Strategies for Enhancing Quality, Utility, & Clarity in Clinical Pharmacology-Related Labeling

A Regulatory Perspective

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- Disclaimer:
  - 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

1. 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)

***Drug = small molecule drugs and biological products**

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

How Developers Often See Approved Prescription Drug Labeling

How Healthcare Providers See Approved Prescription Drug Labeling

Physician's Perception of CP Information in the PDL

What's Wrong?	The Ideal Presentation
• Confusing structure • Too much information • Wrong information • No conveyance of risk • No real guidance	• 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

Slide Courtesy of Kellie Schoolar Reynolds, Pharm.D., Deputy Division Director, Division of Clinical Pharmacology IV
Adapted from information presented by David Juurlink (University of Toronto) at FDA Clinical Pharmacology Advisory Committee Meeting on 9/25/2013

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.

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.

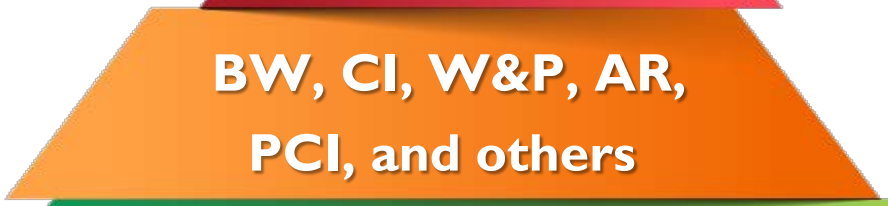
A sentence:

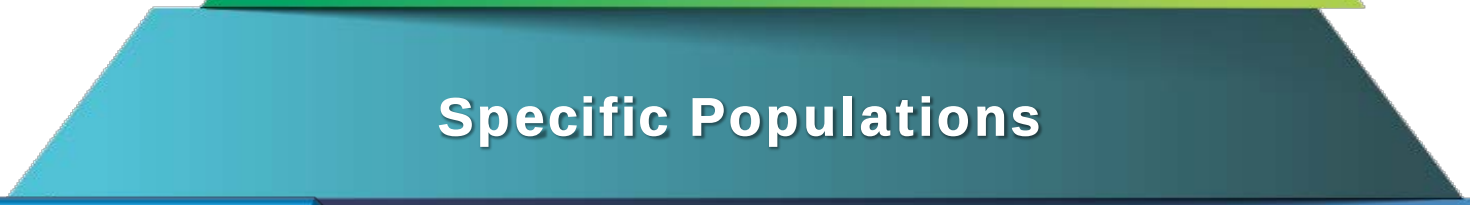
- Is a unit of grammar with one or more words.
- It can be preceded by pauses.
- It can be followed by pauses.
- It starts with a capital letter.
- It ends with a period.
- It can end in other punctuation.

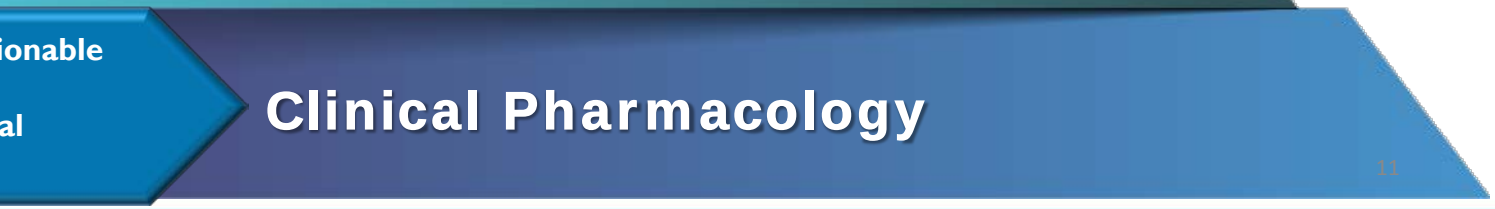
F-K 3.2 FREI 83.0 (Very Easy to Read)

Where is CP Information in PDL?

- Highly Actionable
- Brief
- Limited Context







- Less Actionable
- Detailed
- Additional Context

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

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, $AUC_{0\text{-}INF}$, $AUC_{0\text{-}TAU}$, $AUC_{0\text{-}12hr}$, $t_{1/2}$, Vd, CL)
  - Population definitions (e.g., patients vs. subjects)
  - Dosages outside the approved recommended dosage range (e.g., exposure-response, 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.

CLINICAL PHARMACOLOGY (Section 12)

12.3 Pharmacokinetics

Table x. Pharmacokinetic Parameters of Drugoxide and Its Metabolites

General Information[a,b]				
Drugoxide Exposure		**Cmax**	**AUC**	**CV**
	Single Dose	3.5 µg/mL (1.5 to 5.3)	80.4 µg*h/mL (48.9 to 125.7)	36% to 45%
	Steady-State[c]	4.9 µg/mL (2.1 to 9.9)	68.3 µg*h/mL (26.1 to 120.9)	
Dose Proportionality[c]	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][d]	69% to 83% compared to oral solution			
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[e] **[Fed/fasted] (25th to 75th percentile)** *[see Dosage and Administration (2.1), Clinical Studies (14)]*	**Meal**	**Drugoxide AUC**	**M-2 AUC**	**M-5 AUC**
	Low-fat[f,g]	Increased (Incr.) 40% (Incr. 22% to 68%)	Incr. 38% (Incr. 15% to 75%)	Incr. 25% (Incr. 1% to 69%)
	High-fat[h]	Incr. 53% (Incr. 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				
Elimination half-life[c]	**Drugoxide**	**M-3**	**M-5**	
	30 hours (14 to 58 hours)	23 hours (14 to 32 hours)	56 hours (32 to 70 hours)	
Metabolism				
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[i]				
Primary excretion pathways (% dose (range))	--Feces: Approximately 73% (68% to 76%), [49% as drugoxide and 24% as metabolites] --Urine: Approximately 20% (16% to 25%), [15% as glucuronides]			

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

ADE(ME) Information as a Table

	Component Drug A	Component Drug B	Component Drug C	Component Drug D
General Information[a]				
C_{max} (microgram per mL)	31.5 ±10.6	22.5 ±6.4	31.5 ±6.5	2.4 ±1.2
AUC_{tau} (microgram•hour per mL)	342 ±118.7	142.5 ±48.3	175.5 ±35.7	3.2 ±1.8
C_{trough} (microgram per mL)	5.4 ±2.7	0.3 ± 0.13	1.5 ±0.6	Not Available
Absorption				
T_{max} (h)[b]	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[c]	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[c]	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) UGT1A1 (minor)	Not significantly metabolized	CYP3A (major) CYP2C9 (minor)
Excretion				
Major route of excretion	Metabolism	Metabolism	Renal[e]	Metabolism
% Of dose excreted in urine[d]	8	7	77	<1
% Of dose excreted in feces[d]	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. $t_{1/2}$ values refer to median terminal plasma half-life.
e. Glomerular filtration and active tubular secretion

ADE(ME) Information As a Table for Combination Products

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 1.3- and 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[b]	Ratio (90% CI) of Exposure Measures of Drugoxide [minimum to maximum][a]	
	C_{MAX}	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[c] [Mild RI CLcr: 60-89 mL/min]	1.2 (1.1, 1.3) [0.6 to 1.9]	1.5 (1.4, 1.8) [1.1 to 2.5]
Moderate vs. Normal [Moderate RI CLcr: 30-59 mL/min]	1.4 (1.2, 1.6) [0.8 to 2.5]	2.1 (1.7, 2.6) [1.2 to 3.6]
Severe vs. Normal [Severe RI CLcr: 15-29 mL/min]	1.5 (1.3, 1.8) [1.1 to 2.7]	2.7 (1.9, 3.6) [1.5 to 4.3]
ESRD +/- HD[d] 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

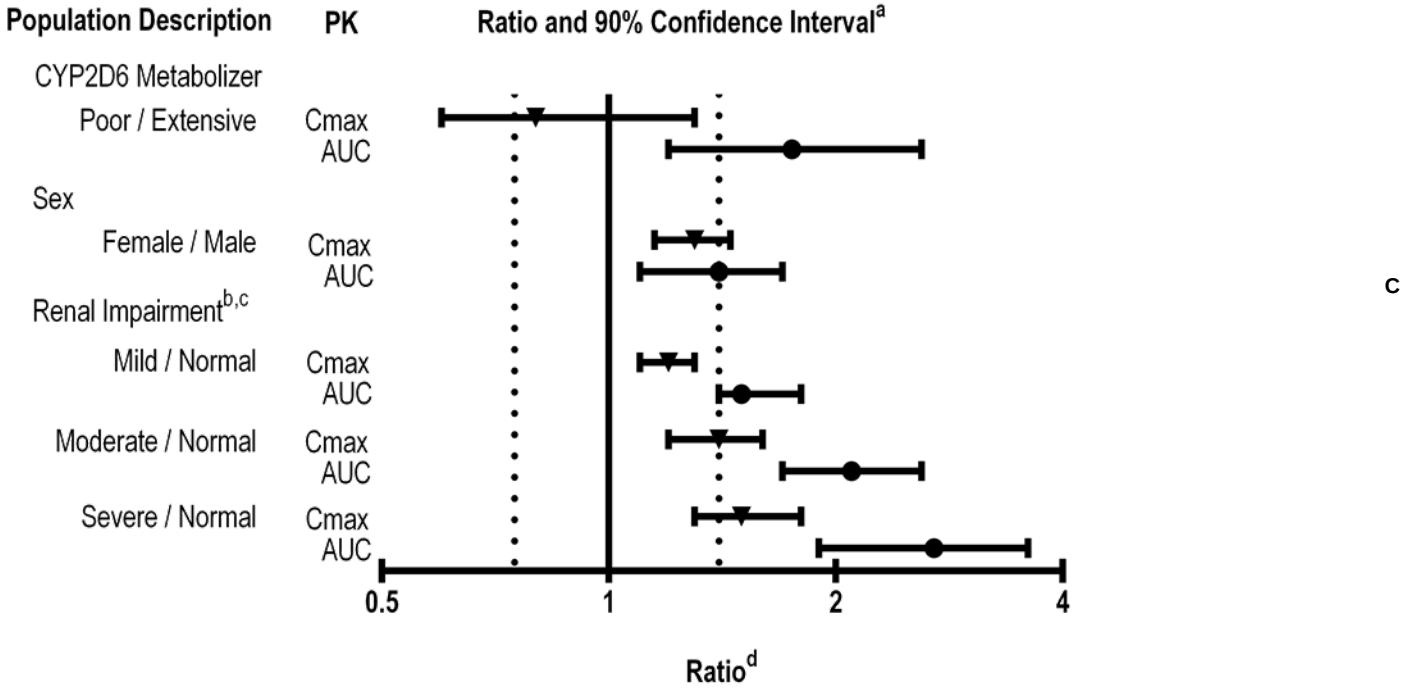
Concomitant Drug (Dosage)	Drugoxide Dosage	Ratio (90% CI) of Exposure Measures of Drugoxide Combination/No Combination [minimum to maximum][a]	
		Cmax	AUC
Ketoconazole (400 mg once daily)	60 mg single dose	1.2 (1.1, 1.4) [0.9 to 1.9]	2.8 (2.3, 3.1) [1.9 to 4.2]
Diltiazem (240 mg once daily)		1.2 (1.1,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



c

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].

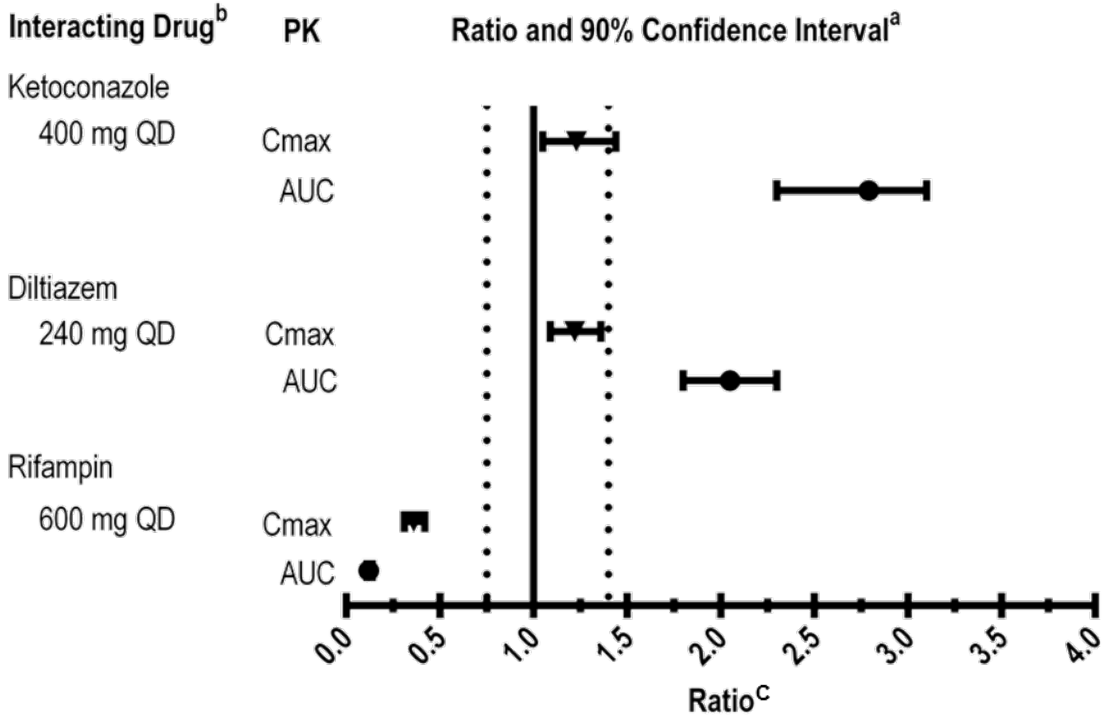
c= Patients with end stage renal disease on or off hemodialysis (ESRD +/- HD) [CLcr: < 15 mL/min] were not studied.

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)

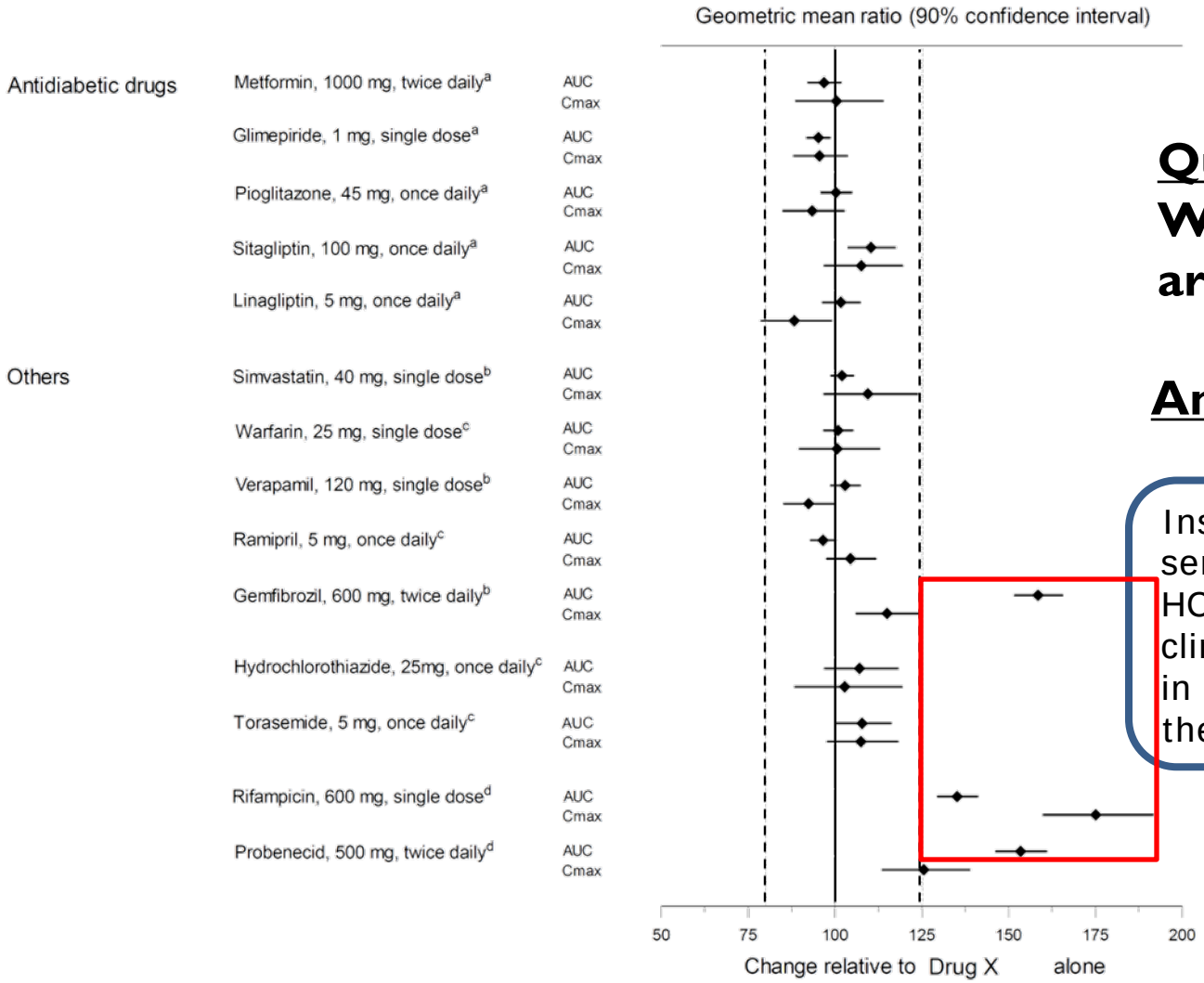
Table X. Established Clinically Relevant Interactions Affecting Drugoxide



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.

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



Question:
Which of these DDI's are clinically significant?

Answer: None

Instead may include one sentence that informs the HCP that there were no clinically significant changes in drugoxide exposure with these drugs.

[a] Drug X ,100 mg, once daily; [b] Drug X, 50 mg, single dose; [c] Drug X ,50 mg, once daily; [d] Drug X 25 mg, single dose

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:	• 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)].* • Increased drugoxide exposure increases the risk of hypotension and syncope *[see Warnings and Precautions (5.x)].*
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,[a] indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole
Strong CYP3A Inducers	
Clinical Implications:	• 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)]*. • Decreased drugoxide exposure may lead to reduced efficacy.
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[b]

[a] 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).
[b] 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 and 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 benzodiazepine.
Examples:	Alprazolam, clonazepam, diazepam, lorazepam, triazolam
Sensitive CYP3A substrates	
Clinical Implications:	• 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)].* • Reduced systemic exposure may decrease therapeutic effect of these CYP3A substrates.
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[a,b]

Concomitant Drug Class: Drug Name	Effect on Concentration[c]	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
H2-receptor antagonists (e.g., Drug C)[d]		May administer H2-receptor antagonists (up to x mg of Drug C twice daily or equivalent dosages of other H2 blockers) simultaneously with or within 12 hours of Drug X.
Proton-pump inhibitors (e.g., Drug D)[d]		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	↑ Drug F	Recommend therapeutic concentration monitoring of Drug F when coadministered with Drug X
Anticonvulsants: Drug G, Drug H, Drug I, Drug J	↓ Drugoxide	May lead to reduced therapeutic effect of drugoxide. Coadministration is not recommended.
Antimycobacterials: Drug K	↓ Drugoxide	May lead to reduced therapeutic effect of drugoxide. Coadministration is not recommended.
HMG-CoA Reductase Inhibitors: Drug L	↑ Drug L	Increased risk of myopathy, including rhabdomyolysis. Coadministration of Drug X with Drug L is not recommended.

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. ↓ = decrease, ↑ = increase; d. *[see Dosage and Administration (2.x)]*

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

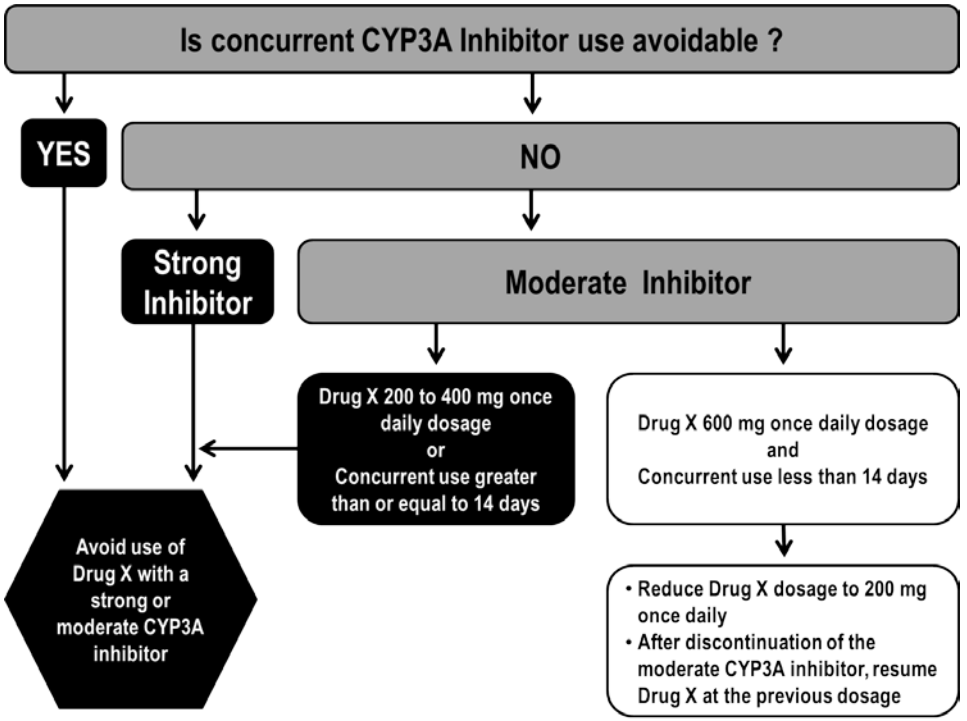
Avoid coadministration of Drug X with moderate CYP3A inhibitors.

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



Complex Dosage Mitigation Strategy (Section 2)

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

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

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.

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.

Email: ocp@fda.hhs.gov

Questions?