Center for Drug Evaluation and Research
Small Business and Industry Assistance
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Part 1 of 2: Drug Interaction Information in the U.S. Prescribing Information



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Disclaimer

- The views and opinions expressed in these presentations represent those of the presenters, and do not necessarily represent an official FDA position.
- The labeling examples in these presentations are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates.

Drug Interactions Are a Significant Cause of Hospital Admissions Because of an Adverse Reaction

In a meta-analysis of 13 observational studies the median clinically significant drug interaction (DI) prevalence rates were:[1]

- 1% for patients admitted to the hospital for any reason
- 22% (308 DI cases/1,683 patients) for patients admitted to the hospital because of an adverse reaction to a drug

[1] Dechanont S, Maphanta S, Butthum B, Kongkaew C. *Hospital admissions/visits associated with drug-drug interactions: a systematic review and meta-analysis.* Pharmacoepidemiol Drug Saf. 2014;23(5):489-497. doi:10.1002/pds.3592. In these studies, medical records, interviews, drug interaction screening programs, adverse reaction reports, and electronic medical records were identified as methods used for detecting DIs.

70 Physicians in Qualitative Study:[1] DRUG INTERACTIONS Section Is One of the "Most Useful" Sections of Labeling

70 physicians discussed preferences and understanding of certain information in the U.S. Prescribing Information. Most useful sections:

- DOSAGE AND ADMINSTRATION (76%)
- **DRUG INTERACTIONS (57%)**
- INDICATIONS AND USAGE (56%)
- CONTRAINDICATIONS (56%)
- ADVERSE REACTIONS (53%)

[1] Sullivan, H.W., Squire, C., Aikin, K.J., Tzeng, J., Ferriola-Bruckenstein, K., Brodsky, E., Trentacosti, A.M., & Johnson, M. (in press). *Physicians' use of and preferences for FDA-approved prescribing information. Research in Social and Administrative Pharmacy*. Available at https://www.sciencedirect.com/science/article/pii/S1551741121002862?via%3Dihub

Drug Interaction Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology at 301-796-5008 or CDER_OCP_GPT@fda.hhs.gov, or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010 or ocod@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Labeling

OVERVIEW: DRUG INTERACTIONS Section

Information about clinically significant drug interactions should be communicated in the DRUG INTERACTIONS section in a manner that is understandable and clinically informative to health care providers, including those with limited clinical pharmacology expertise.

Organization and Format in the DRUG INTERACTIONS Section

- A typical approach to including pharmacokinetic-based DIs is to distribute the information in the following subsections, as appropriate:

  7.1 Effects of Other Drugs on DRUG-A or
  7.2 Effects of DRUG-A on Other Drugs

- If DRUG-A is affected by and has an effect on the concomitant drug, DI information should be included under both subsections

- If there is a DI table, a descriptive statement preceding the table should be included (e.g., “Table X describes clinically significant DIs where concomitant use of another drug affects DRUG-A.”)

DIs = drug interactions

Key DI Elements in the DRUG INTERACTIONS Section

Must describe clinically significant DIs, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods[1]

1. Must include specific practical instructions for preventing or managing clinically significant DIs[1]
2. Must briefly describe the mechanism of clinically significant DIs, if known[1]
3. Should include the clinical effects of clinically significant DIs

DIs = drug interactions

[1] 21 CFR 201.57(c)(8)(i).

Instructions for Preventing or Managing DIs:

DRUG INTERACTIONS Section

Instructions for Preventing or Managing DIs in DRUG INTERACTIONS Section

- Must be accurate,[1] specific,[2] and practical[2] and should be actionable for the health care practitioner
- Avoid vague or ambiguous statements (e.g., “use with caution”, “adjust dosage”)

[1] 21 CFR 201.56(a)(2).
[2] 21 CFR 201.57(c)(8)(i).

Preventing or Managing DIs in DRUG INTERACTIONS Section (1 of 2)

- Contraindicating concomitant use:

  "Concomitant use of DRUG-A with drug-b is contraindicated"

- Concomitant use is generally inadvisable but does not rise to the level of a contraindication:

  "Avoid concomitant use of DRUG-A with drug-b"

- When concomitant use is generally inadvisable but is unavoidable, consider providing recommendation(s) for actionable measures that can be taken to prevent or manage the DI:

  "Avoid concomitant use of DRUG-A with drug-b. If concomitant use is unavoidable, obtain ECGs prior to initiating, during concomitant use, and additionally as clinically indicated"

Preventing or Managing DIs in DRUG INTERACTIONS Section (2 of 2)

- Temporarily discontinuing one of the interacting drugs.
- Provide specific monitoring strategies when concomitant use necessitates additional or increased frequency of monitoring:

  "Monitor liver enzymes weekly for the first four weeks and then monthly when DRUG-A is used concomitantly with drug-b *[see Warnings and Precautions (5.x)]*"

Dosage Modification Information in the DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS Sections

2 DOSAGE AND ADMINISTRATION

...

Reduce the dosage of DRUG-A from 200 mg once daily to 100 mg once daily when used concomitantly with a strong CYP3A inhibitor *[see Drug Interactions (7.x)].*

...

7 DRUG INTERACTIONS

...

Reduce the dosage of DRUG-A when used concomitantly with a strong CYP3A inhibitor *[see Dosage and Administration (2.x)].*

Mechanism of the Clinically Significant DIs:

DRUG INTERACTIONS Section

Mechanism of the Clinically Significant DIs in DRUG INTERACTIONS Section: PK-Based Interactions

For cytochrome P450 and transporter-based DIs:

- Subject drug should be identified as an inhibitor, inducer, or substrate.
- Change in drug exposure should be briefly summarized (e.g., increases drug-a exposure, decreases drug-a exposure), with a cross-reference to the supporting DI information in the *Pharmacokinetics* subsection:

7 DRUG INTERACTIONS

… drug-a is a CYP3A sensitive substrate. Concomitant use of DRUG-A with strong CYP3A inhibitors increase drug-a exposure *[see Clinical Pharmacology (12.3)]*.

PK = pharmacokinetic; DI = drug interaction

Clinical Effects of the Clinically Significant DIs: DRUG INTERACTIONS Section

Clinical Effects of the Clinically Significant DI in DRUG INTERACTIONS Section (1 of 3)

Describing the changes in PK and PD parameters alone is generally insufficient to communicate the clinical effects of a DI on the safety or effectiveness of the drug

PK = pharmacokinetic; PD = pharmacodynamic; DI = drug interaction

Clinical Effects of the Clinically Significant DI in DRUG INTERACTIONS Section (2 of 3)

When data are sufficient to support a clinical effect statement in specific terms, the description of the clinical effects should be specific:

7 DRUG INTERACTIONS

… The concomitant use of DRUG-A with drug-b may increase the risk of bleeding *[see Warnings and Precautions (5.x)].”*

Clinical Effects of the Clinically Significant DI in DRUG INTERACTIONS Section (3 of 3)

When data are not sufficient to support a clinical effect statement in specific terms, the clinical effects should generally be described in broad terms:

7 DRUG INTERACTIONS

… The concomitant use of DRUG-A with drug-b may increase the risk of DRUG-A-associated adverse reactions.

7 DRUG INTERACTIONS

… The concomitant use of DRUG-A with drug-b may reduce effectiveness of DRUG-A.

Drug Interacting Class:
DRUG INTERACTIONS Section

Drug Interacting Class Definition

- A *drug interacting class* is a group of drugs and/or foods that all share a specific characteristic that is relevant to a clinically significant DI
- The shared characteristic that identifies the drug interacting class is often unrelated to the drug's therapeutic class (e.g., strong CYP2C19 inhibitor drug interacting class includes fluconazole, fluoxetine, and ticlopidine).

Name the Drug Interacting Class But Avoid the Drug Names in DRUG INTERACTIONS Section[1]

When there are clinically significant drug interactions of the subject drug with all drugs within a drug interacting class:

- Identify only the drug interacting class, and
- Avoid naming the drugs within the drug interacting class

[1] See the next slide for the exception

Exception: Name Class of Drugs and Individual Drugs in DRUG INTERACTIONS Section

If concomitant use of the subject drug (DRUG-A) with drugs within an interacting drug class (e.g., drug-b, drug-c, drug-d) has different clinical effects or prevention and management instructions, name both the:

- Drug interacting class, and
- Individual drugs within the drug interacting class with their clinical effects and prevention and management instructions:
  - Concomitant use of DRUG-A with drug-b is contraindicated
  - Avoid concomitant use of DRUG-A with drug-c
  - Reduce the DRUG-A dosage when used concomitantly with drug-d)

Only Name Individual Drugs But Avoid Class Name in DRUG INTERACTIONS Section

If some, but not all, of the drugs in a class have a clinically significant interaction with the subject drug, then:

- Only name the individual drugs with the clinically significant interaction
- Avoid naming other drugs without the clinically significant interaction
- Avoid naming the drug class

Content to Avoid in DRUG INTERACTIONS Section

Content to Avoid in DRUG INTERACTIONS Section (1 of 2)

- The DRUG INTERACTIONS section must not repeat details of DI pharmacokinetic studies that are included in the CLINICAL PHARMACOLOGY section[1]

- Generally, DRUG INTERACTIONS section should not describe DIs that are not clinically significant, unless it is important to communicate the absence of a clinically significant DI

DI = drug interaction; [1] See 21 CFR 201.57(c)(8)(i)

Content to Avoid in DRUG INTERACTIONS Section (2 of 2)

- Reduction of immunological response to a vaccine by an immunosuppressive drug is not considered a true DI:
  - Generally, include this information in the W&P section and the *Pharmacodynamics* subsection instead of the DRUG INTERACTIONS section

- Drug incompatibilities[1] are not considered DIs:
  - Therefore, this information should not appear in the DRUG INTERACTIONS section.

DI = drug interaction

[1] For example, unwanted physical and chemical reactions that occur between two or more drugs or between a drug and a diluent when combined in the same container

Example 1: Content to Avoid in DRUG INTERACTIONS Section

7 DRUG INTERACTIONS

~~No formal drug interaction studies have been conducted with DRUG-A.~~

Example 2: Content to Avoid in DRUG INTERACTIONS Section

7 DRUG INTERACTIONS

~~Exercise caution~~ ~~with~~ ~~coadministration~~ ~~with strong CYP3A inhibitors~~ ~~because the~~ ~~plasma concentrations of DRUG-A were increased.~~

Avoid concomitant use of DRUG-A with strong CYP3A inhibitors. Drug-a is a CYP3A4 substrate. Strong CYP3A inhibitors increase drug-a exposure *[see Clinical Pharmacology (12.3)]*, **which may increase the risk of DRUG-A associated adverse reactions.**

Blue: prevention and management of clinically significant DI
Purple: coadministration vs. concomitant
Green: include the subject drug and the other drug
Red: mechanism of clinically significant DI
Gray: clinical effects of clinically significant DI

Drug Interaction Information in Other Sections of Labeling

DI Information in BOXED WARNING Section

FDA may require a boxed warning for certain contraindications or serious warnings, particularly those that may lead to death or serious injury, resulting from a DI[1]

WARNING: SIGNIFICANT DRUG INTERACTIONS WITH CONCOMITANT USE OF DRUG-A WITH A CYP3A SENSITIVE SUBSTRATE OR A STRONG CYP3A INDUCER

- **Prior to prescribing DRUG-A, a strong CYP3A inhibitor, assess the potential for DRUG-A to interact with each of drug(s) the patient is taking and determine if dosage interruption, dosage modification, or additional monitoring is needed *[see Warnings and Precautions (5.x)]*.**
- **Concomitant use of DRUG-A with a *[see Warnings and Precautions (5.x)]*:**
  - **CYP3A sensitive substrate may result in life-threatening or fatal CYP3A sensitive substrate-related adverse reactions.**
  - **Strong CYP3A inducer may result in loss of therapeutic effect of DRUG-A, possibly leading to development of viral resistance.**

[1] 21 CFR 201.57(c)(1).

Dosage or Administration Modifications for DI in DOSAGE AND ADMINISTRATION Section (1 of 4)

- Include in D&A section when there is sufficient information to support specific recommendations for dosage or administration modifications of subject drug to reduce the risk of a DI[1]
- If there is not enough information to support a specific dosage or administration modification for the subject drug, the DI should ordinarily not be discussed in the D&A section

DI = drug interaction

[1] DOSAGE AND ADMINISTRATION (D&A) section must describe dosage modifications needed because of DIs; 21 CFR 201.57(c)(3)(i)(H).

Dosage or Administration Modifications for DI in D&A Section (2 of 4)

- Generally, in the D&A section do not include contraindications or statements about when concomitant use is inadvisable
- However, if dosage modification of the subject drug is recommended when it is used with a subgroup of drugs in a drug interacting class, include recommendations for use of the subject drug for the remaining subgroups in that drug interacting class for completeness

Dosage Modifications for DI in D&A Section (3 of 4)

2.x Dosage Modifications for CYP2C19 Inhibitors

Avoid concomitant use of DRUG-A with strong CYP2C19 inhibitors. Reduce the DRUG-A dosage to 100 mg once daily when used concomitantly with moderate CYP2C19 inhibitors *[see Drug Interactions (7.x)].* No dosage modification is needed for concomitant use of DRUG-A with weak CYP2C19 inhibitors.

~~Drug-a is a CYP2C19 substrate. Strong and moderate CYP2C19 inhibitors increase drug-a exposure, which may increase the risk of adverse reactions.~~

Dosage Modifications for DI in D&A Section (4 of 4)

- If there are specific dosage modifications for one drug, one drug class, or one food consider including a specific subsection title:

  2.x Dosage Modifications for CYP3A Inhibitors

- If there are specific dosage modifications for two or more drugs, drug classes, or foods, consider including the dosage modifications in one subsection with appropriate headings:

  2.x Dosage Modifications for Drug Interactions
  Dosage Modifications for CYP3A Inducers
  …
  Dosage Modifications for P-glycoprotein Inhibitors
  …

DI Information in CONTRAINDICATIONS Section

Must list drugs that are contraindicated because the risk from concomitant use with the subject drug clearly outweighs any possible therapeutic benefit[1]

4 CONTRAINDICATIONS

DRUG-A is contraindicated in patients taking strong CYP1A2 inhibitors *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)].*

[1] 21 CFR 201.57(c)(5)

DI Information in W&P Section (1 of 2)

- Generally only the most clinically significant DIs,[1] if any, should be included in the W&P section.
- W&P section should include:
  - Additional details about the clinical effects of those clinically significant DIs (e.g., severity, outcomes)
  - Brief description of prevention or management instructions
  - Cross-reference to more detailed DI information elsewhere in the labeling

DI = drug interaction

[1] For example, those that lead to treatment failure, drug resistance, or serious safety issues

DI Information in W&P Section (2 of 2)

5 WARNINGS AND PRECAUTIONS

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5.x Severe Hypotension and Syncope with Concomitant Strong CYP1A2 Inhibitors

The concomitant use of DRUG-A with strong CYP1A2 inhibitors is contraindicated *[see Drugs Interactions (7.1)]*.

In Study 1, severe hypotension or syncope requiring medical intervention occurred in 20% of patients treated concomitantly with DRUG-A and a strong CYP1A2 inhibitor compared to 2% in those treated with DRUG-A alone *[see Adverse Reactions (6.1)]*.

DI Information in *Pharmacokinetics* Subsection (1 of 4)

- Both positive and pertinent negative results from clinical studies conducted to evaluate DIs should be included under the Drug Interaction Studies heading
- If clinical DI studies have not been conducted or are inconclusive, then pertinent negative and/or positive results from in vitro DI studies should be included under the Drug Interaction Studies heading

DI Information in *Pharmacokinetics* Subsection (2 of 4)

This subsection should not include instructions to prevent or manage (or the clinical effects of) a clinically significant drug interaction:

12.3 Pharmacokinetics

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Drug Interaction Studies

Strong and Moderate CYP3A Inhibitors: Ketoconazole (strong CYP3A inhibitor) increased the (min-max) ratio of drug-a AUC by 3.9-fold (2.9-5.2) with no changes to Cmax. Fluconazole (moderate CYP3A inhibitor) increased drug-a AUC 2.1-fold (1.8-2.4) *[see Drug Interactions (7.1)].* ~~Strong or moderate CYP3A inhibitors may increase the risk of DRUG-A adverse reactions.~~

DI Is Not Clinically Significant: *Pharmacokinetics* Subsection

If positive findings are discussed under the Drug Interaction Studies heading but the findings are not clinically significant, then an additional statement about the lack of clinical significance of the findings should be included under this heading:

12.3 Pharmacokinetics

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Drug Interaction Studies

Strong CYP1A2 Inhibitors: Fluvoxamine (strong CYP1A2 inhibitor) increased the mean (min-max) ratio of drug-a AUC 1.3-fold (1.1-1.4) and Cmax 1.3-fold (1-1.5). These findings are not clinically significant.

Clinical Significance of DI Not Known: *Pharmacokinetics* Subsection (4 of 4)

If positive findings are discussed under the Drug Interaction Studies heading but the clinical significance of these findings is unknown, then an additional statement that the clinical significance of the findings is unknown should be included under this heading:

12.3 Pharmacokinetics

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Drug Interaction Studies

Strong CYP1A2 Inhibitors: Fluvoxamine (strong CYP1A2 inhibitor) increased the mean (min-max) ratio of drug-a AUC 1.3-fold (1.1-1.4) and Cmax 1.3-fold (1-1.5). The clinical significance of these findings are not known.

One of the Key Takeaways: DI Elements in the DRUG INTERACTIONS Section

Must describe clinically significant DIs, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods[1]

1. Must include specific practical instructions for preventing or managing clinically significant DIs[1]
2. Must briefly describe the mechanism of clinically significant DIs, if known[1]
3. Should include the clinical effects of clinically significant DIs



DIs = drug interactions [1] 21 CFR 201.57(c)(8)(i).


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EXTRA SLIDES:
Full Prescribing Information

DI Information in PATIENT COUNSELING INFORMATION Section (1 of 2)

Include DI Information for HCPs to convey to patients (or caregivers) in this section if:

- It concerns an important risk
- Concomitant use could be initiated by the patient (e.g., an interaction with a nonprescription drug or food).

A complete listing of known DIs should typically not be included in this section because the decision to concomitantly use two prescription drugs generally rests with the HCP at the time of prescribing

DI Information in PATIENT COUNSELING INFORMATION Section (2 of 2)

17 PATIENT COUNSELING INFORMATION

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Sedation and Respiratory Depression

Advise patients or their caregivers of the increased risk of sedation and respiratory depression with concomitant use of DRUG-A and CNS depressants, and to monitor for signs of sedation and respiratory depression when using DRUG-A concomitantly with CNS depressants *[see Warnings and Precautions (5.2)].*

~~Severe Hypotension and Syncope with Concomitant Strong CYP1A2 Inhibitors~~

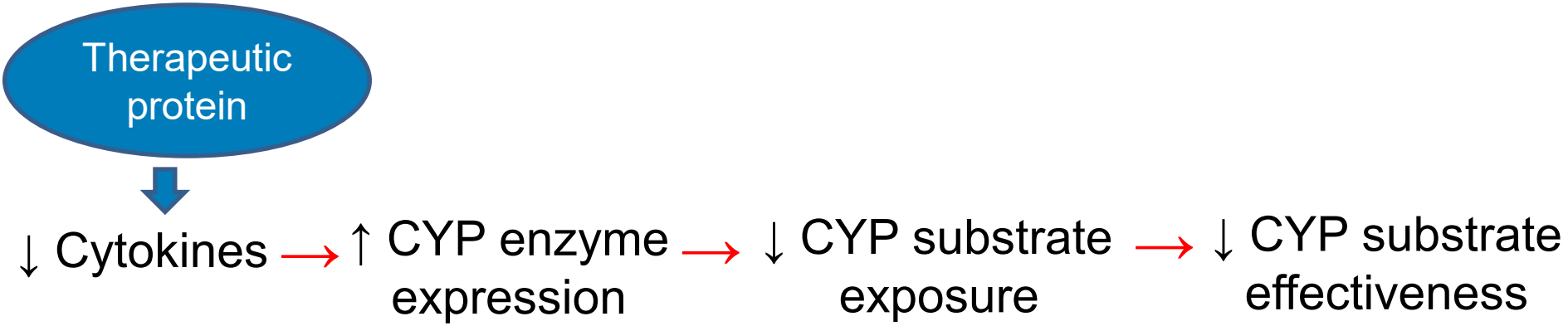
~~The concomitant use of DRUG-A with strong CYP1A2 inhibitors is contraindicated *[see Drugs Interactions (7.1)].*~~

Substrates: DRUG INTERACTIONS Section

DIs with Concomitant Use of Therapeutic Proteins with CYP Substrates: DRUG INTERACTIONS Section

DI with Concomitant Use of a Therapeutic Protein with CYP Substrates: DRUG INTERACTIONS Section

Therapeutic proteins that reduce the level of pro-inflammatory cytokines could increase expression of certain CYP enzymes, resulting in decreased CYP substrate exposure, which may reduce CYP substrate effectiveness



DI with Concomitant Use of a Therapeutic Protein with CYP Substrates: DRUG INTERACTIONS Section

7.x Effects of DRUG-X on Other Drugs

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Certain CYP Substrates

For CYP substrates where minimal decreases in the concentration may reduce CYP substrate effectiveness, monitor for reduced effectiveness of the CYP substrate upon DRUG-A initiation.

Increased concentrations of cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation associated with certain diseases including *[insert diseases or conditions that the drug is approved to treat in which this statement applies]* may suppress the formation of CYP enzymes. Therapeutic proteins, including DRUG-A, that decrease the concentrations of these pro-inflammatory cytokines may increase the formation of CYP enzymes resulting in decreased CYP substrate exposure.

Absence of a Clinically Significant DI:

DRUG INTERACTIONS Section

Communicating the Absence of a Clinically Significant DI in DRUG INTERACTIONS Section: Situation #1

Concomitant use of DRUG-A and all strong CYP3A4 inhibitors (e.g., drug-b, drug-c, drug-d, drug e) results in a clinically significant DI except for drug-z

- Concomitant use of DRUG-A and drug-b, DRUG-A and drug-c, DRUG-A and drug-d, DRUG-A and drug-e all have clinically significant DIs
- But concomitant use of DRUG-A and drug-z does not have a clinically significant DI

Situation #1: Communicating the Absence of a Clinically Significant DI in DRUG INTERACTIONS Section

Communicate the absence of a clinically significant DI if DRUG-A has clinically significant DIs with all drugs in a drug interacting class (e.g., strong CYP3A inhibitors) except for one drug (e.g., drug-z) in this class

7.x Effects of Other Drugs on DRUG-A

Strong CYP3A Inhibitors

… Reduce the DRUG-A dosage when used concomitantly with strong CYP3A inhibitors *[see Dosage and Administration (2.x)],* except with drug-z. No dosage modification is recommended for DRUG-A when used concomitantly with drug-z.

Drug-a is a CYP3A substrate. Strong CYP3A inhibitors increase drug-a exposure, which may increase the risk of DRUG-A-associated adverse reactions. Although drug-z is a strong CYP3A inhibitor, the interaction with DRUG-A is not clinically significant *[see Clinical Pharmacology (12.3)].*

Situation #2: Communicating the Absence of a Clinically Significant DI in DRUG INTERACTIONS Section (1 of 2)

DRUG-A, DRUG-B, DRUG-C, DRUG-D, etc. are members of a class (tyrosine kinase inhibitors)

- DRUG-A and drug-1 do **not** have a clinically significant DI
- DRUG-B and drug-1 have a clinically significant DI
- DRUG-C and drug-1 have a clinically significant DI
- DRUG-D and drug-1 have a clinically significant DI

Situation #2: Communicating the Absence of a Clinically Significant DI in DRUG INTERACTIONS Section (2 of 2)

Communicate the absence of a clinically significant DI if a drug class (includes DRUG-A, DRUG-B, DRUG-C, DRUG-D, etc.) is known to have a clinically significant interaction with a drug (e.g., drug-1); however, the subject drug (e.g., DRUG-A) does not interact with drug-1.

7.x Absence of Clinically Significant Interaction with Drug-1

…

No dosage modification is recommended for DRUG-A when used concomitantly with drug-1.

Although it is a tyrosine kinase inhibitor, DRUG-A does not have a clinically significant interaction with drug-1 *[see Clinical Pharmacology (12.3)].*

Drug Interference with Laboratory Test(s) Information in Labeling

Drug Interference Information in DRUG INTERACTIONS Section[1]

- Must contain practical guidance on known interference of the drug with laboratory tests[2]
- A clinically significant drug-test interference should be included in this section when an erroneous test result would negatively affect clinical decision-making (e.g., false positive hemoccult test, false negative HIV test)
- Should provide instructions to prevent or manage the interference and the clinical effect(s) of the interference, if feasible.

[1] W&P section must briefly describe the drug interference with laboratory tests and cross-reference to the DRUG INTERACTIONS section for more details. 21 CFR 201.57(c)(6)(iv).
[2] 21 CFR 201.57(c)(8)(ii).

Drug Interference Information in DRUG INTERACTIONS Section

7 DRUG INTERACTIONS

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7.x Interference of DRUG-A with Platelet Tests

When performing platelet tests in DRUG-A-treated patients, run blood samples within four hours of blood collection or collect blood samples in tubes containing citrate.

Drug-a interferes with automated platelet counts (platelet clumping) when blood samples are collected in tubes containing ethylenediaminetetraacetic acid (EDTA), which may lead to unevaluable or falsely decreased platelet counts *[see Warnings and Precautions (5.x)].*

Pharmacodynamic Changes Due to the Drug: Accurate Test Results

Accurate test results reflecting changes in a PD parameter caused by the drug are not considered a laboratory test interference and should not be included in the DRUG INTERACTIONS section but may be appropriate for the *Pharmacodynamics* subsection

12 CLINICAL PHARMACOLOGY

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12.2 Pharmacodynamics

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After administration of Norethindrone Acetate and Ethinyl Estradiol Tablets plasma HDL and triglyceride concentrations increased, and LDL concentrations decreased. These pharmacodynamic changes were not clinically significant.

PD = pharmacodynamic

EXTRA SLIDES: DI Information in the Highlights of Prescribing Information

DI Information in Highlights

- Drug Interactions heading in the Highlights must include a concise summary of the information required under the DRUG INTERACTIONS section of the FPI[1]
- Should typically include, but is not limited to, a listing of the most clinically significant DIs and the practical instructions for preventing or managing those clinically significant DIs

----------DRUG INTERACTIONS----------

- *Strong CYP3A Inhibitors:* Avoid concomitant use with DRUG-A (7.x).
- *Moderate CYP3A Inhibitors:* Reduce DRUG-A dosage to 50 mg once daily (2.x, 7.x).
- *Hepatotoxic Drugs:* In patients with (7.x):
  - Hepatic impairment: Avoid concomitant use with DRUG-A.
  - Normal hepatic function: Monitor liver enzymes weekly for the first four weeks and then monthly during concomitant use with DRUG-A.

[1] 21 CFR 201.57(a)(12).

Numerous Clinically Significant DIs in Highlights Drug Interactions Heading

- When a drug has numerous clinically significant DIs, it may not be possible to concisely summarize each clinically significant DI and their prevention or management instructions under the Drug Interactions heading
- Include (1) DIs that are most critical to the safe and effective use of the drug; and (2) a statement to alert the HCP to the presence of additional DI information in the DRUG INTERACTIONS section of the FPI.

----------DRUG INTERACTIONS----------

- QT-prolonging Drugs: Avoid concomitant use with DRUG-A (7.x).
- See full prescribing information for additional clinically significant drug interactions and recommended dosage modifications due to drug interactions (2.x, 7.x).

DI Information in D&A and Drug Interactions Headings in Highlights

Dosage modifications of the subject drug and drugs affected by the subject drug due to DIs should be included under the Drug Interactions heading instead of the D&A heading

----------DOSAGE AND ADMINISTRATION----------

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See full prescribing information for DRUG-A dosage modifications due to drug interactions (2.x).

…

----------DRUG INTERACTIONS----------

- *Strong CYP1A2 Inhibitors:* Avoid concomitant use with DRUG-A. If concomitant use is unavoidable, reduce DRUG-A dosage to 50 mg once daily (2.x, 7.x).
- *Drug-b:* Reduce DRUG-A dosage to 50 mg once daily (2.x, 7.x).

…