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U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

A Recipe for Clinical Pharmacology Information in Labeling That is Easy to Digest

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- The views and opinions expressed in this presentation represent those of the presenter, and do not necessarily represent an official FDA position.
- The labeling examples in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates.
- Reference to any marketed products is for illustrative purposes only and does not constitute endorsement by the FDA.

Learning Objectives

- Describe stakeholder experiences regarding clinical pharmacology-related information in labeling
- Provide an overview of key labeling regulations for the CLINICAL PHARMACOLOGY and DRUG INTERACTIONS sections of labeling
- List strategies to enhance the development of clinical pharmacology information in labeling
- Explore different labeling formats (e.g., tables, figures, structured text) to further enhance the presentation of clinical pharmacology information in labeling

Clinical Pharmacology Labeling Footprint

HIGHLIGHTS OF PRESCRIBING INFORMATION

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.

Note: Other sections/subsections of Prescribing Information may also contain clinical pharmacology information

Clinical Pharmacology Labeling Initiative

Key US Prescribing Information Regulations

DRUG INTERACTIONS Section[a]

- Must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice)
  - Should include the clinical implication(s) of the drug interaction[b]
- Must contain specific practical instructions for preventing or managing them.
- The mechanism(s) of the interaction, if known, must be briefly described.
- This section must also contain practical guidance on known interference of the drug with laboratory tests

CLINICAL PHARMACOLOGY Section[a]

- Must summarize what is known about the established mechanism(s) of the drug's action in humans or contain a statement about the lack of information.
- Must include a description of any biochemical or physiologic pharmacologic effects of the drug or active metabolites related to the drug's clinical effect, adverse effects or toxicity.
- Must be included exposure-response relationships and time course of pharmacodynamic response or a statement about the lack of information.
- Must describe the clinically significant pharmacokinetics of a drug or active metabolites
- Must include the results of pertinent human or in vitro pharmacokinetic studies that establish the absence of an effect.

[a] 21 CFR 201.57

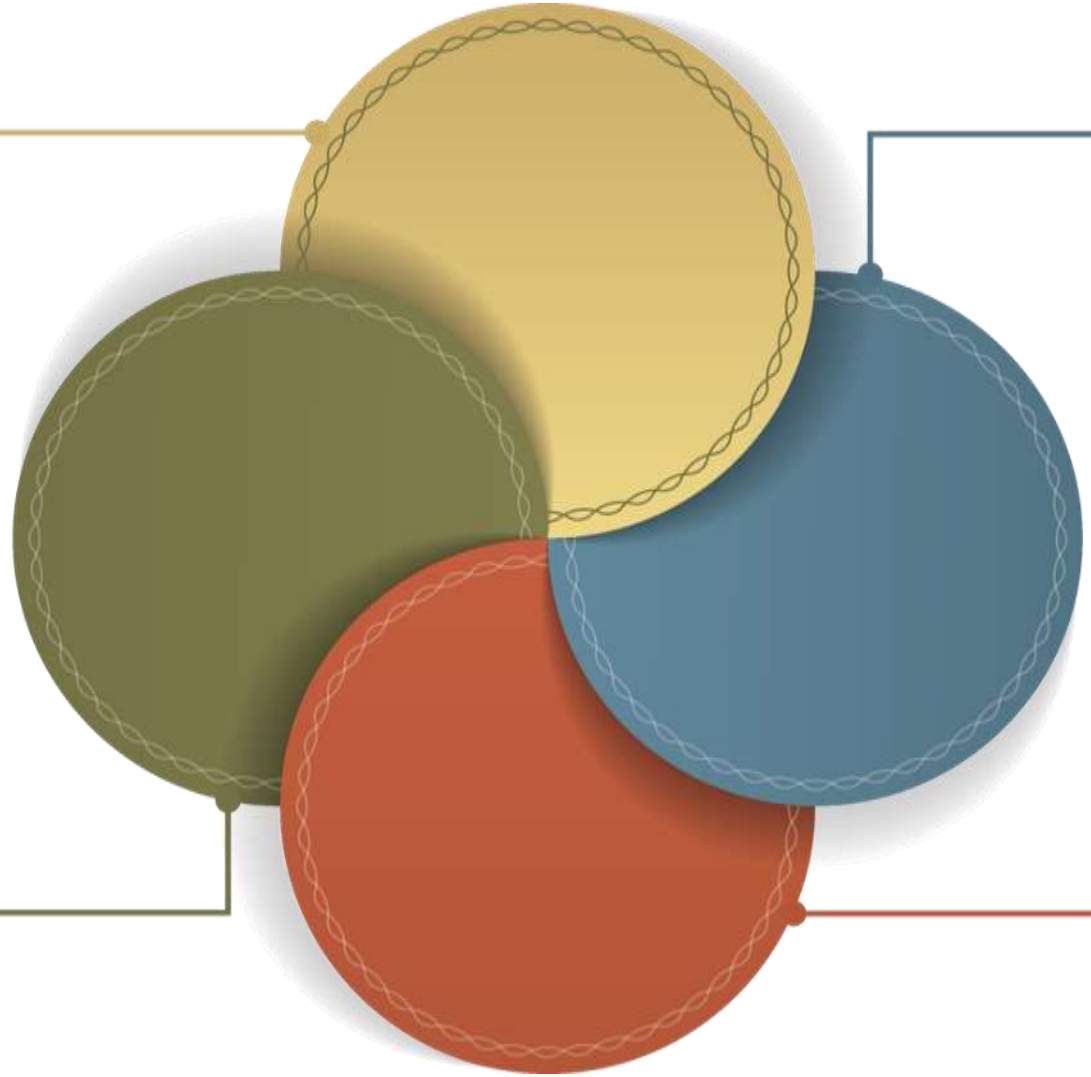
[b] Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications (draft guidance)

HCP Perception of Prescribing Information

What's Wrong?	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

Strategies to Enhance Clinical Pharmacology Labeling Development

Cross Referencing Reduces Redundancy



Significance, mechanism, and recommendations

Details that support regulatory conclusions and recommendations

Specific dosage modification recommendations

Significant safety and/or efficacy concerns

Clinical Significance

- Is the information essential for the safe and effective prescribing of the drug?
- Does it provide clinically important context for essential information in a cross-referenced section?
- Can non essential contextual information be omitted?

- Detailed PK results from NHV and patients
- Detailed PK results from unapproved dosage forms[a]
- Plasma and whole blood distribution
- Multiple volumes of distribution
- Inactive metabolite data

NHV = Normal healthy volunteers

[a] Unapproved indications, uses, and dosages must not be implied or suggested [see 21 CFR 201.57(c)(2)(iv and v) and 21 CFR 201.57(c)(3)(ii)]

Drug Interactions: CLINICAL PHARMACOLOGY Section

Preferred Example:

12.3 Pharmacokinetics

Drug Interaction Studies

Strong CYP3A Inhibitors: Coadministration with a strong CYP3A inhibitor (ketoconazole) 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:

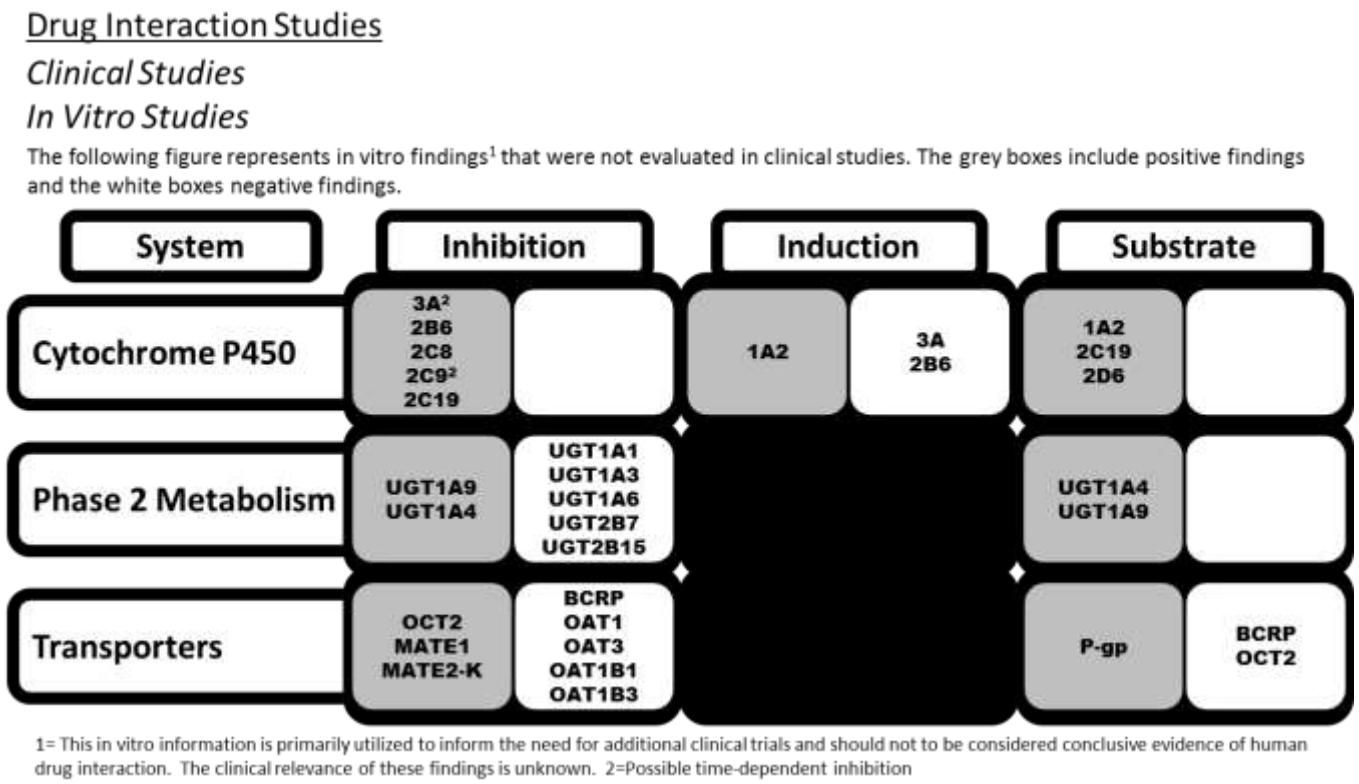
12.3 Pharmacokinetics

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)]*.

Is In Vitro Information Useful?

- Establish the absence of a DDI effect
- Characterize protein binding, DDI potential, metabolic and transporter pathways in the absence of clinical information
- In vitro information may be included in addition to in vivo if essential to understanding the clinical results
- Generally in *Pharmacokinetics* subsection of CLINICAL PHARMACOLOGY section
  - Rarely in DRUG INTERACTIONS section unless clinically important



Modeling and Simulation

- Pharmacokinetics subsection in the CLINICAL PHARMACOLOGY section includes majority of quantitative information from modeling and simulation
  - Include concise description of results of PBPK approaches conducted if they are clinically important and informative
  - Should also include model design information that may inform prescribing decisions, if necessary
    - Rationale for including additional contextual information should be clear
  - Generally, if quantitative PBPK information is deemed sufficient to inform a regulatory decision in place of a dedicated clinical study, then an explicit statement that information is based upon a specific analysis is not needed

21 CFR 201.56; Federal Register 71 (1/24/2006); Guidance: *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*; and Draft Guidance: *Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications*

Technical Language

- Can this information be described in a simpler way?
- Is additional information to explain the impact on safe and effective prescribing needed?
- Can this be understood by a healthcare provider who is not a clinical pharmacologist?
- Is the intended interpretation/ action clinically intuitive from the information proposed?

- "Drug X showed time-dependent PK with a 13% decrease in steady state clearance…"
- "Increasing the Drug X dose from 50 to 150 mg once daily resulted in a slightly less than proportional increase in drugoxide steady-state Cmax and AUC…"
- "Drugoxide is an inhibitor of the BCRP and P-gp efflux transporters with IC_{50} values of 50 µM and 273 µM…"

Clarity, Readability, and Utility

- Use active voice
- Provide sufficient detail to inform prescribing decisions
  - Actions should be clear and specific
  - Clinically significant information should be clearly identified
  - Avoid redundancy between labeling sections
  - Brevity encouraged
- Avoid vague recommendations such as “monitor closely” or “use with caution” that are not clinically “value added”
- Use white space, text attributes (bolding, bulleted lists, etc.)
- Use tables and figures where appropriate to enhance readability, clarity, and utility of complex or dense content

DRUG INTERACTIONS Section as Text

No Enhancements Used

7 DRUG INTERACTIONS

Drugoxide undergoes metabolism by CYP3A. Use with a strong CYP3A inhibitor will increase drugoxide exposure (i.e., C_{max} and AUC) resulting in an increased syncope risk. Reduce the dosage of Drug X when coadministered with strong CYP3A inhibitors (e.g., clarithromycin, cobicistat, conivaptan, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, and voriconazole.) *[see Dosage and Administration (2.x), Warnings and Precautions (5.x) and Clinical Pharmacology (12.3)]*.

DRUG INTERACTIONS Section as Text

Enhancements Used

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Drug X

Strong CYP3A Inhibitors

Reduce Drug X dosage when using concomitantly with strong CYP3A inhibitors *[see Dosage and Administration (2.x)]*.

Drugoxide undergoes metabolism by CYP3A. Concomitant use with a strong CYP3A inhibitor increases drugoxide C_{max} and AUC which may increase syncope risk *[see Warnings and Precautions (5.x) and Clinical Pharmacology (12.3)]*.

The following are some examples of strong CYP3A inhibitors: clarithromycin, cobicistat, conivaptan, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, and voriconazole.

DRUG INTERACTIONS Section Alternative Displays

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on DRUG X

Table X. Effect of Other Drugs on DRUG X

Strong CYP3A Inhibitors[a]	
Clinical Impact	Concomitant use with a strong CYP3A inhibitor increases drugoxide AUC *[see Clinical Pharmacology (12.3)]* which may increase the risk of DRUG X toxicities.
Prevention or Management	Reduce DRUG X dosage when used concomitantly with a strong CYP3A inhibitor *[see Dosage and Administration (2.x)]*.
Examples[b]	clarithromycin, cobicistat, conivaptan, elvitegravir and ritonavir, grapefruit juice[c], idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, and voriconazole
Strong CYP3A Inducers[d]	
Clinical Impact	Concomitant use with a strong CYP3A inducer decreases drugoxide AUC *[see Clinical Pharmacology (12.3)]* which may reduce DRUG X efficacy.
Prevention or Management	Avoid concomitant use with a strong CYP3A inducer.
Examples[b]	Carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort[e]

[a] Strong inhibitors increase the AUC of sensitive index substrates of a given metabolic pathway ≥ 5-fold.
[b] These examples are a guide and not considered a comprehensive list of all possible drugs that may fit this category. The healthcare provider should consult appropriate references for comprehensive information.
[c] The effect of grapefruit juice on CYP3A4 enzymes (e.g., strong vs. moderate inhibition) depends on its brand, concentration, and preparation.
[d] Strong inducers decrease the AUC of sensitive index substrates of a given metabolic pathway by ≥5-fold.
[e] The induction potency of St. John's wort may vary widely based on preparation.

DRUG INTERACTIONS Section Alternative Displays

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)]*

Clinical Pharmacology Section Alternative Displays

Table x. Pharmacokinetic Parameters of Drugoxide and Its Metabolites

General Information[a,b]				
Drugoxide exposure		**C_{max}**	**AUC**	**CV**
	Single dose	3.5 mcg/mL (1.5 to 5.3)	80.4 mcg*h/mL (48.9 to 125.7)	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)	• 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) 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	• 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[h]				
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]			

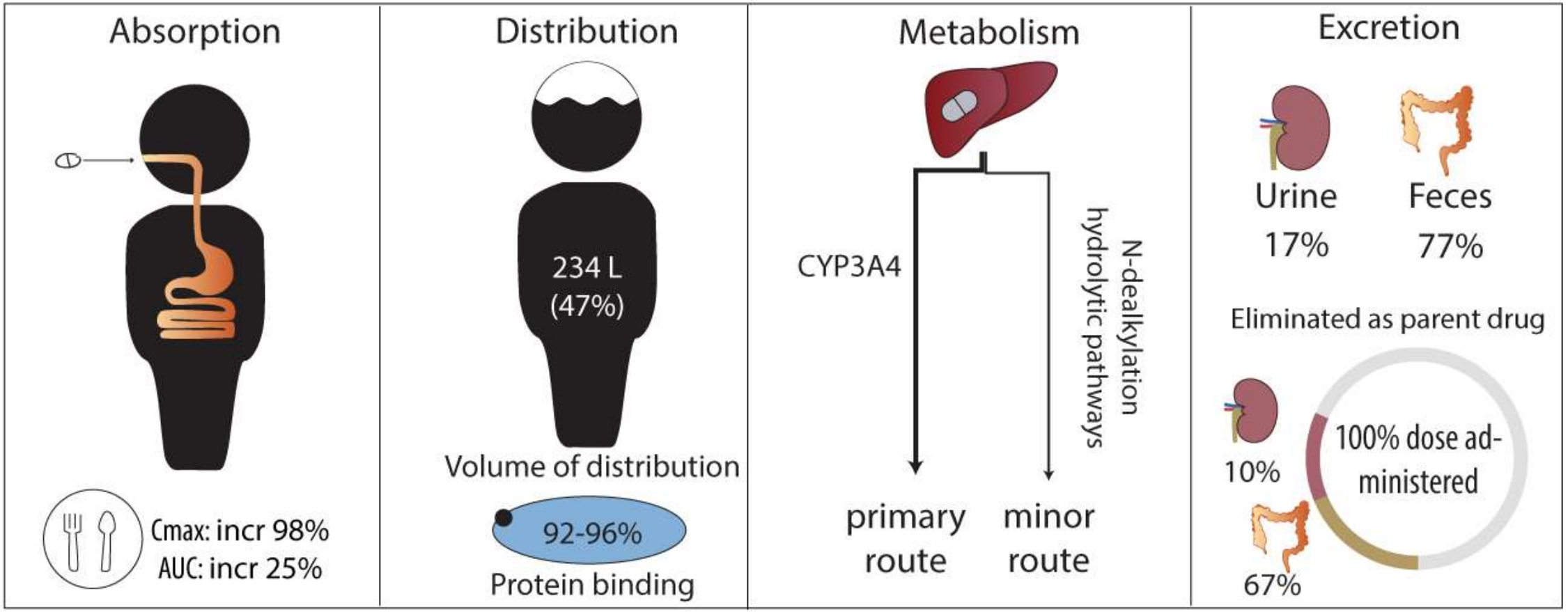
[a] The pharmacokinetics of drugoxide and its active metabolites were characterized in patients following a single dose of 100 mg Drug X after a light breakfast (e.g., a bowl of cereal with full fat milk or 2 slices of bread with cheese) unless otherwise specified
[b] Pharmacokinetic parameters are presented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

Clinical Pharmacology Section Alternative Displays

	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

PK Parameters as a Figure?



Courtesy Giang Ho, LHC ORISE Fellow

Clinical Pharmacology Section Alternative Displays

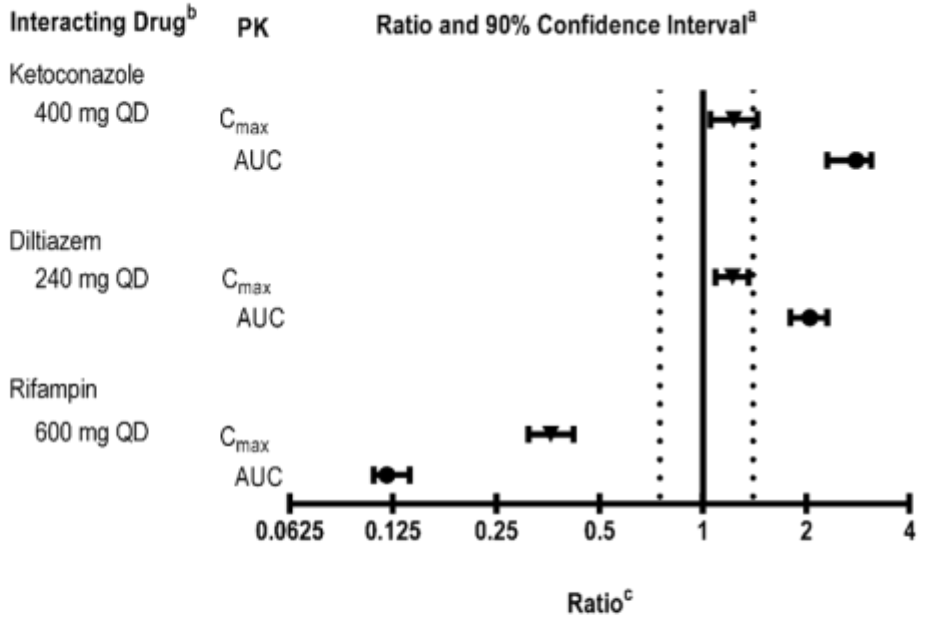
Table X. Clinically Significant Interactions Affecting Drugoxide			
Concomitant Drug (Dosage)	**Drugoxide Dosage**	**Ratio (90% CI) of Exposure Measures of Drugoxide Combination/No Combination [minimum to maximum][a]**	
		C_{max}	**AUC**
Ketoconazole (400 mg once daily)	60 mg single dose	1.2 (1.1, 1.4) [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.

Clinical Pharmacology Section Alternative Displays

Table X. Clinically Significant Interactions Affecting Drugoxide



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

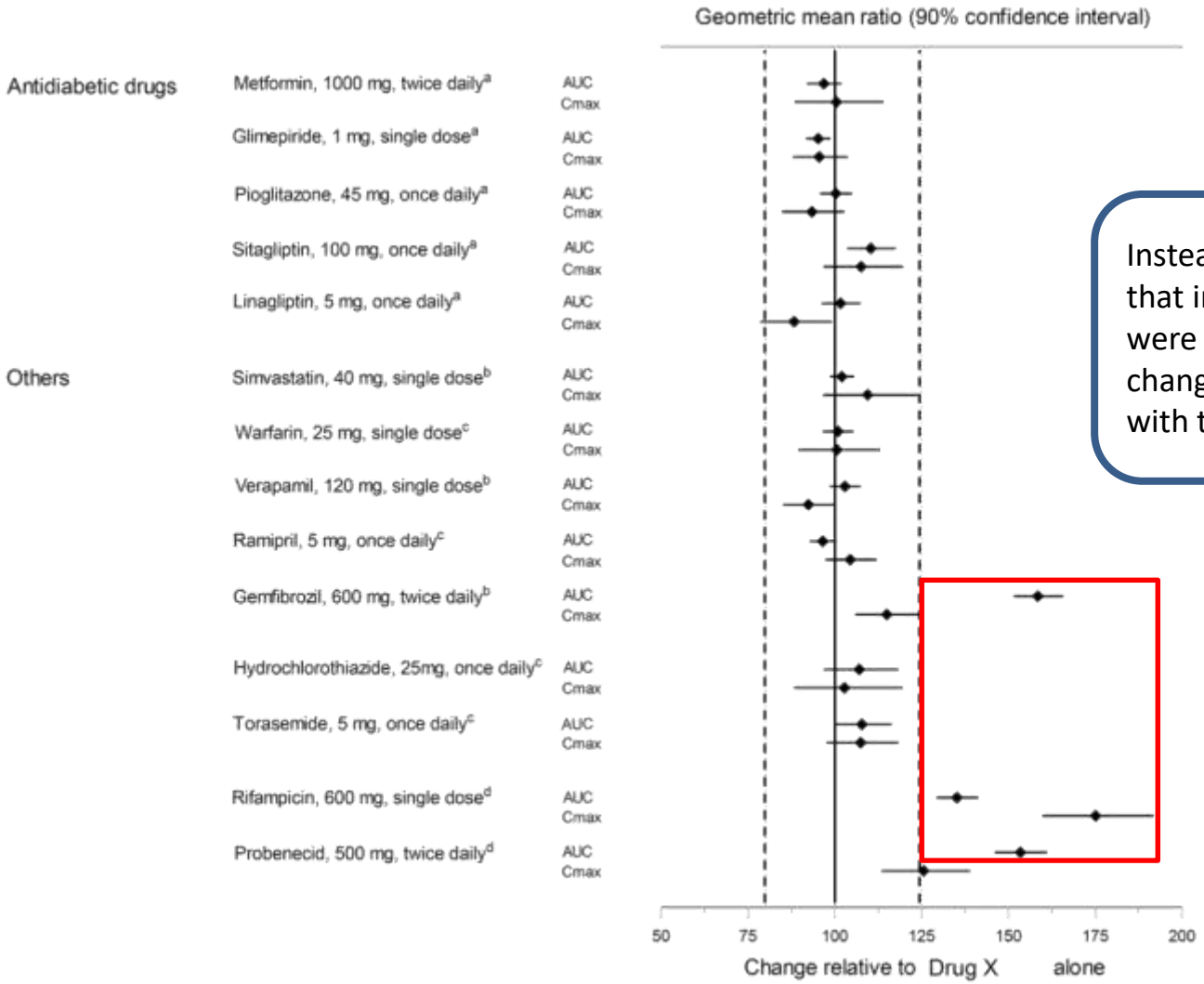
[b] Drug X administered as a 60 mg single dose.

[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.

Are 90% CI essential for safe effective prescribing?

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



[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

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

DOSAGE & ADMINISTRATION Section Alternative Displays

2 DOSAGE AND ADMINISTRATION

2.3 Dose Modification for Use with a Moderate CYP3A4 Inhibitor

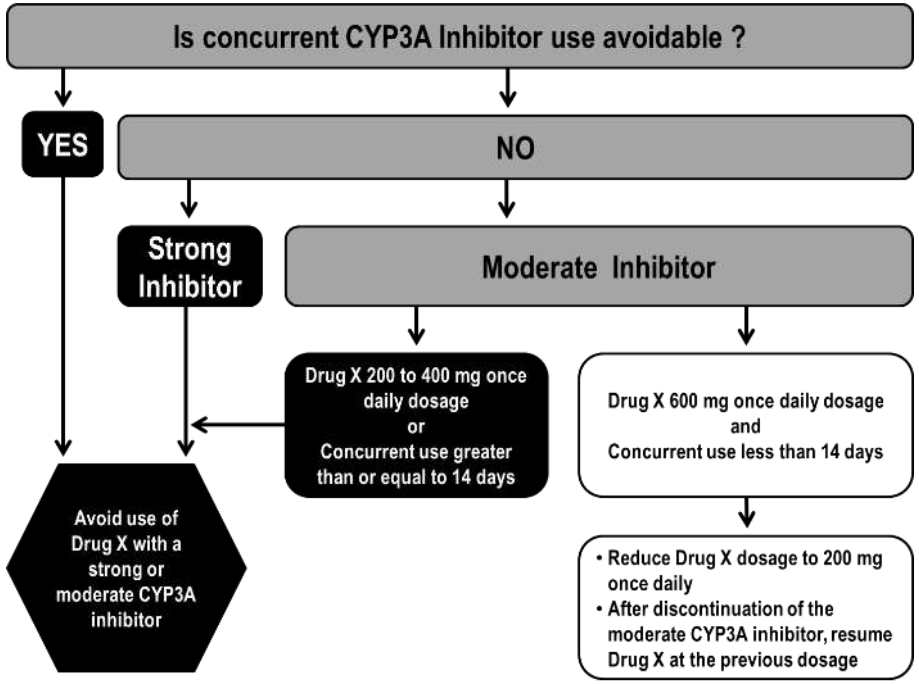
Avoid concurrent use of Drug X with moderate CYP3A inhibitors.

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 CYP3A4 Inhibitor

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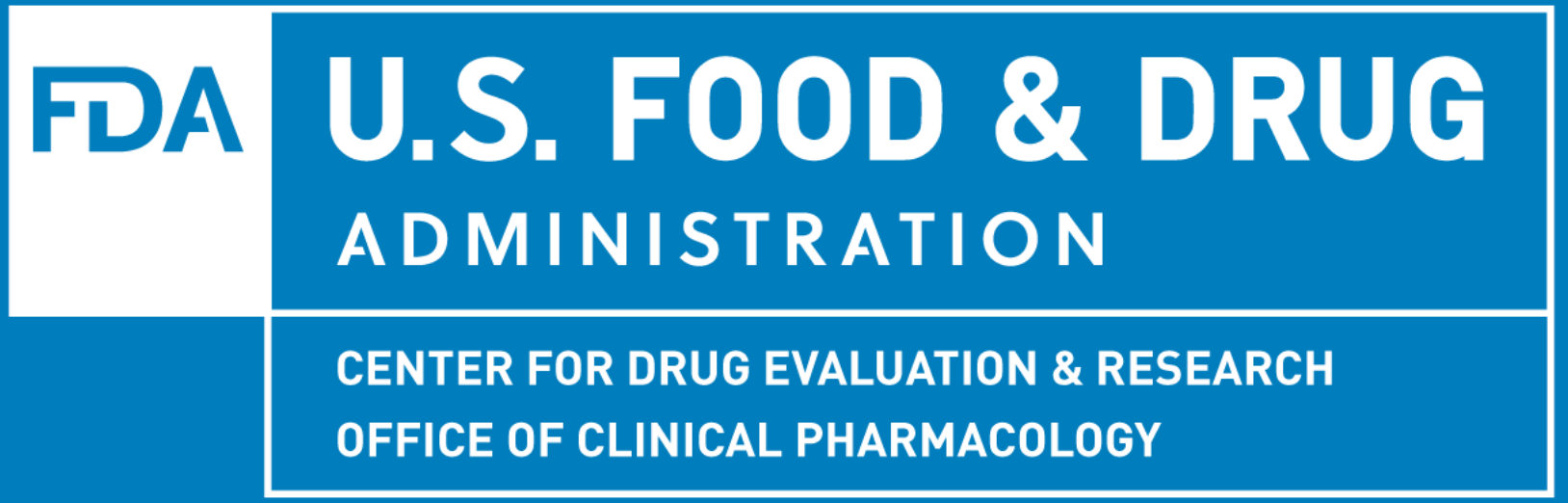
Question : The preferred format for drug-drug interaction information in subsection 12.3 Pharmacokinetics of the Prescribing Information is:

a. Text
b. Tabular
c. Figure or graphic
d. a&b
e. No preferred format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