

### Strategies for Enhancing Quality, Utility, & Clarity in Clinical Pharmacology-Related Labeling A Regulatory Perspective

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  - The views expressed in this presentation are personal opinion and do not reflect the official policy of the FDA.
- Disclosures:
  - The presenter has no disclosures related to the content of this presentation.



## **Learning Objectives**

- I. Describe key US Prescription Drug\* Labeling (PDL) Regulations
- 2. Identify where clinical pharmacology (CP) related information is found in labeling
- 3. Assess health care provider (HCP) perception of CP related labeling
- 4. Describe strategies to enhance clarity and readability in CP labeling
  - a. CLINICAL PHARMACOLOGY (Section 12)
  - b. DRUG INTERACTIONS (Section 7)
  - c. DOSAGE AND ADMINISTRATION (Section 2)



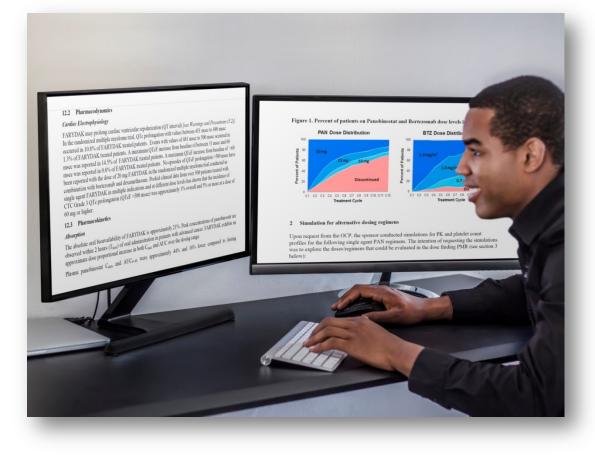
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Prescription Drug Labeling (PDL) is One of the Greatest Outward Expressions of the Work We Do



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How Developers Often See Approved Prescription Drug Labeling



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# How Healthcare **Providers See Approved Prescription Drug** Labeling



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# Physician's Perception of CP Information in the PDL

#### What's Wrong?

- Confusing structure
- Too much information
- Wrong information
- No conveyance of risk
- No real guidance

#### The Ideal Presentation

- Easy to access and navigate
- Minimizes pharmacology jargon
- Clinically intuitive structure
- Imparts sense of severity or risk
- Provides risk management instructions
- Omits unnecessary information
- Up to date



## **Key PDL Regulations**

- PDL must contain a summary of the **essential scientific information** needed for the safe and effective use of the drug.
  - PDL is written for the health care practitioner (HCP) audience, because prescription drugs require "professional supervision of a practitioner licensed by law to administer such drug."
- PDL must be **informative and accurate** and neither promotional in tone nor false or misleading in any particular.
- PDL **must be updated** when new information becomes available that causes the labeling to become inaccurate, false, or misleading.
- PDL must be based whenever possible on data derived from human experience.
  - Conclusions based on animal data but necessary for safe and effective use of the drug in humans **must be identified** as such and included with human data in the appropriate section of the labeling.



### **PDL Information as Text**

- Should not be so detailed and lengthy the reader skims or dismisses it.
  - Include only essential information that informs prescribing decisions or is necessary for the safe and effective use of the drug.
  - Actionable information should be clear and concise.
    - Avoid vague statements such as "monitor closely" or "use with caution."
  - Use active voice.
- Use font attributes, headings, bulleted lists, and shorter paragraphs to increase white space and readability wherever possible.
  - Formatting suggestions are outlined in guidances to assure consistency.



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A sentence is a structurally independent grammatical unit of one **or** more words in speech **often** preceded **and** followed by pauses **and** in writing begun with a capital letter **and** ended with a period **or** other end punctuation.

F-K 16.0 FREI 00.0 (Very, Very Difficult to Read)

# VS.

A sentence:

- Is a unit of grammar with one or more words.
- It can be preceded by pauses.
- It can be followed by pauses.
- It starts with a capital letter.
- It ends with a period.
- It can end in other punctuation.

#### F-K 3.2 FREI 83.0 (Very Easy to Read)



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### Where is CP Information in PDL?



• Limited Context

Highlights

D&A: Dosage and Administration BW: Boxed Warning CI: Contraindications W&P:Warnings and Precautions AR: Adverse Reactions PCI: Patient Counseling Information

BW, CI, W&P, AR, PCI, and others

**Drug Interactions** 

**Specific Populations** 

- Less Actionable
- Detailed
- Additional Context

**Clinical Pharmacology** 



### General Principles for CP-Related Information in PDL

- Present essential information only and in a way that is understandable to HCPs who may not have specific CP expertise.
  - Use a format that best accommodates the breadth and complexity of the information and ensures clarity and understanding (i.e., Text, Tables, Figures).
    - Avoid repetition of detailed information in multiple sections.
  - Report PK and PD values as mean (arithmetic or geometric) or median with a measure of variability (i.e., standard deviation and/or minimum and maximum values).
  - Avoid subjective wording and implying unapproved uses or dosages.



### General Principles for CP-Related Information in PDL

- Maintain formatting consistency throughout the entire PDL.
  - Sections/subsections/headings/subheadings and cross-referencing
  - Units and abbreviations (e.g.,  $T_{MAX}$ ,  $C_{MAX}$ ,  $C_{MIN}$ , AUC, AUC<sub>0-INF</sub>, AUC<sub>0-TAU</sub>, AUC<sub>0-12hr</sub>,  $t_{1/2}$ , Vd, CL)
  - Population definitions (e.g., patients vs. subjects)
  - Dosages outside the approved recommended dosage range (e.g., exposureresponse, proportionality, absorption PK) should generally be expressed in terms of the highest and lowest recommended dosage.



### Disclaimer

 The following tables and figures presented today are meant to be thought provoking and represent examples of possible formats of various clinical pharmacology- related information commonly found in labeling.

 These examples should not be considered templates, limit other possible formats, or constrain the use of other information fields that may be required for a particular drug.



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# **CLINICAL PHARMACOLOGY (Section 12)**

#### **12.3 Pharmacokinetics**

#### Table x. Pharmacokinetic Parameters of Drugoxide and Its Metabolites

General Information <sup>a,b</sup>							
			Cmax		AUC		CV
Drugoxide Exposure	Single D	ose	3.5 μg/mL (1.5 to 5.3)		80.4 μg*h/mL (48.9 to 125.7)		36% to 45%
	Steady-State <sup>c</sup>		4.9 μg/mL (2.1 to 9.9)		68.3 μg*h/mL (26.1 to 120.9)		5070 10 4570
Dose Proportionality <sup>c</sup>	The steady-state AUC of drugoxide increases less than dose proportionally at dosages greater than 50 mg (0.5 times the approved recommended dosage).						
Absorption							
Bioavailability [tablet] <sup>d</sup>	69% to 83%	compa	red to oral solution	m			
Tmax [tablet] Median (range)	4 hours (2-23 hours)						
Enterohepatic Recycling (EHR)	Drugoxide undergoes EHR. Multiple plasma concentration peaks were observed across the 24-hour dosing interval.						
Effect of Food <sup>e</sup> [Fed/fasted]	Meal	Drugoxide AUC			M-2 AUC		M-5 AUC
(25 <sup>th</sup> to 75 <sup>th</sup> percentile) [see Dosage and Administration	Low-fat <sup>f,g</sup>	Increased (Incr.) 40% (Incr. 22% to 68%)		(	Incr. 38% (Incr. 15% to 75%)		Incr. 25% (Incr. 1% to 69%)
(2.1), Clinical Studies (14)]	High-fat <sup>h</sup>		Incr. 53% . 30% to 81%)		Decreased (Decr.) 22% (Decr. 40% to Incr. 20%)		Decr. 51% (Decr. 72% to 27%)
Distribution							
Plasma Protein Binding Drugoxide and metabolites greater than 99%							
Elimination							
	Drugoxide				M-3		M-5
Elimination half-life <sup>c</sup>	30 hours				23 hours		56 hours
	(14 to 58 hours)		urs)	(14 to 32 hours)			(32 to 70 hours)
Metabolism	0.11.4	CTIDA					
Primary metabolic pathways	Oxidation: CYP3A4 Conjugation: UGT1A1						
Active Metabolites	M-3 (N-oxide) and M-5 (N-oxide and N-desmethyl) Both have similar in vitro pharmacological activity and steady-state concentrations as drugoxide						
Excretion <sup>1</sup>							
Primary excretion pathways (% dose (range))						24% as metabolites]	

Abbreviations: Cmax= maximum concentration; AUC= area under the time-concentration curve; CV=coefficient of variation; Tmax= Time to maximum concentration

a = The pharmacokinetics (PK) of drugoxide and its active metabolites were characterized in patients following a single Drug X dose of 100 mg after a light breakfast (e.g., a bowl of cereal with full fat milk or 2 slices of bread with cheese) unless otherwise specified.

b=Pharmacokinetic parameters are presented as geometric mean (range) unless otherwise specified.

c= Following repeat administration of 100 mg Drug X after a light breakfast on a once daily for 21 days on and 7 days off regimen

d= Following an investigational oral solution (20 mg/mL) formulation, 80 mg (4 - 20 mg tablets) or 100 mg tablet after fasting at least 8 hours

e= Following a single Drug X dose of 100 mg in healthy volunteers after a specified diet

f= 319 calories and 8.2 grams fat

g=Drug X was administered with a low-fat meal in Studies 1 and 2

h=945 calories and 54.6 grams fat

i= Arithmetic mean; following a single 120 mg dose of an investigational radiolabeled oral solution of drugoxide in healthy fasted volunteers



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# ADE(ME) Information as a Table



	Component Drug A	Component Drug B	Component Drug C	Component Drug D
General Information <sup>a</sup>				
C <sub>max</sub> (microgram per mL)	31.5 ±10.6	22.5 ±6.4	31.5 ±6.5	2.4 ±1.2
AUC <sub>tau</sub> (microgram•hour per mL)	342 ±118.7	142.5 ±48.3	175.5 ±35.7	3.2 ±1.8
C <sub>trough</sub> (microgram per mL)	5.4 ±2.7	0.3 ± 0.13	1.5 ±0.6	Not Available
Absorption				
T <sub>max</sub> (h) <sup>b</sup>	3 (1 to 4.5)	2 (1 to 4)	2.4 (1 to 3.5)	1.1 (0.6 to 2)
Effect of light meal (relative to fasting): AUC Ratio <sup>c</sup>	1.42 (1.2, 1.6)	1.13 (0.93, 1.25)	0.87 (0.8, 1.00)	1.20 (1.1 1.35)
Effect of high fat meal (relative to fasting): AUC Ratio <sup>c</sup>	1.9 (1.75, 2.2)	0.87 (0.71, 0.98)	0.91 (0.87, 1.00)	1.25 (1.12, 1.33)
Distribution				
% Bound to human plasma proteins	~97	~99	<8	~75
Blood-to-plasma ratio	0.8	0.7	1	0.55
Elimination				
$t_{1/2} (h)^{d}$	14 ±4.8	4.3 ±1.4	11 ±2.7	0.63 ±0.27
Metabolism				
Metabolic Pathway	CYP3A (major) CYP2D6 (minor)	CYP3A (major) Not significan UGT1A1 (minor) metabolized		CYP3A (major) CYP2C9 (minor)
Excretion				
Major route of excretion	Metabolism	Metabolism	Renal <sup>e</sup>	Metabolism
% Of dose excreted in urine <sup>d</sup>	8	7	77	<1
% Of dose excreted in feces <sup>d</sup>	90	88	15	45

a. Exposure measures are presented as Mean ± Standard deviation

b. Tmax are presented as Median (minimum to maximum)

c. Values refer to geometric mean ratio in AUC [fed / fasted] and (90% confidence interval). Light meal is ~400 kcal, 20% fat; High fat meal=~800 kcal, 50% fat.

d. t<sub>1/2</sub> values refer to median terminal plasma half-life.

e. Glomerular filtration and active tubular secretion

### ADE(ME) Information As a Table for Combination Products



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# DDI Information as Text (Section 12)

### **12.3 Pharmacokinetics**

#### Drug Interaction Studies

Coadministration of a single 40 mg dose of drugoxide with the strong CYP3A inhibitor ketoconazole (200 mg twice daily for 14 days) increased the Cmax and AUC of drugoxide by 1.3- and 2-fold, respectively, compared to when drugoxide was given alone in 14 Healthy volunteers. Tmax was unchanged. A reduced starting dosage is recommended [see Dosage and Administration (2.x), Drug Interactions (7.x)].

# VS.

#### **12.3 Pharmacokinetics**

#### **Drug Interaction Studies**

Strong CYP3A Inhibitors: The Cmax and AUC of drugoxide increased by 1.3and 2-fold, respectively, following coadministration of a drugoxide tablet formulation at the approved recommended dosage with ketoconazole [see Dosage and Administration (2.x), Drug Interactions (7.x)].



# Specific Populations as a Table (Section 12)

Table X: Established Clinically Relevant Drugoxide Exposure Changes in Specific Populations

Population Characteristic <sup>b</sup>	Ratio (90% CI) of Exposure Measures of Drugoxide [minimum to maximum]ª			
-	C <sub>MAX</sub>	AUC		
CYP2D6 Metabolizer				
Poor vs. Extensive	0.8 (0.6, 1.3) [0.4 to 1.9]	1.8 (1.2, 2.6) [0.9 to 3.2]		
Sex				
Female vs. Male	1.3 (1.2, 1.4) [0.7 to 2.1]	1.4 (1.1, 1.7) [0.8 to 2.6]		
Renal Impairment (RI)				
Mild vs. Normal <sup>c</sup>	1.2 (1.1, 1.3)	1.5 (1.4, 1.8)		
[Mild RI CLcr: 60-89 mL/min]	[0.6 to 1.9]	[1.1 to 2.5]		
Moderate vs. Normal	1.4 (1.2, 1.6)	2.1 (1.7, 2.6)		
[Moderate RI CLcr: 30-59 mL/min]	[0.8 to 2.5]	[1.2 to 3.6]		
Severe vs. Normal	1.5 (1.3, 1.8)	2.7 (1.9, 3.6)		
[Severe RI CLcr: 15-29 mL/min]	[1.1 to 2.7]	[1.5 to 4.3]		
ESRD +/- HD <sup>d</sup> vs. Normal [ESRD CLcr: < 15 mL/min]	Not Studied	Not Studied		

a= [see Dosage and Administration (2.1) and Use in Specific Populations (8.6)]

b= Drug X administered as 60 mg single dose unless otherwise specified

c=The degree of renal impairment was based upon Cockcroft-Gault calculated creatinine clearance (CLcr). Normal renal function was considered a CLcr greater than or equal to 90 mL/min d= End stage renal disease on or off hemodialysis ESRD +/- HD

No clinically significant changes in drugoxide exposure were associated with the following population characteristics: mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, age (18-79 years), and race (Asian and Caucasian). The pharmacokinetics of drugoxide in severe (Child-Pugh C) hepatic impairment have not been evaluated.



### **DDI Information as a Table (Section 12)**

 Table X. Established Clinically Relevant Interactions Affecting Drugoxide

Concomitant Drug (Dosage)	Drugoxide Dosage	Ratio (90% CI) of Exposure Measures of Drugoxide Combination/No Combination [minimum to maximum] <sup>a</sup>			
(Dosage)		Cmax	AUC		
Ketoconazole		1.2 (1.1, 1.4)	2.8 (2.3, 3.1)		
(400 mg once daily)		[0.9 to 1.9]	[1.9 to 4.2]		
Diltiazem	60 mg single dose	1.2 (1.1, 1.4)	2.1 (1.8, 2.3)		
(240 mg once daily)		[0.5 to 2.9]	[0.9 to 3.8]		
Rifampin		0.36 (0.31, 0.42)	0.12 (0.11, 0.14)		
(600 mg once daily)		[0.26 to 0.55]	[0.08 to 0.16]		

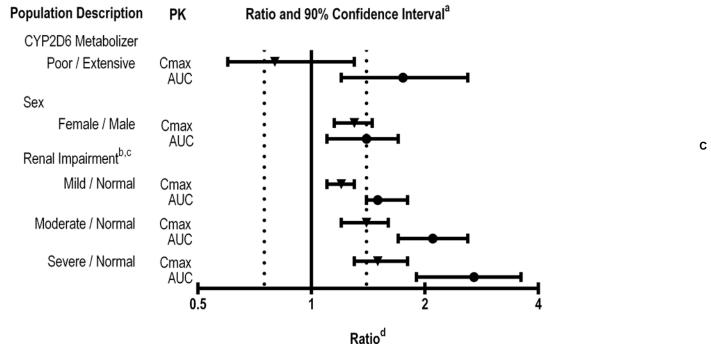
a= [see Dosage and Administration (2.x) and Drug Interactions (7)]

No clinically significant changes in exposure were observed for drugoxide when coadministered with each of the following concomitant medications in drug interaction trials: Drug A, Drug B, and Drug C.



# Specific Populations as a Figure (Section 12)

Table X. Established Clinically Relevant Drugoxide Exposure Changes in Specific Populations



a= Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations [see Dosage and Administration (2.1) and Use in Specific Populations (8.6)].

b= The degree of renal impairment was based upon Cockcroft-Gault calculated creatinine clearance (CLcr) and categorizes as follows: Normal [CLcr: greater than or equal to 90 mL/min], Mild [CLcr: 60-89 mL/min], Moderate [CLcr: 30-59 mL/min], and Severe [CLcr: 15-29 mL/min].

c= Patients with end stage renal disease on or off hemodialysis (ESRD +/- HD) [CLcr: < 15 mL/min] were not studied. d= Log base 2 scale

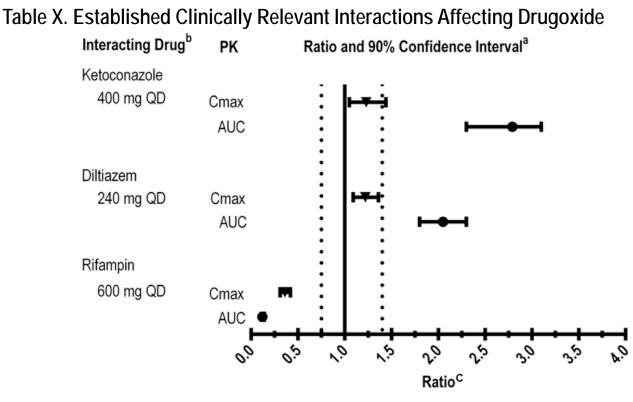
No clinically significant changes in drugoxide exposure were associated with the following population characteristics: mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, age (18-79 years), and race (Asian and Caucasian). The pharmacokinetics of drugoxide in severe (Child-Pugh C) hepatic impairment have not been evaluated.

# DDI Information as a Figure (Section 12)



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a= Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations [see Dosage and Administration (2.1) and Drug Interactions (7)].
 b= Drugoxide administered as a 60 mg single dose.

c= Log base 2 scale

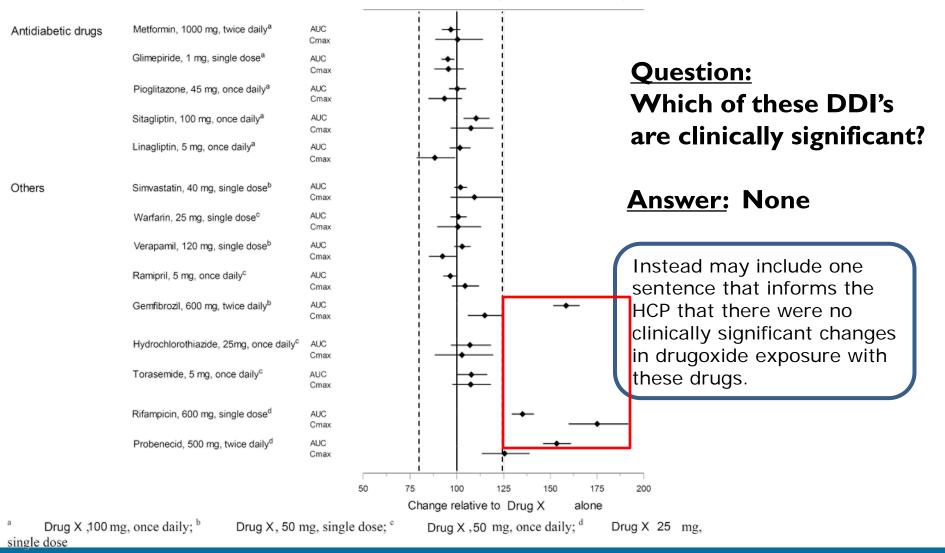
No clinically significant changes in exposure were observed for drugoxide when coadministered with each of the following concomitant medications in drug interaction trials: Drug A, Drug B, and Drug C.



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### Clearly Identify Significant DDI Effects in Text, Tables, and Figures

Geometric mean ratio (90% confidence interval)





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# **DRUG INTERACTIONS (Section 7)**



# DDI Information as Text (Section 7)

### 7 DRUG INTERACTIONS

Drugoxide undergoes metabolism by CYP3A. Use with a strong CYP3A inhibitor will increase drugoxide exposure (i.e., Cmax and AUC) resulting in an increased syncope risk. Reduce the dosage of Drug X when coadministered with strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole) [see Dosage and Administration (2.x) and Clinical Pharmacology (12.3)].

### **No Enhancements**



# Revised DDI Information as Text (Section 7)

### 7 DRUG INTERACTIONS

### 7.1 Effects of Other Drugs on Drug X

### Strong CYP3A Inhibitors

Reduce the dosage of drugoxide when coadministered with strong CYP3A inhibitors [see Dosage and Administration (2.x)].

Drugoxide undergoes metabolism by CYP3A. Use with a strong CYP3A inhibitor will increase drugoxide exposure (i.e., Cmax and AUC) resulting in an increased syncope risk [see Warnings and Precautions (5.x) and Clinical Pharmacology (12.3)].

The following are some examples of strong CYP3A Inhibitors: boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole.

### **Enhancements Used**



### DDI Information as a Table (Section 7)

#### 7 DRUG INTERACTIONS

Tables X and Y include drugs which demonstrated a clinically important drug interaction with Drug X that affects drugoxide or drugs co-administered with Drug X, respectively.

Table X. Clinically Significant Drug Interactions Involving Drugs That Affect Drug X

Strong CYP3A Inhibitors	
Clinical Implications:	<ul> <li>Concomitant use of Drug X with a strong CYP3A4 inhibitor increased the exposure of drugoxide compared to the use of Drug X alone [see Clinical Pharmacology (12.3)].</li> <li>Increased drugoxide exposure increases the risk of hypotension and syncope [see Warnings and Precautions (5.x)].</li> </ul>
Prevention or Management:	When using Drug X concomitantly with a strong CYP3A inhibitor, reduce the Drug X dosage [see Dosage and Administration (2.x)].
Examples:	Boceprevir, clarithromycin, conivaptan, grapefruit juice, <sup>a</sup> indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole
Strong CYP3A Inducers	
Clinical Implications:	<ul> <li>Concomitant use of Drug X with a strong CYP3A inducer decreased the exposure of drugoxide compared to the use of Drug X alone [see Clinical Pharmacology (12.3)].</li> <li>Decreased drugoxide exposure may lead to reduced efficacy.</li> </ul>
Prevention or Management:	The concomitant use of Drug X with a strong CYP3A inducer is not recommended
Examples:	Carbamazepine, phenytoin, rifampin, St. John's wort <sup>b</sup>

<sup>a</sup> The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength). <sup>b</sup> The effect of St. John's wort varies widely and is preparation-dependent.



#### Table Y:Clinically Significant Drug Interactions Involving Drugs Affected by Drug X

Benzodiazepines			
Clinical Implications:	Concomitant use of Drug X with benzodiazepines was associated with increased sedation a orthostatic hypotension [see Warnings and Precautions (5.x)].		
Prevention or Management:	Monitor sedation and blood pressure. Consider reducing the dosage of Drug X and/or the penzodiazepine.		
Examples:	Alprazolam, clonazepam, diazepam, lorazepam, triazolam		
Sensitive CYP3A substrates			
Clinical Implications:	<ul> <li>Concomitant use of Drug X with CYP3A substrates may decrease systemic exposure of these substrates due to strong induction of this metabolic pathway [see Clinical Pharmacology (12.3)].</li> <li>Reduced systemic exposure may decrease therapeutic effect of these CYP3A substrates.</li> </ul>		
Prevention or Management:	Co-administration of Drug X is generally not recommended with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index unless Its approved labeling contains specific recommendations that address this issue (e.g., the dosage can be safely titrated using therapeutic drug monitoring).		
Examples:	Alfentanil,, aprepitant, budesonide, buspirone, conivaptan, cyclosporine, darifenacin, darunavir, dasatinib, dihydroergotamine, dronedarone, eletriptan, eplerenone, ergotamine, everolimus, felodipine, fentanyl, fluticasone, indinavir, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, pimozide, quetiapine, quinidine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, ticagrelor, tipranavir, tolvaptan, triazolam, and vardenafil.		



### **Antimicrobials/Antivirals**

#### 7 DRUG INTERACTIONS

#### 7.1 Established and Potentially Significant Drug Interactions

Table X provides a listing of potential clinically significant drug Interactions between Drug X and Other Drugs

#### Table X: Potential Clinically Significant Drug Interactions between Drug X and Other Drugs<sup>a,b</sup>

Concomitant Drug Class: Drug Name	Effect on Concentration <sup>c</sup>	Clinical Comment
Acid Reducing Agents:	↓ Drugoxide	Drugoxide solubility decreases as pH increases. Drugs that increase gastric pH
		are expected to decrease concentration of drugoxide.
Antacids (e.g., Drug A and Drug B)		Recommend separating antacid and Drug X administration by at least four
		hours
		May administer H2-receptor antagonists (up to x mg of Drug C twice daily or
H2-receptor antagonists (e.g., Drug C) <sup>d</sup>		equivalent dosages of other H2 blockers) simultaneously with or within 12
		hours of Drug X.
Proton-pump inhibitors (e.g., Drug D) <sup>d</sup>		May administer PPIs (up to x mg of Drug D once daily or equivalent dosages of
		other PPIs) simultaneously with Drug X under fasting conditions.
Antiarrhythmics:	↑ Drug F	Recommend therapeutic concentration monitoring of Drug F when
Drug F		coadministered with Drug X
Anticonvulsants:	↓ Drugoxide	May lead to reduced therapeutic effect of drugoxide. Coadministration is not
Drug G, Drug H, Drug I, Drug J	_	recommended.
Antimycobacterials:	↓ Drugoxide	May lead to reduced therapeutic effect of drugoxide. Coadministration is not
Drug K		recommended.
HMG-CoA Reductase Inhibitors:	↑ Drug L	Increased risk of myopathy, including rhabdomyolysis. Coadministration of
Drug L		Drug X with Drug L is not recommended.
a. This table is not all inclusive: h. These data are h	L asod on drug intoractiv	n studies or predicted based upon similar characteristics to the drugs evaluated in these

a. This table is not all inclusive; b. These data are based on drug interaction studies or predicted based upon similar characteristics to the drugs evaluated in these studies; c.  $\downarrow$  = decrease,  $\uparrow$  = increase; d. [see Dosage and Administration (2.x)]



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# **DOSAGE AND ADMINISTRATION (Section 2)**



# **DDI Information as Text (Section 2)**

#### 2.x Dosage Modifications for Concomitant Use with Strong CYP3A Inhibitors

Decrease the dosage of Drug X by 50% to 10 mg twice a day when coadministered with drugs that are strong inhibitors of CYP3A [see Drug Interactions (7.x) and Clinical Pharmacology (12.3)].



## Multidimensional Approach (Section 2)

### 2.x Dosage Modifications for Concomitant Use with Strong CYP3A Inhibitors

Concomitant use of strong CYP3A inhibitors taken:

- Chronically (e.g., ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, nefazodone) with Drug X is not recommended.
- For 7 days or less (e.g., antifungals and antibiotics) with Drug X, consider interrupting Drug X therapy until the strong CYP3A inhibitor is no longer needed.

# Alternative Displays (Text vs. Figure)

#### 2 DOSAGE AND ADMINISTRATION

2.3 Dose Modification for Use with a Strong or Moderate CYP3A Inhibitor

#### Strong CYP3A Inhibitor

The coadministration of Drug X with strong CYP3A4 inhibitors is not recommended [see Drug Interactions (7) and Clinical Pharmacology (12.3)].

#### Moderate CYP3A Inhibitor

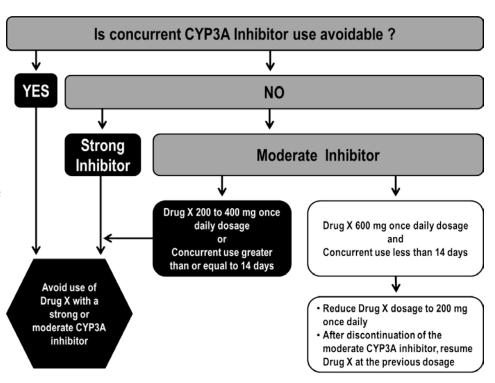
Avoid coadministration of Drug X with moderate CYP3A inhibitors.

If concurrent short term (14 days or less) use of moderate CYP3A inhibitors including certain antibiotics (e.g., erythromycin, ciprofloxacin) is unavoidable for patients who are taking a Drug X 600 mg daily dosage:

- Reduce Drug X dose to 200 mg.
- After discontinuation of a moderate CYP3A inhibitor, resume Drug X at the previous dose [see Drug Interactions (7) and Clinical Pharmacology (12.3)].

#### 2 DOSAGE AND ADMINISTRATION

2.3 Dose Modification for Use with a Strong or Moderate CYP3A Inhibitor





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### Complex Dosage Mitigation Strategy (Section 2)



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Table X: Recommended Dosage Adjustments in Patients Taking Strong CYP2D6 Inhibitors, CYP3A Inhibitors, and/or CYP3A Inducers<sup>a</sup> and/or in Patients who are CYP2D6 Poor Metabolizers.

Current	Dosing	Perpetrators				Modified	Modified
Dosage	Frequency	2D6 Poor	Concurrent/ strong				Frequency
(mg)	(hours)	Metabolizer	CYP2D6 INH	CYP3A INH	CYP3A IND	Dosage	(hours)
		Yes	No	Yes	No	Avoid Use	NA
			No	No	Yes	400 mg	6
200 mg	6		Yes	No	No	200 mg	6
200 Mg	0	No	No	Yes	No	200 mg	6
		NO	Yes	Yes	No	Avoid Use	NA
			No	No	Yes	400 mg	6
		6 No	Yes	No	No	200 mg	6
100 mg	400 mg 6		No	Yes	No	200 mg	6
400 Mg			Yes	Yes	No	Avoid Use	NA
			No	No	Yes	600 mg	6
	/	No	Yes	No	No	400 mg	6
			No	Yes	662	400 mg	6
600 mg 12	NO	Yes	Yes	No	Avoid Use	NA	
		No	No	Yes	600 mg	6	
	Yes	No	Yes	No	Avoid Use	NA	
		ies	No	No	Yes	400 mg	6
	12	12 No	Yes	No	No	600 mg	12
			No	Yes	662	600 mg	12
			Yes	Yes	No	Avoid Use	NA
			No	No	Yes	400 mg	6

INH= inhibitor; IND= inducer; NA= not applicable; a= CYP3A inducers taken for greater than 2 weeks



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# Tips for Communicating CP-Related Information in Labeling

- Communicate with the Agency early and often.
  - Don't wait until the final stages of an NDA/BLA review.
- Include your rationale for proposed clinical pharmacology-related information in labeling and mitigation strategies in the Clinical Pharmacology Summary in the NDA/BLA
- Provide sufficient detail in labeling to inform prescribing decisions for clinical pharmacology-related information.
  - Actions should be clear and specific.
  - Clinically significant clinical pharmacology-related information should be clearly identified.
  - Avoid redundancy between sections containing clinical pharmacology-related information.
  - Brevity encouraged.
- Use white space, text attributes, tables, and figures where appropriate to enhance readability, clarity, and utility.



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### How Are We Doing?

- YOU can help OCP achieve its goal of translating its regulatory reviews into understandable and actionable labeling language
- Provide feedback on the quality, clarity, and utility of clinical pharmacology-related information in the professional and consumer drug labeling you are using.



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### **Questions?**

