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Updating Prescription Drug and Biological Product Labeling

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Prescribing Information (PI)



- Written for healthcare providers and must:¹
 - Contain a summary of essential scientific information needed for safe and effective use of the **human prescription drug or biological product**
 - Be informative and accurate and neither promotional in tone nor false or misleading
 - Be updated when new information becomes available that causes labeling to become inaccurate, false, or misleading

- Also known as “package insert”; however, FDA recommends using term “prescribing information”

¹ 21 CFR 201.56(a)(1) and (2)

“Old” Format Labeling¹



“Old” Format Labeling Sections
BOXED WARNING
DESCRIPTION
CLINICAL PHARMACOLOGY
INDICATION AND USAGE
CONTRAINDICATIONS
WARNINGS
PRECAUTIONS
ADVERSE REACTIONS
DRUG ABUSE AND DEPENDENCE
OVERDOSAGE
DOSAGE AND ADMINISTRATION
HOW SUPPLIED



Subsections in PRECAUTIONS Section
General
Information for Patients
Laboratory Tests
Drug Interactions
Drug/Laboratory Test Interactions
Carcinogenesis, Mutagenesis, Impairment of Fertility
Pregnancy
Labor and Delivery
Nursing Mothers
Pediatric Use
Geriatric Use

¹ “Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs”; 44 FR 37434 (June 26, 1979), 21 CFR 201.80

Physician Labeling Rule (PLR) Format Labeling



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol

Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR Medication Guide.

Revised: M/201Y

¹ Although Highlights of Prescribing Information (Highlights) is only shown on this slide, PLR labeling includes Highlights, Table of Contents, and Full Prescribing Information. "Requirements on Content and Format of Labeling for Human Prescription Drug⁵ and Biological Products" 71 FR 3922 (January 24, 2006)

PLR Format Labeling¹



Key Merits:

- Information ordered according to clinical importance
- Contains a concise summary of critical information (i.e., Highlights)
- Contains a Table of Contents
- Has numbered sections and subsections

Goals:²

- Make information easier for healthcare providers to access, read, and use
- Reduce medication errors

¹ Applications/supplements required to have PLR format labeling are NDAs, BLAs, and efficacy supplements approved on or after June 30, 2001

² "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" 71 FR 3922 (January 24, 2006); 78 FR 8446 (February 6, 2013)

Updating Labeling is Application Holder's Responsibility

- Application holder should review labeling at least annually for outdated information¹
- Application holder must update labeling when new information becomes available that causes labeling to become inaccurate, false, or misleading²
 - “a drug ... shall be deemed to be misbranded ... (i)f its labeling is false or misleading”³



¹ Implementing PLR Content and Format Requirements Guidance

² 21 CFR 201.56(a)(2); ³ FD&C Act [section 352(a) of the U.S.C.]

Principles of Updating Labeling¹

- Ensure labeling meets statutory/regulatory requirements and is consistent with final guidance recommendations²
- Ensure consistent message
- Improve organization/formatting³
- Update terminology and remove/revise outdated, misleading, or clearly inapplicable information^{3,4}
- Consider adding/modifying indications, usages, and/or dosages³



¹ Implementing PLR Content and Format Requirements Guidance; ² Final guidances represents the Agency's current thinking (alternative approaches are acceptable if they satisfy statutes/regulations)

³ If applicable; ⁴ 21 CFR 201.56(a)(2) and 21 CFR 201.56(d)(4)

Ensure Labeling Meets Statutory/Regulatory Requirements and is Consistent with Final Guidance Recommendations¹

- Recent statutes/regulations, for example:
 - Pregnancy and Lactation Labeling Rule (PLLR)²
 - Limited population pathway drugs³
 - Susceptibility test interpretive criteria⁴

- Recent final labeling guidances,¹ for example:
 - Clinical Pharmacology Section of Labeling
 - Patient Counseling Information Section of Labeling
 - Naming of Drug Products Containing Salt Drug Substances

⁴ See PLR Requirements for Prescribing Information website for other labeling guidances (final guidances represents the Agency's current thinking – alternative approaches are acceptable if they satisfy statutes/regulations):

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

² Final PLLR rule; 79 FR 72064 (December 4, 2014)

³ 21st Century Cures Act (Section 506 of FD&C Act); ⁴ 21st Century Cures Act (Section 511A of FD&C Act)

Ensure Consistent Message in Labeling: Unclear Prevention/Mitigation Strategies (Before)¹



4 CONTRAINDICATIONS

DRUG-X is **contraindicated** in patients with severe renal impairment
[see Warnings and Precautions (5.3)].

5 WARNINGS AND PRECAUTIONS

5.3 Increased Risk of Adverse Reaction-Y in Patients with Severe Renal Impairment

DRUG-X is **not recommended** in patients with severe renal impairment

8 USE IN SPECIFIC POPULATIONS

8.6 Renal Impairment

DRUG-X may be used in patients with severe renal impairment;
however, if DRUG-X is used in such patients **be cautious**.

¹ To see other examples of labeling inconsistencies see *Consistency in Labeling and Methods to Optimize Communication in Labeling*: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM584740.pdf>; this example 10 does not contain all the required and recommended elements for these sections/subsections.

Ensure a Consistent Message in Labeling: Unclear Prevention/Mitigation Strategies (After)¹



4 CONTRAINDICATIONS

DRUG-X is **contraindicated** in patients with severe renal impairment [see *Warnings and Precautions (5.3)*].

5 WARNINGS AND PRECAUTIONS

5.3 Increased Risk of Adverse Reaction-Y in Patients with Severe Renal Impairment

DRUG-X is **contraindicated** in patients with severe renal impairment.

8 USE IN SPECIFIC POPULATIONS

8.6 Renal Impairment

DRUG-X is **contraindicated** in patients with severe renal impairment.

¹ To see other examples of labeling inconsistencies see *Consistency in Labeling and Methods to Optimize Communication in Labeling*: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM584740.pdf>; this example does not contain all the required and recommended elements for these sections/subsections. 11

Improve Organization/Formatting (Before)

2 DOSAGE AND ADMINISTRATION

2.1 General

The recommended DRUGOXIDE dosage is 10 mg twice daily. Dosage interruption is recommended for the management of neutropenia [see *Dosage and Administration* (2.3)]. The DRUGOXIDE dosage should be reduced to 10 mg once daily in patients:

- With moderate hepatic impairment
- Receiving strong CYP3A4 inhibitors (e.g., ketoconazole)

2.5 General Considerations for Administration

- DRUGOXIDE should not be used in patients with severe hepatic impairment
- It is recommended that DRUGOXIDE not be initiated in patients with an absolute neutrophil count less than 1000 cells/mm³.
- Concomitant use of DRUGOXIDE with strong CYP3A4 inducers may result in reduced clinical response to DRUGOXIDE.

2.6 Dosage Modifications

Table 1: Dosage Adjustments for Neutropenia

ANC value (cells/mm ³)	Recommendation
Greater than 1000	No change in dosage
500-1000	Interrupt dosage until ANC is greater than 1000
Less than 500	Discontinue DRUGOXIDE

ANC = absolute neutrophil count

Improve Organization/Formatting (After)

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended DRUGOXIDE oral dosage is 10 mg twice daily.

2.2 Dosage Modifications due to Neutropenia

Obtain an absolute neutrophil count (ANC) prior to starting DRUGOXIDE. The use of DRUGOXIDE is not recommended in patients with an ANC less than 1000 cells/mm³. See Table 1 for recommended dosage adjustments if significant neutropenia occurs during DRUGOXIDE administration.

Table 1: Dosage Adjustments for Neutropenia

ANC value (cells/mm ³)	Recommendation
Greater than 1000	No change in dosage
500-1000	Interrupt dosage until ANC is greater than 1000
Less than 500	Discontinue DRUGOXIDE

2.3 Dosage Modifications with Concomitant Use of Strong CYP3A4 Inhibitors

Reduce the DRUGOXIDE dosage to 10 mg once daily in patients taking concomitant strong CYP3A4 inhibitors [see *Drug Interactions (7.2)*].

2.4 Dosage Modifications in Patients with Hepatic Impairment

Reduce the DRUGOXIDE dosage to 10 mg once daily in patients with moderate hepatic impairment (DRUGOXIDE is not recommended in patients with severe hepatic impairment) [see *Use in Specific Populations (8.7)*]



Update Terminology and Remove/Revise Outdated, Misleading, or Clearly Inapplicable Information in Labeling¹ (1 of 2)

- Update terminology
 - From juvenile rheumatoid arthritis (JRA) to juvenile idiopathic arthritis (JIA)
 - From Wegener’s granulomatosis to granulomatosis with polyangiitis
 - From major depressive episode without melancholia to major depressive disorder

- Change “in man” to “in patients” (if product is approved for use in men and women)

¹ 21 CFR 201.56(a)(2) and 21 CFR 201.56(d)(4)

Update Terminology and Remove/Revise Outdated, Misleading, or Clearly



Inapplicable Information in Labeling¹ (2 of 2)

- Remove investigational name of product
- Remove products that are not generally available in U.S. (e.g., cisapride, rofecoxib, gatilfoxacin, pergolide, sparfloxacin, astemizole, cerivastatin, troglitazone)
- Remove recommendations that are no longer standard of care (e.g., assess “liver biopsies” prior to and during treatment)
- Ensure that unapproved indications/usages and dosing regimens are not implied or suggested²

¹ 21 CFR 201.56(a)(2) and 21 CFR 201.56(d)(4)

² 21 CFR 201.57(c)(2)(iv) and (v) and 21 CFR 201.57(c)(3)(ii)

Consider Adding/Modifying New Indications, Usages, and/or Dosages

PDUFA VI removed efficacy supplement fee to help ensure labeling is accurate based upon most current clinical data¹

FROM:

2 DOSAGE AND ADMINISTRATION

The recommended IV dosage of DRUG-X for the treatment of adenocarcinoma of the breast is 12 mg/kg for 4 consecutive days and then 6 mg/kg on Days 6, 8, 10, and 12. Repeat course every 30 days.

TO:

2 DOSAGE AND ADMINISTRATION

The recommended intravenous dosage of DRUG-X, in combination with cyclophosphamide and other cytotoxic drugs, for the treatment of adenocarcinoma of the breast is 500 mg/m² or 600 mg/m² on Days 1 and 8 every 28 days for 6 cycles.

¹ Prescription Drug User Fee Amendments of 2017 (Prescription Drug User Fee Rates for Fiscal Year 2018, 82 FR 43244)

CDER's Efforts to Improve Labeling



- Frequently review entire labeling during supplement review (not just firm's proposed changes to labeling)
- Continue to improve labeling resources
 - PLR Requirements for Prescribing Information website
- Publish new labeling guidances
- Dedicated labeling review specialists
 - Associate Directors for Labeling (ADLs)
- Public outreach
 - November 2017 CDER Prescription Drug Labeling Conference

PLR Requirements for Prescribing Information Website¹



- PLR Final Rule and Labeling Requirements
- Labeling Guidances
- Labeling Presentations – Labeling Content
- Articles with Labeling Content
- PLLR Labeling
- Labeling Presentations – Labeling Review Process and Resources
- Sample Templates and Format Labeling Tools
- Product Quality-Related Resources for Prescribing Information
- ANDA Labeling Guidances
- Established Pharmacologic Class Resources
- Additional Labeling Resources

¹ <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

Opportunities for Application Holders to Update Labeling



Before submitting any supplement to an NDA/BLA, review entire labeling and assess if information is outdated, misleading, unclear, and/or inapplicable

- PLLR conversion labeling supplements provides an opportunity to assess and update entire labeling
- Voluntary PLR conversion of “old” format labeling



Thank You



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Back Up Slides

CDER Prescription Drug and Biological Product Labeling in PLR Format¹

Month/Year	Proportion of CDER Prescription Drug and Biological Product Labeling in PLR Format (NDAs/BLAs only)
January 2014	~ 45%
January 2016	~ 56%
January 2017	~ 61%
January 2018	~ 63%

NDAs = New Drug Applications; BLAs = Biologics License Applications; CDER = Center Drug Evaluation and Research

¹ Analyses based on Structured Product Labeling (SPL) files - generally only includes marketed products and excludes repackers, relabelers, and redistributor labeling

CDER Novel Drug Approvals Website¹



No.	Drug Name	Active Ingredient	Approval Date	FDA-approved use on approval date
9.	Akynzeo	fosnetupitant and palonosetron	4/19/2018	To prevent acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy
8.	Crysvita	burosumab-twza	4/17/2018	To treat adults and children ages 1 year and older with x-linked hypophosphatemia (XLH), a rare, inherited form of rickets Press Release Drug Trials Snapshot
7.	Tavalisse	fostamatinib	4/17/2018	To treat thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) Drug Trials Snapshot
6.	Ilumya	tildrakizumab	3/20/2018	To treat adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy Drug Trials Snapshot
5.	Trogarzo	ibalizumab-uiyk	3/6/2018	To treat HIV patients who have limited treatment options Press Release Drug Trials Snapshot
4.	Erleada	apalutamide	2/14/2018	To treat a certain type of prostate cancer using novel clinical trial endpoint Press Release

In my view, labeling quality has improved over the last several years!

¹ <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm592464.htm>