

The Ins and Outs Of Presenting Clinical Pharmacology Information in Prescription Drug Labeling

Mongthuong T. Tran, Pharm.D., BCPS

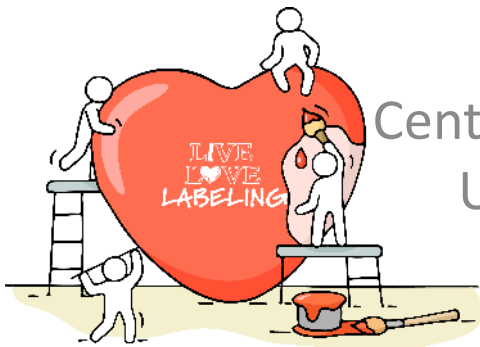
Labeling and Health Communication Specialist

Office of Clinical Pharmacology (OCP)

Office of Translational Sciences (OTS)

Center for Drug Evaluation and Research (CDER)

U.S. Food and Drug Administration (FDA)



Disclaimer

- Any tables and figures presented today are meant to be illustrative only; these examples are not intended to limit the use of other possible formats and approaches to convey critical information

Disclosures

- The presenter has no disclosures related to the content of this presentation

Objectives

- Understand key regulations that impact clinical pharmacology content in prescription drug labeling (PDL)
- Describe where clinical pharmacology content is found in PDL
- Describe the content structure of the Clinical Pharmacology section in PDL
- Identify alternative methods of communicating complex clinical pharmacology content

Key PDL Regulations

- Must contain summary of essential scientific information needed for the safe and effective use of the drug^a
- Is written for health care practitioner (HCP) audience^b
- Must be informative and accurate^a
- Must be updated when new information becomes available^a
- Must not be promotional in tone, false, or misleading^a
- Must be based whenever possible on data derived from human experience^a

^a 21 CFR 201.56

^b PLR FR 71 on 1/24/2006

PDL Contents

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

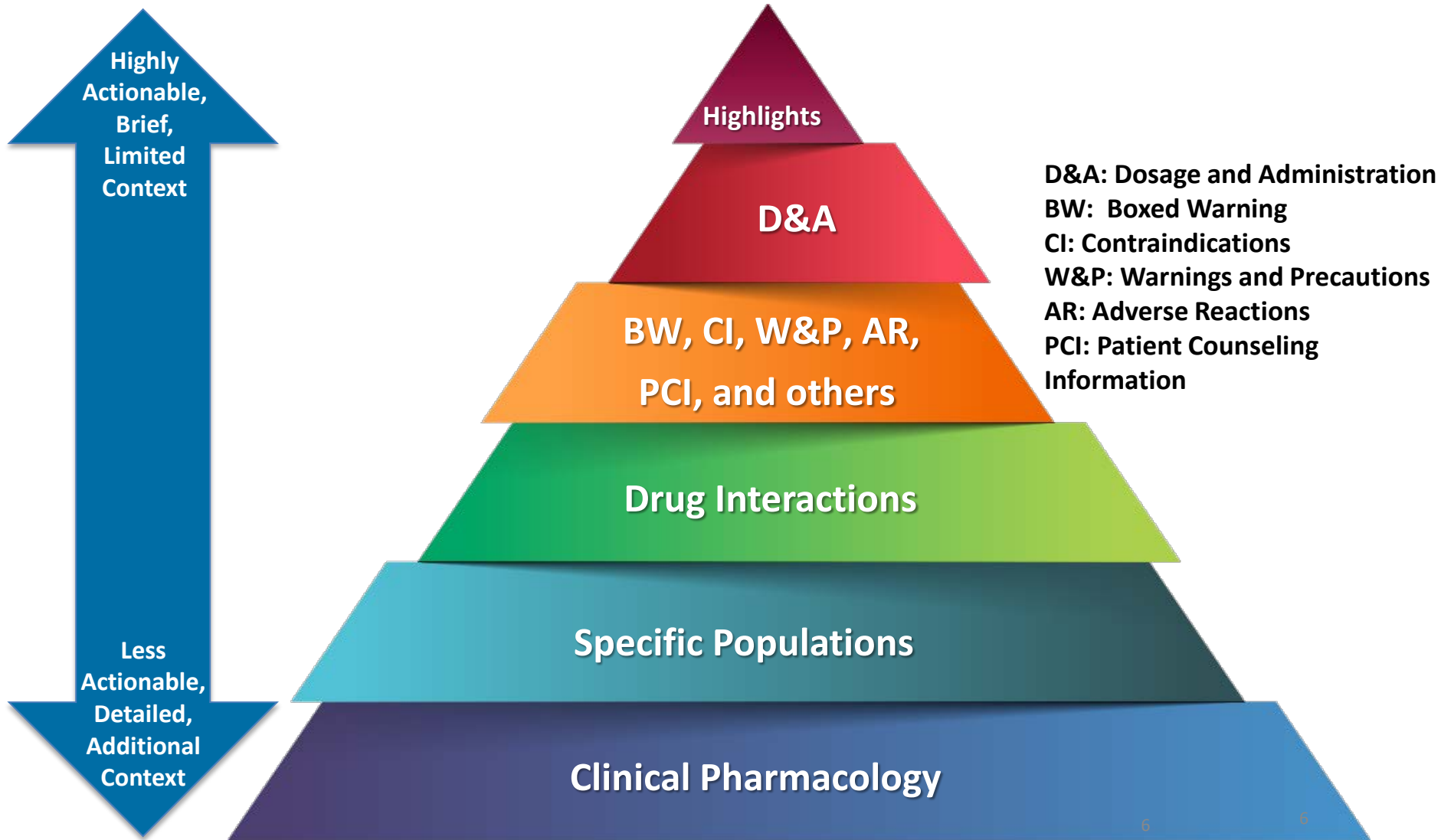
15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

Clinical Pharmacology Footprint





CDER Labeling Initiative

- PDL Improvement & Enhancement Initiative (PDLIEI) established 2013
 - Enhance the safe and effective use of prescription drugs by facilitating optimal communication through PDL
 - Increase percentage of PDLs that complies with PLR content and format requirements
 - Develop and evaluate approaches to enhance clarity, utility, and comprehension of PDL across CDER
 - Foster consistency in PDL across CDER by establishing guidances and best practices

Guidance Highlights

New Guidance for Industry:

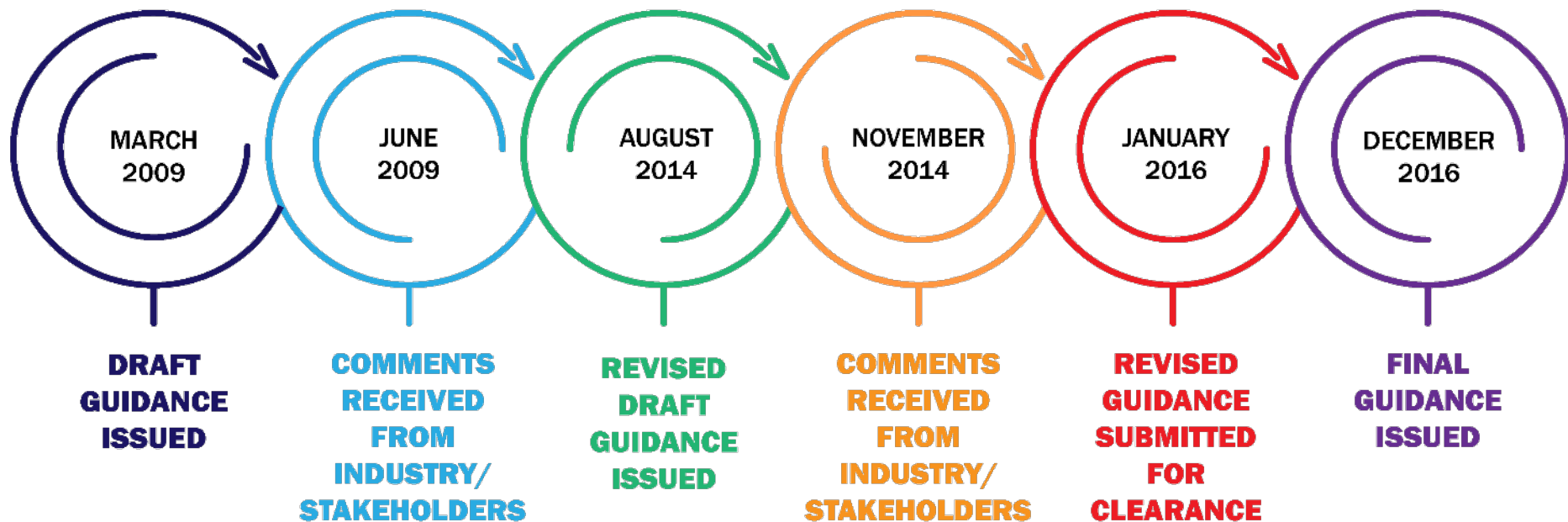
Clinical Pharmacology Section of Labeling

for Human Prescription Drug and
Biological Products –Content and Format



12. CLINICAL PHARMACOLOGY

Evolution of Section 12 Guidance



12 Clinical Pharmacology Layout*

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

Cardiac Electrophysiology

12.3 Pharmacokinetics

Absorption

Food Effect

Distribution

Elimination

Metabolism

Excretion

Specific Populations

Geriatric Patients

Pediatric Patients

Male and Female Patients

Racial or Ethnic Groups

Patients with Renal Impairment

Patients with Hepatic Impairment

Pregnant Women

Drug Interaction Studies

12.4 Microbiology

12.5 Pharmacogenomics

12.x Additional Subsections

General Principles for Section 12



DOs



Be understandable to HCPs who may not have expertise in Clinical Pharmacology



Include positive and pertinent negative findings that are informative for the safe and effective use of the drug



Include information on racemate and additive effects



Use a consistent approach to distinguish headings and subheadings within sections (e.g., underlining for headings and italics for subheadings)



Use consistent units for all parameters and include measures of dispersion



Include relevant component information only for fixed dose combination drugs

CONTENT AND ORGANIZATION

DON'Ts

Avoid inaccurate, false, misleading or promotional information



Avoid subjective wording (e.g., “fast” or “rapidly”) and general terms (e.g., “systemic exposure”) unless words/terms are qualified (e.g., “systemic exposure (AUC)”)



Do not imply or suggest unapproved indications/uses or dosing regimens



Avoid inclusion of animal or in vitro information unless essential to understand dosing or drug interaction information



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12.x Additional Subsections

12.1 Mechanism of Action (MOA)



- Summarize drug's established MOA at various levels based on what is known
 - e.g., cellular, receptor, membrane, tissue, target organ, whole body
- Include MOA for each approved indication or about clinically significant adverse reactions associated with drug
- Describe antimicrobial MOA in subsection 12.4 Microbiology
 - e.g., “Drugoxide is an antibacterial drug [see *Microbiology (12.4)*]”

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12.x Additional Subsections

12.2 Pharmacodynamics (PD)

- Summarize PD effects, exposure-response and exposure-safety relationships related to clinical effect, adverse effects, or toxicity
 - Must include statement indicating lack of relevant PD data, if appropriate
 - Support actionable therapeutic drug monitoring information found in other sections
- Summarize information supporting clinical impact of anti-product antibody formation on PD without a clinically significant change in PK

12.2 Pharmacodynamics (PD)

- Include concise description of key drug interaction or specific population studies with a clinically significant impact on PD that is independent of PK changes
 - May include listing of relevant concomitant drugs or specific populations without a clinically significant impact on PD
- Include nonclinical animal PD data if necessary for understanding of pharmacology data in humans

12.2 Pharmacodynamics (PD)



Cardiac Electrophysiology Heading

- Describe the drug's effect on QT interval
 - Omit heading if effect is unknown
 - Summarize if no effect (i.e., thorough QT trial is negative)
 - e.g., “At a dose X times the maximum approved recommended dose, Drug Y does not prolong the QT interval to any clinically relevant extent.”
- Include dose(s) studied or exposure range observed, and any dose- or exposure-response relationships
 - Discuss clinically significant risks associated with QT prolongation in other sections (e.g., BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS)

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12.3 Pharmacokinetics (PK)

- Include introductory paragraph that describes general, clinically significant PK properties
 - PK linearity/nonlinearity
 - Unique drug characteristics (e.g., modified release, oral disintegrating tablet, prodrug)
 - Expected drug exposure (e.g., C_{\max} , AUC, time to steady state, accumulation ratio following multiple dosing, changes in PK over time)

12.3 Pharmacokinetics (PK)

Absorption Heading

- Include information related to rate/extent of absorption of oral and other non-IV routes of administration
- Also include, if applicable:
 - First-pass effect
 - Mechanisms affecting bioavailability
 - Absorption PK
 - Sources of variability
 - Absorption at different injection or application sites

12.3 Pharmacokinetics (PK)

Effect of Food Subheading

- Present clinically relevant results of food(s) or meal(s) used with respect to total calories and composition (fat, carbohydrate, protein)
 - Generally include mean change and variability for relevant PK exposure measures
 - Present clinical implications of exposure changes if known
- Consider summarizing if no clinically significant PK changes with food or if unknown

12.3 Pharmacokinetics (PK)

Distribution Heading

- Volume of distribution
 - Include additional discussion for understanding drug's activity or safety (e.g., large V_d contributes to a long terminal $t_{1/2}$)
- Protein binding
- Distribution to other tissues, when appropriate

Elimination Heading

- Include introductory paragraph that describes total body CL and $t_{1/2}$
 - $t_{1/2}$ should usually be based on time to reach steady state (i.e., effective $t_{1/2}$)
 - Include long terminal $t_{1/2}$ if impacts safety or effectiveness
 - Include dosage associated with $t_{1/2}$ when drug exhibits nonlinear elimination within approved recommended dosage range

12.3 Pharmacokinetics (PK)

Metabolism Subheading

- Describe pathways, contribution of specific enzymes, and major metabolites, and source of information
 - Identify pathways that have been ruled out if there is uncertainty in metabolic pathways
- Describe metabolite's activity including its metabolite-to-parent exposure ratio and contribution to activity in relation to parent drug

Excretion Subheading

- Include pathways, extent, and mechanism of excretion
 - e.g., describe mechanism for renal excretion (glomerular filtration, active secretion, or reabsorption)
 - Include contribution of transporters involved

Table x. Pharmacokinetic Parameters of Drugoxide and Its Metabolites

General Information ^{a,b}				
Drugoxide exposure	Single dose	C _{max} 3.5 mcg/mL (1.5 to 5.3)	AUC 80.4 mcg*h/mL (48.9 to 125.7)	CV 36% to 45%
	Steady-state ^c	4.9 mcg/mL (2.1 to 9.9)	68.3 mcg*h/mL (26.1 to 120.9)	
Dose proportionality ^c	The steady-state AUC of drugoxide increases less than dose proportionally at dosages > 50 mg (0.5 times the approved recommended dosage)			
Absorption				
Bioavailability [tablet] ^d	69% to 83% compared to oral solution			
T _{max} [tablet] median (range)	4 hours (2 to 23 hours)			
Enterohepatic recycling (EHR)	<ul style="list-style-type: none"> Drugoxide undergoes EHR Multiple plasma concentration peaks were observed across the 24-hour dosing interval 			
Effect of food ^e [fed/fasted] (25 th to 75 th percentile) [see Dosage and Administration (2.1) and Clinical Studies (14)]	Meal	Drugoxide AUC	M-3 AUC	M-5 AUC
	Low-fat ^f	Increased (Incr.) 40% (Incr. 22% to 68%)	Incr. 38% (Incr. 15% to 75%)	Incr. 25% (Incr. 1% to 69%)
	High-fat ^g	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 t _{1/2} ^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	<ul style="list-style-type: none"> Oxidation: CYP3A4 Conjugation: UGT1A1 			
Active metabolites	<ul style="list-style-type: none"> 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 ^h				
Primary excretion pathways (% dose (range))	<ul style="list-style-type: none"> Feces: Approximately 73% (68% to 76%), [49% as drugoxide and 24% as metabolites] Urine: Approximately 20% (16% to 25%), [15% as glucuronides] 			

^a The pharmacokinetics of drugoxide and its active metabolites were characterized in patients following a single dose of 100 mg Drug X 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 regimen for 21 days on and 7 days off

^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 dose of 100 mg Drug X in healthy volunteers after a specified diet

^f Low-fat meal is 319 calories and 8.2 grams fat; Drug X was administered with a low-fat meal in Studies 1 and 2

^g High-fat meal is 945 calories and 54.6 grams fat

^h Arithmetic mean; following a single dose of 120 mg investigational radiolabeled oral solution of drugoxide in healthy fasted volunteers

12.3 Pharmacokinetics: Table



	Component Drug A	Component Drug B	Component Drug C	Component Drug D
General Information^a				
C _{max} (mcg/mL)	31.5 ± 10.6	22.5 ± 6.4	31.5 ± 6.5	2.4 ± 1.2
AUC _{tau} (mcg*hr/mL)	342 ± 118.7	142.5 ± 48.3	175.5 ± 35.7	3.2 ± 1.8
C _{trough} (mcg/mL)	5.4 ± 2.7	0.3 ± 0.1	1.5 ± 0.6	Not available
Absorption				
T _{max} (hr) ^b	3 (1 to 4.5)	2 (1 to 4)	2.4 (1 to 3.5)	1.1 (0.6 to 2)
Effect of Food^a				
Light meal AUC ratio ^c	1.4 (1.2, 1.6)	1.1 (0.9, 1.3)	0.9 (0.8, 1.0)	1.2 (1.1, 1.4)
High-fat meal AUC ratio ^c	1.9 (1.7, 2.2)	0.9 (0.7, 1.0)	0.9 (0.8, 1.0)	1.2 (1.1, 1.3)
Distribution				
% bound to human plasma proteins	Approximately (Approx.) 97	Approx. 98	< 8	Approx. 75
Blood-to-plasma ratio	0.8	0.7	1.0	0.6
Elimination				
t _{1/2} (hr) ^d	14 ± 4.8	4.3 ± 1.4	11 ± 2.7	0.6 ± 0.3
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	8	7	77	< 1
% of dose excreted in feces	90	88	15	45

^a Exposure measures are presented as mean ± SD

^b T_{max} is presented as median (minimum to maximum)

^c AUC ratio [fed/fasted] is presented as geometric mean (90% CI). Light meal is approx. 400 kcal, 20% fat; High-fat meal is approx. 800 kcal, 50% fat.

^d Terminal plasma t_{1/2} is presented as median ± SD

^e Glomerular filtration and active tubular secretion

12.3 Pharmacokinetics (PK)

Specific Populations Heading

- Include listing of subpopulations under heading instead of under different subheadings if no PK studies/analyses or no clinically significant PK changes
 - e.g., “No clinically significant differences in the pharmacokinetics of Drug X were observed in patients with mild renal impairment (CLcr 60 to 89 mL/min as estimated by Cockcroft-Gault (C-G)), any degree of hepatic impairment, or in geriatric patients. The effect of moderate to severe renal impairment (CLcr < 60 mL/min, C-G) with or without hemodialysis on the pharmacokinetics of Drug X is unknown.”
- Provide PK information regarding lactation only in 8.2 Lactation under USE IN SPECIFIC POPULATIONS

12.3 Pharmacokinetics (PK)

Geriatric Patients Subheading

- Compare results of subjects ≥ 65 years of age to younger adult populations where possible
- May use age breakpoints other than 65 years or describe results based on ranges in ages

Pediatric Patients Subheading

- Include only PK information for approved pediatric indications for patients from birth to < 17 years of age
- Include PK information only in 8.4 Pediatric Use if safety and effectiveness have not been established

Male and Female Patients Subheading

- Present description and results of studies/analyses that identified PK differences between male and female subjects

Racial or Ethnic Groups Subheading

- Present description and results of studies/analyses that identified PK differences among race/ethnicity groups

12.3 Pharmacokinetics (PK)

Patients with Renal Impairment Subheading

- Present studies/analyses that identified PK differences in subjects with varying degrees of renal impairment relative to normal renal function
 - Include classification and how renal function was determined (e.g., Direct, C-G, MDRD)
 - Generally include mean change and variability for relevant PK exposure measures

Patients with Hepatic Impairment Subheading

- Present studies/analyses that identified PK differences in subjects with varying degrees of hepatic impairment relative to normal hepatic function
 - Include classification and how hepatic function was determined (e.g., Child-Pugh, MELD, NCI)
 - Generally include mean change and variability for relevant PK exposure measures

Pregnant Women Subheading

- Present description and results of any human data included in 8.1 Pregnancy

Specific Populations: Table



Table X: Established Clinically Relevant Drug:exposure Changes in Specific Populations		
Population Characteristic ^b	Ratio (90% CI) of Exposure Measures of Drug X ^a	
	C _{max}	AUC
CYP2D6 Metabolizer		
Poor vs. Extensive	0.8 (0.6, 1.3)	1.8 (1.2, 2.6)
Sex		
Female vs. Male	1.3 (1.2, 1.4)	1.4 (1.1, 1.7)
Renal Impairment^{c,d}		
Mild vs. Normal	1.2 (1.1, 1.3)	1.5 (1.4, 1.8)
Moderate vs. Normal	1.4 (1.2, 1.6)	2.1 (1.7, 2.6)
Severe vs. Normal	1.5 (1.3, 1.8)	2.7 (1.9, 3.6)

^a [see DOSAGE AND ADMINISTRATION (2.1) and USE IN SPECIFIC POPULATIONS (8)].

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

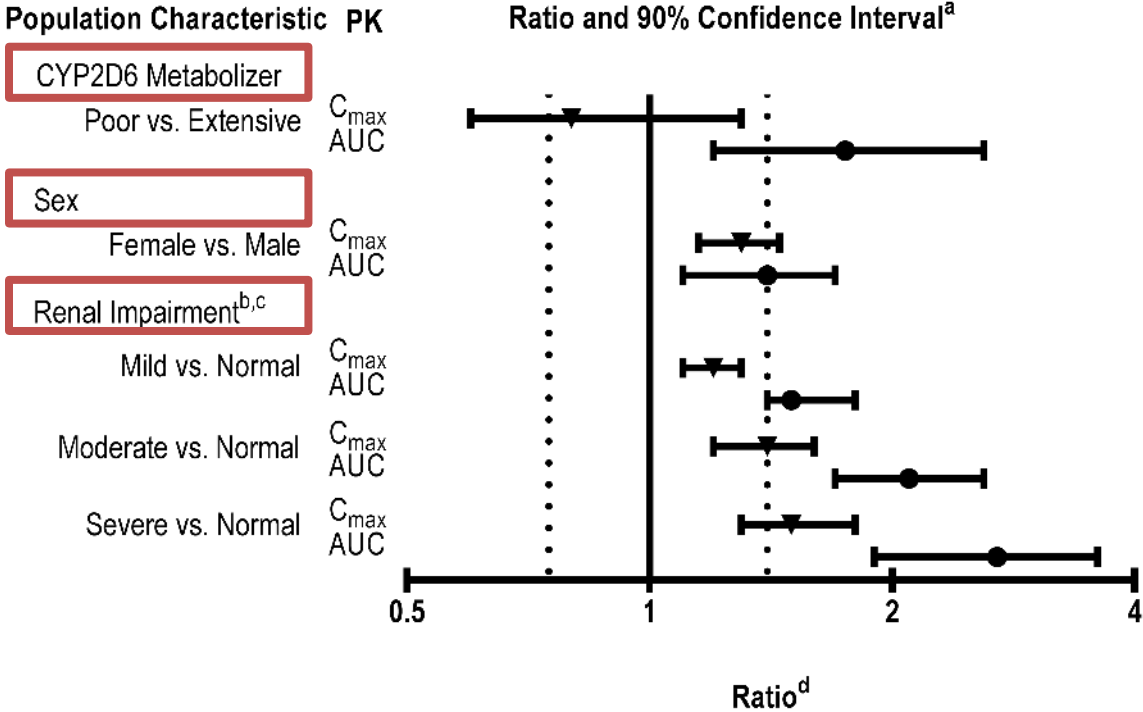
^c Degree of renal impairment was determined by Cockcroft-Gault calculated creatinine clearance (CL_{cr}); normal (CL_{cr} ≥ 90 mL/min), mild (CL_{cr} 60-89 mL/min), moderate (CL_{cr} 30-59 mL/min), and severe (CL_{cr} 15-29 mL/min).

^d End stage renal disease (CL_{cr} < 15 mL/min) with or without hemodialysis was not studied.

No clinically significant changes in Drug X exposure were associated with the following population characteristics: mild to severe hepatic impairment (Child-Pugh A to C), age (18-79 years), and race (Asian and Caucasian). The pharmacokinetics of Drug X in pediatric patients is unknown.

Specific Populations: Figure

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)*].

^b Degree of renal impairment was determined by Cockcroft-Gault calculated creatinine clearance (CLcr); normal (CLcr ≥ 90 mL/min), mild (CLcr 60-89 mL/min), moderate (CLcr 30-59 mL/min), and severe (CLcr 15-29 mL/min).

^c End stage renal disease (CLcr < 15 mL/min) with or without hemodialysis was not studied.

^d Log base 2 scale

No clinically significant changes in Drug X exposure were associated with the following population characteristics: mild to severe hepatic impairment (Child-Pugh A to C), age (18-79 years), and race (Asian and Caucasian). The pharmacokinetics of Drug X in pediatric patients is unknown.

12.3 Pharmacokinetics (PK)

Drug Interaction Studies Heading

- Briefly describe both positive and pertinent negative results of drug interactions studies
 - Include listing of studied drugs where no clinically relevant interaction was observed
 - Generally include mean change and variability for relevant PK exposure measures
- Do not repeat specific actionable instructions included in DRUG INTERACTIONS section

Drug Interaction Studies: Text



Preferred Example:

12.3 Pharmacokinetics

Drug Interaction Studies

Strong CYP3A Inhibitors: Coadministration with ketoconazole (strong CYP3A inhibitor) increased drugoxide C_{\max} by 1.3-fold and AUC by 2-fold, *[see Dosage and Administration (2.x) and Drug Interactions (7.x)]*.

Non-Preferred Example:

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 C_{\max} and AUC of drugoxide by 1.3 and 2-fold, ~~respectively~~, compared to when drugoxide was given alone in ~~14 healthy volunteers~~. T_{\max} was unchanged. ~~A reduced starting dosage is recommended~~ *[see Dosage and Administration (2.x) and Drug Interactions (7.x)]*.

Drug Interaction Studies: Table



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	
		C _{max}	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]

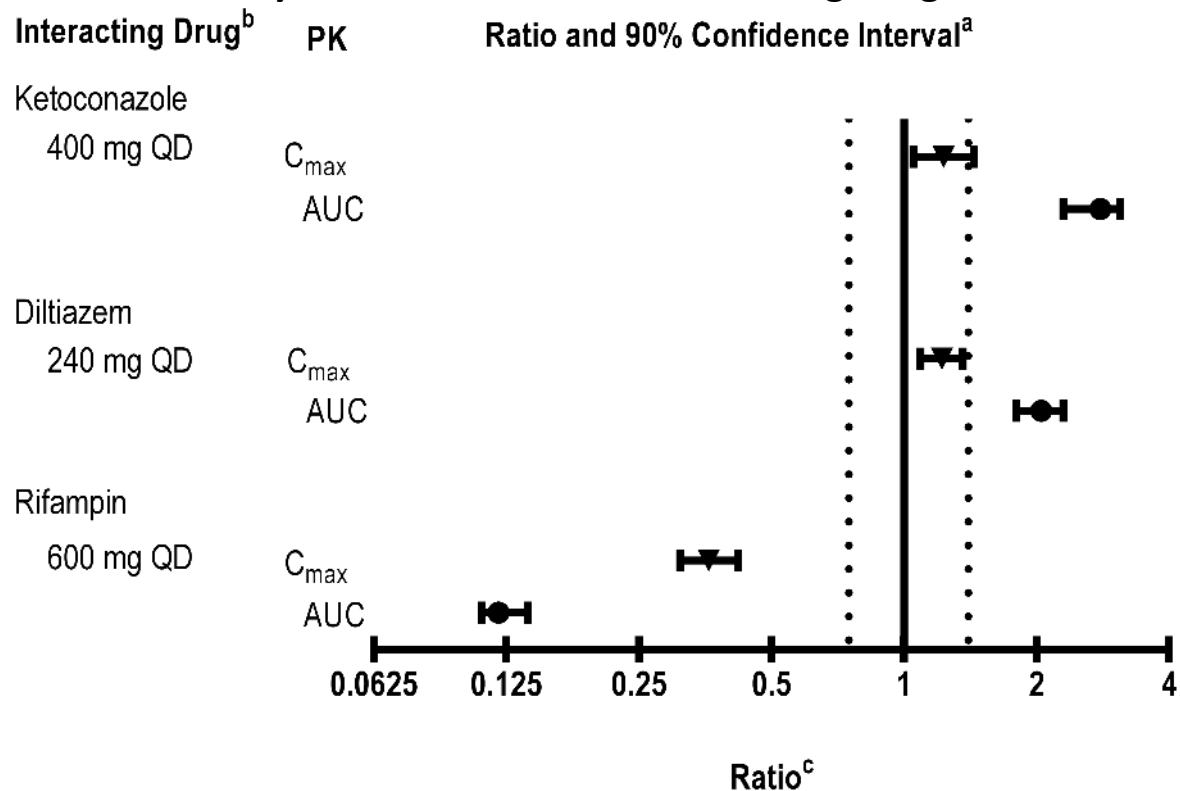
^a [see Dosage and Administration (2.x) and Drug Interactions (7)]

No clinically significant changes in exposure were observed for drugoxide when coadministered with Drug A, Drug B, or Drug C.

Drug Interaction Studies: Figure



Table X. Established Clinically Relevant Interactions Affecting Drug X



^a Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations [see *Dosage and Administration (2.x) and Drug Interactions (7)*].

^b Drug X 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 Drug A, Drug B, or Drug C.

Summary Highlights

GENERAL

- Clarity for HCP without CP expertise
- How to include unapproved dosages
- Consistency of units
- Use of measures of dispersion
- Acceptability of text, tables, & figures
- Description of racemate & effects of additives
- Guidelines for creating subsections
- Relevant component information only for fixed dose combination drugs

MOA

- For approved indications &/or significant safety issues
- No speculation of untested MOAs
- Relevant animal and in vitro information, if needed

PHARMACODYNAMICS

- Biochemical or physiologic pharmacologic effect
- Effects on relevant PD biomarkers or clinical measures
- Exposure-response (E-R) & exposure-safety (E-S) relationships
- Lack of relevant PD, E-R, or E-S data
- Information supporting clinical impact of therapeutic drug monitoring (TDM) or anti-product antibody (APA) formation
- PD-specific drug interactions or patient characteristic effects
- Effect on QT interval & E-R
- Standard language for no QT effect

PHARMACOKINETICS

- General PK before headings
- Revised format for elimination, metabolism & excretion
- No “bioequivalence” or comparative PK data
- Rate & extent of absorption & factors affecting it
- Absorption for different injection or application sites
- Distribution & binding
- Effective half-life ($t_{1/2}$), clearance (CL) & contributions to CL
- Dosage associated with nonlinear $t_{1/2}$
- Biotransformation & excretion pathways
- Active metabolite-to-parent exposure ratio & potency

SPECIFIC POPULATIONS

- Brief description of studies and results for clinically significant PK differences in subpopulations
- Consolidated list of nonsignificant PK differences
- Revised subpopulation subheadings
- Determination of organ function (e.g., Cockcroft-Gault CL_{cr})
- Revisions per PLLR

DDI STUDIES

- Brief description of studies and results for clinically significant PK differences for DDI
- Consolidated list of nonsignificant PK differences
- No repetition of actionable instructions

Conclusions

- Communicate essential and accurate information for HCP to safely and effectively prescribe drugs
- Present clinical pharmacology information in a consistent manner that adheres to regulations and guidances
- Consider using alternative methods to enhance readability and clarity

Information For Industry

Click for:

- [Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format](#)
- [Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers](#)
- [PLR Requirements for Prescribing Information](#)
- [Drugs@FDA: FDA Approved Drug Products](#)
- [PDF of today's slides](#)
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