PENGAD 800-631-6989

Prescriptions

Filled	ID	Written	Drug	ICD-10	QTY	Days	Prescriber	Rx #	Pharm
08/09/2019	1	08/09/2019	HYDROCODONE-ACETAMIN 5-325 MG	M1990	12.0	3	AD GOM	01834190	NEVAD (
04/11/2019	1	01/21/2019	ZOLPIDEM TARTRATE 5 MG TABLET		30.0	30	GA DAU	01743834	NEVAD (

Filled	ID	Written	Drug	ICD-10	QTY	Days	Prescriber	Rx #	Pharmacy*	Refills	Daily Dose	Pymt Type	PMP
02/25/2019	1	01/21/2019	ZOLPIDEM TARTRATE 5 MG TABLET		30.0	30	GA DAU	01743834	NEVAD (7984)	1/2		Comm Ins	NV
01/22/2019	1	01/21/2019	ZOLPIDEM TARTRATE 5 MG TABLET		30.0	30	GA DAU	01743834	NEVAD (7984)	0/2		Comm Ins	NV
12/07/2018	1	12/07/2018	ZOLPIDEM TARTRATE 5 MG TABLET		30.0	30	GA DAU	01724235	NEVAD (7984)	0/2		Comm Ins	NV
01/26/2017	2	01/26/2017	OXYCODONE-ACETAMINOPHEN 10-325		120.0	30	DA MIC	1374878	COSTC (8926)	0/0	60.0 MME	Private Pay	NV
01/26/2017	2	01/26/2017	ALPRAZOLAM 1 MG TABLET		180.0	90	DA MIC	1374916	COSTC (8926)	0/0		Private Pay	NV
01/26/2017	2	01/26/2017	ZOLPIDEM TARTRATE 10 MG TABLET		90.0	90	DA MIC	1374917	COSTC (8926)	0/0		Private Pay	NV
08/30/2016	2	08/30/2016	OXYCODONE-ACETAMINOPHEN 10-325		120.0	30	RO CAR	1344910	COSTC (8926)	0/0	60.0 MME	Private Pay	NV
08/30/2016	2	08/30/2016	ALPRAZOLAM 0.5 MG TABLET		360.0	60	RO CAR	1344909	COSTC (8926)	0/0		Private Pay	NV
08/30/2016	2	08/30/2016	ZOLPIDEM TARTRATE 10 MG TABLET		90.0	90	RO CAR	1344911	COSTC (8926)	0/0		Private Pay	NV
06/21/2016	2	06/21/2016	TRAMADOL HCL 50 MG TABLET		240.0	30	RO CAR	1332716	COSTC (8926)	0/0	40.0 MME	Private Pay	NV
06/03/2016	2	06/03/2016	OXYCODONE-ACETAMINOPHEN 10-325		120.0	30	RO CAR	1329498	COSTC (8926)	0/0	60.0 MME	Private Pay	NV
06/03/2016	2	06/03/2016	ALPRAZOLAM 0.5 MG TABLET		360.0	60	RO CAR	1329513	COSTC (8926)	0/0		Private Pay	NV
06/03/2016	2	06/03/2016	ZOLPIDEM TARTRATE 10 MG TABLET		90.0	90	RO CAR	1329499	COSTC (8926)	0/0		Private Pay	NV
05/17/2016	2	05/14/2016	BUPRENORPHINE 2 MG TABLET SL		60.0	30	DA MIC	1326552	COSTC (8926)	0/3	4.0 mg	Private Pay	NV
03/07/2016	2	03/04/2016	ALPRAZOLAM 1 MG TABLET		180.0	60	RO CAR	1312760	COSTC (8926)	0/0		Private Pay	NV
03/07/2016	2	03/04/2016	ZOLPIDEM TARTRATE 10 MG TABLET		90.0	90	RO CAR	1312759	COSTC (8926)	0/0		Private Pay	NV
03/04/2016	2	03/04/2016	TRAMADOL HCL 50 MG TABLET		240.0	30	RO CAR	1312553	COSTC (8926)	0/0	40.0 MME	Private Pay	NV
03/04/2016	2	03/04/2016	OXYCODONE-ACETAMINOPHEN 10-325		120.0	30	RO CAR	1312554	COSTC (8926)	0/0	60.0 MME	Private Pay	NV
12/30/2015	2	12/29/2015	OXYCODONE-ACETAMINOPHEN 10-325		120.0	30	RO CAR	1299302	COSTC (8926)	0/0	60.0 MME	Private Pay	NV
12/29/2015	2	12/29/2015	ALPRAZOLAM 0.5 MG TABLET		360.0	60	RO CAR	1299270	COSTC (8926)	0/0		Private Pay	NV
12/24/2015	2	12/24/2015	ZOLPIDEM TARTRATE 10 MG TABLET		90.0	90	DA MIC	1298628	COSTC (8926)	0/0		Private Pay	NV
10/27/2015	2	10/27/2015	TRAMADOL HCL 50 MG TABLET		240.0	30	DA MIC	1286745	COSTC (8926)	0/0	40.0 MME	Private Pay	NV
09/21/2015	2	09/21/2015	ALPRAZOLAM 0.5 MG TABLET		360.0	60	DA MIC	1279705	COSTC (8926)	0/0		Private Pay	NV
09/21/2015	2	09/19/2015	ZOLPIDEM TARTRATE 10 MG TABLET		90.0	90	RO CAR	1279517	COSTC (8926)	0/0		Private Pay	NV
08/15/2015	2	08/15/2015	OXYCODONE-ACETAMINOPHEN 10-325		120.0	30	RO CAR	1273348	COSTC (8926)	0/0	60.0 MME	Private Pay	NV
07/15/2015	2	07/15/2015	TRAMADOL HCL 50 MG TABLET		240.0	30	RO CAR	1268128	COSTC (8926)	0/0	40.0 MME	Private Pay	NV
07/15/2015	2	07/15/2015	ALPRAZOLAM 0.5 MG TABLET		360.0	60	RO CAR	1268129	COSTC (8926)	0/0		Private Pay	NV

Filled	ID	Written	Drug	ICD-10	QTY	Days	Prescriber	Rx #	Pharmacy*	Refills	Daily Dose	Pymt Type	PMP
07/15/2015	2	07/15/2015	ZOLPIDEM TARTRATE 10 MG TABLET		90.0	90	RO CAR	1268130	COSTC (8926)	0/0		Private Pay	NV
05/27/2015	2	05/21/2015	OXYCODONE-ACETAMINOPHEN 10-325		120.0	30	DA MIC	1259527	COSTC (8926)	0/0	60.0 MME	Private Pay	NV
04/18/2015	2	04/15/2015	ZOLPIDEM TARTRATE 10 MG TABLET		90.0	90	DA MIC	1252703	COSTC (8926)	0/0		Private Pay	NV
04/15/2015	2	04/15/2015	TRAMADOL HCL 50 MG TABLET		240.0	30	DA MIC	1252169	COSTC (8926)	0/0	40.0 MME	Private Pay	NV
03/21/2015	2	03/21/2015	ZOLPIDEM TARTRATE 10 MG TABLET		30.0	30	RO CAR	4438682	VONS (4083)	0/3		Comm Ins	NV
02/07/2015	2	02/06/2015	OXYCODONE-ACETAMINOPHEN 10-325		120.0	30	RO CAR	2214081	VONS (4083)	0/0	60.0 MME	Comm Ins	NV
01/02/2015	2	01/02/2015	ALPRAZOLAM 0.5 MG TABLET		360.0	60	DA MIC	1232577	COSTC (8926)	0/3		Private Pay	NV
11/20/2014	2	08/08/2014	ZOLPIDEM TARTRATE 10 MG TABLET		90.0	90	DA MIC	1206104	COSTC (8926)	1/3		Private Pay	NV
11/08/2014	2	11/07/2014	TRAMADOL HCL 50 MG TABLET		240.0	30	RO CAR	1222913	COSTC (8926)	0/0	40.0 MME	Private Pay	NV
09/19/2014	2	09/19/2014	OXYCODONE-ACETAMINOPHEN 10-325		120.0	30	DA MIC	1212991	COSTC (8926)	0/0	60.0 MME	Private Pay	NV
08/09/2014	2	08/08/2014	ALPRAZOLAM 0.5 MG TABLET		360.0	60	DA MIC	1206103	COSTC (8926)	0/0		Private Pay	NV
08/09/2014	2	08/08/2014	ZOLPIDEM TARTRATE 10 MG TABLET		90.0	90	DA MIC	1206104	COSTC (8926)	0/3		Private Pay	NV
06/20/2014	2	03/18/2014	ZOLPIDEM TARTRATE 10 MG TABLET		90.0	90	RO CAR	1181605	COSTC (8926)	1/3		Private Pay	NV
05/05/2014	2	05/05/2014	ALPRAZOLAM 0.25 MG TABLET		180.0	30	RO CAR	1189966	COSTC (8926)	0/3		Comm Ins	NV
03/20/2014	2	03/18/2014	OXYCODONE-ACETAMINOPHEN 10-325		120.0	30	RO CAR	1181860	COSTC (8926)	0/0	60.0 MME	Comm Ins	NV
03/18/2014	2	03/18/2014	ZOLPIDEM TARTRATE 10 MG TABLET		90.0	90	RO CAR	1181605	COSTC (8926)	0/3		Private Pay	NV
06/12/2013	2	03/19/2013	ALPRAZOLAM 0.25 MG TABLET		180	30	Da Mic	1114102	COSTC (8926)	1/3		Comm Ins	NV
05/06/2013	2	05/02/2013	OXYCODONE-ACETAMINOPHEN 10-325		120	30	Ro Car	1123383	COSTC (8926)	0/0	60.0 MME	Comm Ins	NV
03/19/2013	2	03/19/2013	ALPRAZOLAM 0.25 MG TABLET		180	30	Da Mic	1114102	COSTC (8926)	0/3		Comm Ins	NV
01/04/2013	2	08/28/2012	ALPRAZOLAM 0.25 MG TABLET		180	30	Da Mic	1076793	COSTC (8926)	2/3		Comm Ins	NV
12/07/2012	2	12/07/2012	HYDROCODON-ACETAMINOPH 7.5-500		20	5	Wi Mar	4432682	VONS (4083)	0/0	30.0 MME	Comm Ins	NV
11/12/2012	2	08/28/2012	ALPRAZOLAM 0.25 MG TABLET		180	30	Da Mic	1076793	COSTC (8926)	1/3		Comm Ins	NV
11/05/2012	2	10/05/2012	ZOLPIDEM TARTRATE 10 MG TABLET		30	30	Da Mic	4432271	VONS (4083)	0/0		Comm Ins	NV
10/10/2012	2	10/10/2012	ZOLPIDEM TARTRATE 10 MG TABLET		90	90	Da Mic	1084352	COSTC (8926)	0/0		Private Pay	NV
09/23/2012	2	03/29/2012	ZOLPIDEM TARTRATE 10 MG TABLET		30	30	Da Mic	4431014	VONS (4083)	3/3		Comm Ins	NV
08/28/2012	2	08/28/2012	ALPRAZOLAM 0.25 MG TABLET		180	30	Da Mic	1076793	COSTC (8926)	0/3		Comm Ins	NV
08/10/2012	2	08/07/2012	OXYCODONE-ACETAMINOPHEN 10-325		120	30	Ro Car	1073573	COSTC (8926)	0/0	60.0 MME	Comm Ins	NV

Filled	ID	Written	Drug	ICD-10	QTY	Days	Prescriber	Rx #	Pharmacy*	Refills	Daily Dose	Pymt Type	PMP
08/09/2012	2	03/29/2012	ZOLPIDEM TARTRATE 10 MG TABLET		30	30	Da Mic	4431014	VONS (4083)	2/3		Comm Ins	NV
07/07/2012	2	03/29/2012	ZOLPIDEM TARTRATE 10 MG TABLET		30	30	Da Mic	4431014	VONS (4083)	1/3		Comm Ins	NV
03/29/2012	2	03/29/2012	ZOLPIDEM TARTRATE 10 MG TABLET		30	30	Da Mic	4431014	VONS (4083)	0/3		Comm Ins	NV
01/03/2012	2	07/21/2011	ALPRAZOLAM 0.25 MG TABLET		180	30	Da Mic	4519423	STORE (3423)	2/3		Comm Ins	NV
11/26/2011	2	11/24/2011	ENDOCET 10-650 MG TABLET		90	30	Da Mic	2209177	VONS (4083)	0/0	45.0 MME	Comm Ins	NV
11/26/2011	2	11/24/2011	ZOLPIDEM TARTRATE 10 MG TABLET		30	30	Da Mic	4429106	VONS (4083)	0/0		Comm Ins	NV
09/15/2011	2	09/15/2011	ZALEPLON 10 MG CAPSULE		30	30	Da Mic	4520380	STORE (3423)	0/1		Comm Ins	NV
09/13/2011	2	07/21/2011	ALPRAZOLAM 0.25 MG TABLET		180	30	Da Mic	4519423	STORE (3423)	1/3		Comm Ins	NV
07/21/2011	2	07/21/2011	ALPRAZOLAM 0.25 MG TABLET		180	30	Da Mic	4519423	STORE (3423)	0/3		Comm Ins	NV

*Pharmacy is created using a combination of pharmacy name and the last four digits of the pharmacy license number.

**Per CDC guidance, the MME conversion factors prescribed or provided as part of medication-assisted treatment for opioid use disorder should not be used to benchmark against dosage thresholds meant for opioids prescribed for pain. Buprenorphine products have no agreed upon morphine equivalency, and as partial opioid agonists, are not expected to be associated with overdose risk in the same dose-dependent manner as doses for full agonist opioids. MME = morphine milligram equivalents. mg = dose in milligrams.*

Prescribers

Name	Address	City	State	Zip	Phone
ROBERTO C CARILLO	3320 N BUFFALO DR	LAS VEGAS	NV	89129	(702) 869-6190
ROBERTO C CARILLO	3320 N BUFFALO DR	LAS VEGAS	NV	89129	(702) 869-6190
GAUTAM DAULAT	3416 N BUFFALO DR	LAS VEGAS	NV	89129-7424	(702) 565-4917
ADRIAN Q GOMEZ	7391 W CHARLESTON BLVD	LAS VEGAS	NV	89117-1577	(702) 962-7800
William R Maranon	1040 S. RAINBOW BLVD	LAS VEGAS	NV	89145	
DANKA K MICHAELS	3320 N BUFFALO DR	LAS VEGAS	NV	89129	(702) 869-6190

Dispensers

Pharmacy	Address	City	State	Zip	Phone
VONS PHARMACY #1688 (4083)	820 S RAMPART BLVD	LAS VEGAS	NV	89145	(702) 946-5333
STORE01838 (3423)	702 SW 8TH STREET	BENTONVILLE	AR	72716-0445	(702) 656-7331

Pharmacy	Address	City	State	Zip	Phone
NEVADA CVS PHARMACY, L.L.C. (7984)	8320 W CHEYENNE AVE	LAS VEGAS	NV	89129-2147	(702) 658-1229
COSTCO WHOLESALE CORPORATION (8926)	801 S PAVILION CENTER DR	LAS VEGAS	NV	89144	(702) 352-2055

Disclaimer:

Report contents are based on data entered by dispensers and their staff, and may contain errors. The Board of Pharmacy recommends independent verification with dispensers when prudent or necessary. Willful disclosure of prescription information may be subject to disciplinary action, civil penalties or criminal action.

Todd B. Kilde

Request to appeal denial of Unemployment Benefits

Employment Security Division Adjudication Center
500 East Third Street Carson City, NV 89713-0035
Tel (775) 684-0302 Fax (775) 684-0338 Tel (702) 486-7999 Fax (702) 486-7987

RE: BLUE POINT DEVELOPMENT INC
Claimant ID: 5140562
Issue ID: 3404992
Week End Date: 10/29/2016
Date Mailed: 11/10/2016
Last Day to Appeal:11/21/2016
Decision Date:11/09/2016

Employer: Bluepoint Development
SS#: 564-10-0592

To Whom it May Concern,

There were a multitude of reasons I probably should have quit way before I did. Unfortunately when the inappropriate moral behavior of Tom Pickens began to effect the work place it was more than I was willing to accept. When I accepted the position at Bluepoint it was based on the sales pitch given to me by Tom Pickens (Owner of Bluepoint Development). I was told "we" could make a lot of money with limited travel. My intentions were to eventually purchase a home and move my wife to Las Vegas. I even put a down payment on a house and only backed out because the appraisal came in low. Thank god, because of what was to follow. I stopped looking or thinking about moving my wife out when the instability of company and company decisions became unsteady. I began to travel more than ever. Spending weeks and months at a time away from Las Vegas. Business travel was never scheduled ahead of time so I was unable to schedule my own flights to go home and see my wife ahead of time .

In 3 ½ years I never received a raise, yet he has his mistress and step son on payroll,I neither of which are doing anything for the company. He has spent hundreds of thousands of Bluepoint Developments revenues on his wife's business, personal use and mistress, yet unwilling to give raises or yearly bonuses as promised. Tom went from being transparent to secretive and deceitful (one could actually say paranoid).

Toms erratic behavior began a couple years ago when the company received a $1,000,000 bonus. This is when things changed for the worse. Toms ego became inflated and he became very narcissistic. He would only stay at 5-star hotels, rent Range Rovers or hire a driver. Yet find it unacceptable for an employee to turn in receipts for food when traveling for business.

Tom stopped coming to Las Vegas over a year ago, stating that he had to be at the site. Only to find out it was because he's been having an affair for at least a year now. All you have to do is look at the project he's running and its obvious he's been focused on his affair not the project. Needless to say, it's well behind schedule and he hasn't implemented any tools for it to succeed.

Everybody in the office has thought he may be having an affair or mental break down for months because of his behavior and non- existence. He has probably spent 2-weeks in the office over the last year. He would rarely respond to emails or text and rarely would return phone calls. Originally it felt odd when he was gone. After a while it felt odder when he would be in town.

His personal assistant Sarah Nicora was the first to quit because she couldn't put up with his lies and being put in the position to have to lie for him anymore. The final straw for me was when I was asked at the last minute to go to Marco Island. When I say last minute I'm talking about being told at 9:30 in the morning and on a flight by 1;00 in the afternoon. All fine and dandy because I was used to the last-minute plans. This last minute trip was because his mistress ended up calling his wife and letting her know she was pregnant so he had to make a mad dash home (I found this out later).

The final straw came when he came back to Marco and I was there with him. I believe it was the 8th of October but I could be off a day or two. He left the job early, when I arrived at the company condo his mistress was there folding my clothes that I had left in the dryer. I was shocked, embarrassed and found it unbelievable and extremely immoral. He must have thought it was ok for her to move back in since the cat was out of the bag and everybody knew about his affair now. I went into my bedroom and never came out until they left for dinner. I was completely in shock that he felt it was acceptable to put me in that awkward of a position. When I came out and saw she had moved in her cat box, dishes and clothes it was more than I was willing to put up with. Tom had stopped talking to me months ago and I didn't feel comfortable enough to talk to him about it. I was done with his lies and deceitful ways. Bluepoint Development doesn't have an HR department or anyone with a title. In fact there's really only two people in the office. That would be Dara Lesmeister and Art Zargaryan. I called Dara Lesmeister and told her to book me a flight back to Las Vegas and that I could not put up with his behavior anymore and had to quit. I also called Art Zargaryan and told him the same thing.

So, for Tom to say that he didn't' know why I left is an outright lie. One of many that he has become very comfortable telling over the last couple of years. I never received a phone call or email from Tom asking me anything much less why I left. All you need I don't see how an employer can incorporate this behavior into the workplace and find it acceptable. Therefore I am appealing your decision and request that you reconsider. Thank you!
to do is call Art, Dara or Sarah and they will confirm what I've stated.

Below is a list of contacts that can confirm the unethical and unacceptable behavior Bluepoint Development employees are subject to.

Contacts –

Sarah Nicora - 650-722-9244 Bluepoint Development
Art Zargaryan – 818-331-4677 Bluepoint Development
Dara Lesmeister -702-622-0899 Bluepoint Development
Dr. Danka Michaels –702-604-0381 Tom Pickens Wife (separated)

For an employer to incorporate this behavior into the workplace and find it acceptable is unacceptable on moral and ethical grounds. Therefore I am appealing your decision and request that you reconsider. Thank you!

Signature:_____
Todd Kilde

Electronically Filed
3/20/2020 1:04 PM
Steven D. Grierson
CLERK OF THE COURT

DISTRICT COURT

CLARK COUNTY, NEVADA

****

THOMAS A. PICKENS, PLAINTIFF
VS.
DANKA K. MICHAELS,
DEFENDANT.

CASE NO: D-17-560737-D

DEPARTMENT J

NOTICE OF HEARING

TO: John D. Jones, Esq.

Jennifer V. Abrams, Esq.

Please be advised that the above-entitled matter has been scheduled for **Non-Jury Trial (Day 3)** to be heard by the Honorable Dianne Steel at the Family Courts and Services Center, 601 N. Pecos Rd., Las Vegas, Nevada, on **June 3, 2020** at the hour of **9:00 AM** in **Department J.**

YOUR PRESENCE IS NECESSARY.

HONORABLE RENA G. HUGHES

By: /s/ Tristana Cox
Tristana Cox
Judicial Executive Assistant

Rena G. Hughes
District Judge
Department J
LAS VEGAS, NV 89155

Docket 83491 Document 2022-05932

CERTIFICATE OF MAILING

I hereby certify that on the above file stamp date:

☒ I have e-served pursuant to NEFCR 9 and/or placed a copy of the foregoing NOTICE in the appropriate attorney folder located in the Clerk of the Court's Office of:

Jennifer Abrams, Esq.

John Jones, Esq.

/s/Tristana Cox
Tristana Cox
Judicial Executive Assistant
Department J

DISTRICT COURT

CLARK COUNTY, NEVADA

****

THOMAS A. PICKENS, PLAINTIFF
VS.
DANKA K. MICHAELS,
DEFENDANT.

CASE NO: D-17-560737-D

DEPARTMENT J

NOTICE OF HEARING

TO: John D. Jones; Michele Touby Lobello; Paul A. Lemcke; Thomas A. Pickens; Jennifer V. Abrams

Please be advised that the above-entitled matter has been scheduled for **Non-Jury Trial** to be heard by the Honorable Rena G. Hughes at the Family Courts and Services Center, 601 N. Pecos Rd., Las Vegas, Nevada, on the **3rd day of June, 2020** at the hour of **9:00 AM** in **Department J.**

YOUR PRESENCE IS NECESSARY.

HONORABLE RENA G. HUGHES

By: _____
Tristana Cox
Judicial Executive Assistant

CERTIFICATE OF MAILING

I hereby certify that on the above file stamp date:

☐ I placed a copy of the foregoing Notice of Hearing in the appropriate attorney folder located in the Clerk of the Court's Office or

☐ mailed, via first-class mail, postage fully prepaid, the foregoing Notice of Hearing to:

Jennifer V. Abrams
6252 South Rainbow Blvd., Suite 100
Las Vegas, NV 89118

John D. Jones
10777 W Twain AVE STE 300
Las Vegas, NV 89135

Michele Touby Lobello
10777 W Twain AVE STE 300
Las Vegas, NV 89135

Tristana Cox
Judicial Executive Assistant
Department J

DISTRICT COURT

CLARK COUNTY, NEVADA

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THOMAS A. PICKENS, PLAINTIFF
VS.
DANKA K. MICHAELS,
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By: _____
Tristana Cox
Judicial Executive Assistant

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Tristana Cox
Judicial Executive Assistant
Department J

DISTRICT COURT

CLARK COUNTY, NEVADA

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THOMAS A. PICKENS, PLAINTIFF
VS.
DANKA K. MICHAELS,
DEFENDANT.

CASE NO: D-17-560737-D

DEPARTMENT J

NOTICE OF HEARING

TO: John D. Jones; Michele Touby Lobello; Paul A. Lemcke; Thomas A. Pickens; Jennifer V. Abrams

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YOUR PRESENCE IS NECESSARY.

HONORABLE RENA G. HUGHES

By: _____
Tristana Cox
Judicial Executive Assistant

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Las Vegas, NV 89118

John D. Jones
10777 W Twain AVE STE 300
Las Vegas, NV 89135

Michele Touby Lobello
10777 W Twain AVE STE 300
Las Vegas, NV 89135

Tristana Cox
Judicial Executive Assistant
Department J

Electronically Filed
6/24/2020 11:34 AM
Steven D. Grierson
CLERK OF THE COURT

SAO

Jennifer V. Abrams, Esq.
Nevada State Bar Number: 7575
THE ABRAMS & MAYO LAW FIRM
6252 South Rainbow Blvd., Suite 100
Las Vegas, Nevada 89118
Tel: (702) 222-4021
Fax: (702) 248-9750
Email: jvagroup@theabramslawfirm.com
Attorney for Defendant

Eighth Judicial District Court
Family Division
Clark County, Nevada

THOMAS A. PICKENS, individually, and as trustee of the LV Blue Trust, Plaintiff, vs. DANKA K. MICHAELS, individually, and as trustee of the Mich-Mich Trust, Defendant.	Case No.: D-17-560737-D Department: J

STIPULATION AND ORDER TO CONTINUE DAY THREE OF TRIAL

COME NOW the parties, Plaintiff, THOMAS A. PICKENS (hereinafter referred to as "Tom"), by and through his attorney of record, Michele T. LoBello, Esq., of Black & LoBello, and Defendant, DANKA K. MICHAELS (hereinafter referred to as "Danka"), by and through her

attorney of record, Jennifer V. Abrams, Esq., of The Abrams & Mayo Law Firm, and hereby stipulate to the following:

WHEREAS day three (3) of trial is set for June 3, 2020, at 9:00 a.m.;

WHEREAS the parties desire to participate in mediation before the third day of trial;

WHEREAS due to the COVID-19 pandemic and social distancing precautions, mediation was continued from May 15, 2020 to June 25, 2020;

THEREFORE,

IT IS HEREBY STIPULATED AND AGREED that the third day of trial be continued until the Court's first available date after July 6, 2020 to allow the parties time to mediate, and if mediation is successful prepare the paperwork necessary to finalize this case, or if mediation is unsuccessful allow the parties time to prepare for the third day of trial.

THE ABRAMS & MAYO LAW FIRM

/s/ Jennifer V. Abrams, Esq.
Jennifer V. Abrams, Esq.
Nevada State Bar Number: 7575
6252 S. Rainbow Blvd., Suite 100
Las Vegas, Nevada 89118
Attorney for Defendant

BLACK & LOBELLO

Michele LoBello
Michele T. LoBello, Esq.
Nevada State Bar Number: 5527
10777 W. Twain Ave., Suite 300
Las Vegas, Nevada 89135
Attorney for Plaintiff

ORDER

Based upon the stipulation of the parties,

IT IS HEREBY ORDERED that the third day of trial shall be continued to the 20th day of July, 2020, at 9am.

Dated this 11th day of ~~May~~ June, 2020.

_____
DISTRICT COURT JUDGE
for Judge Steel

Respectfully Submitted:

THE ABRAMS & MAYO LAW FIRM

/s/ *Jennifer V. Abrams, Esq.*
Jennifer V. Abrams, Esq.
Nevada State Bar Number: 7575
6252 South Rainbow Blvd., Suite 100
Las Vegas, Nevada 89118
Attorney for Defendant