

Consistency in Labeling and Methods to Optimize Communication in Labeling

Eric Brodsky, MD

**Associate Director, Labeling Development Team
Office of New Drugs**

**Center for Drug Evaluation and Research (CDER)
Food and Drug Administration (FDA)**

Disclaimer



- 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.

Overview



- 1) Consistent message throughout prescribing information (PI)
- 2) Considerations for:
 - CLINICAL STUDIES section
 - Product-quality information in PI
- 3) Quality PI check prior to approval

See extra slides for other labeling considerations

Topic #1: Consistent Message in PI

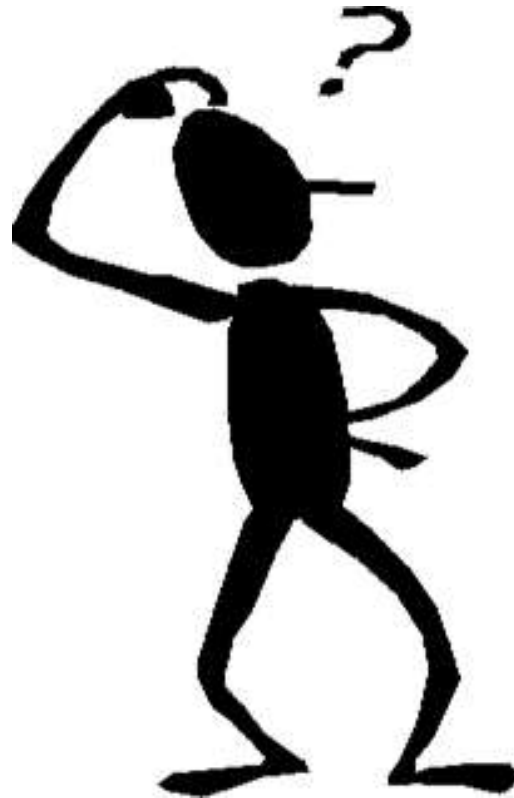


Examples



- Fictitious examples
 - May not include all regulatory/statutory requirements for each section/subsection
- Examples derived from approved labeling

Unclear Indicated/Approved Population



Approved/Indicated for (1) Only Pediatric Patients or (2) Adults and Pediatric Patients?

1 INDICATIONS AND USAGE

DRUG-X is indicated for the treatment of **patients** with Condition-Y.

2 DOSAGE AND ADMINISTRATION

Prior to treating **adults** with DRUG-X, assess for the presence of **coronary artery disease** [see *Warnings and Precautions* (5.1)].

The recommended dosage in **pediatric patients** is 100 mg orally once daily

14 CLINICAL STUDIES

The efficacy of DRUG-X in the treatment of Condition-Y was established from two randomized, placebo-controlled trials in **pediatric patients** aged 11 to 16 years old with Condition-Y.



Option #1: Indicated Only in Pediatric Patients \geq 11 Years Old



1 INDICATIONS AND USAGE

DRUG-X is indicated for the treatment of **pediatric** patients 11 years of age and older with Condition-Y.

2 DOSAGE AND ADMINISTRATION

~~Prior to treating adults with DRUG-X, assess for the presence of coronary artery disease [see Warnings and Precautions (5.1)]~~

The recommended dosage in **pediatric** patients 11 years of age and older is 100 mg orally once daily.

14 CLINICAL STUDIES

The efficacy of DRUG-X in the treatment of Condition-Y was established from two randomized, placebo-controlled trials in **pediatric** patients aged 11 to 16 years old with Condition-Y.



Option #2: Indicated in Adults and Pediatric Patients \geq 11 Years Old



1 INDICATIONS AND USAGE

DRUG-X is indicated for the treatment of adults and pediatric patients 11 years of age and older with Condition-Y.

2 DOSAGE AND ADMINISTRATION

Prior to treating adults with DRUG-X, assess for the presence of coronary artery disease [see *Warnings and Precautions* (5.1)]

The recommended dosage in adults and pediatric patients 11 years of age and older is 100 mg orally once daily.

Implied or Suggested Unapproved Dosage Regimen



Implied or Suggested Dosage Regimen

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended DRUG-X dosage is 10 mg once daily.

Inconsistent

Consistent

14 CLINICAL STUDIES

14.1 Clinical Studies in Ulcerative Colitis

Study 1 was a double-blind, placebo-controlled, dosage-ranging 6-week trial in patients with ulcerative colitis in which patients were randomized to receive placebo, DRUG-X 10 mg once daily, or DRUG-X 20 mg once daily.

Both DRUG-X groups showed improved Mayo scores compared to the placebo group at Week 6 (see Table 5).

Table 5: Efficacy Results at Week 6 in Patients with Ulcerative Colitis in Study 1

	Placebo (n=76)	DRUG-X 10 mg once daily (n=80)
Proportion of Patients with Mayo Score ≤ 2	6%	19%
Proportion of patients with a decrease from baseline in the Mayo score by $\geq 30\%$	30%	52%

Avoid Implied or Suggested Unapproved Indication/Use/Dosage



Indications/uses and dosing regimens must not be implied or suggested in other sections of labeling if not included in I&U section or D&A section, respectively¹

I&U = INDICATIONS AND USAGE; D&A = DOSAGE AND ADMINISTRATION

¹ 21 CFR 201.57(c)(2)(iv) and (v); 21 CFR 201.57(c)(3)(ii); 21 CFR 201.57(c)(15)(i); and 21 CFR 201.56(a)(3)



Option #1: Both Dosages Approved

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended DRUG-X dosage is 10 mg or 20 mg once daily.

14 CLINICAL STUDIES

14.1 Clinical Studies in Ulcerative Colitis

Study 1 was a double-blind, placebo-controlled, dosage-ranging 6-week trial in patients with ulcerative colitis in which patients were randomized to receive placebo, DRUG-X 10 mg once daily, or DRUG-X 20 mg once daily. Both DRUG-X groups showed improved Mayo scores compared to the placebo group at Week 6 (see Table 5).

Consistent

Table 5: Efficacy Results at Week 6 in Patients with Ulcerative Colitis in Study 1

	Placebo (n=76)	DRUG-X 10 mg once daily (n=80)	DRUG-X 20 mg once daily (n=79)
Proportion of Patients with Mayo Score ≤ 2	6%	19%	23%
Proportion of patients with a decrease from baseline in the Mayo score by $\geq 30\%$	30%	52%	56%



Option #2a: Only One Approved Dosage



2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended DRUG-X dosage is 10 mg once daily.

14 CLINICAL STUDIES

14.1 Clinical Studies in Ulcerative Colitis

Study 1 was a randomized, double-blind, placebo-controlled 6-week trial of DRUG-X in patients with ulcerative colitis. In this trial, patients who received DRUG-X 10 mg once daily showed improved Mayo scores compared to patients who received placebo at Week 6 (see Table 5).

Consistent

Table 5: Efficacy Results at Week 6 in Patients with Ulcerative Colitis in Study 1

	Placebo (n=76)	DRUG-X 10 mg once daily (n=80)
Proportion of Patients with Mayo Score ≤ 2	6%	19%
Proportion of patients with a decrease from baseline in the Mayo score by $\geq 30\%$	30%	52%



Option #2b: Only One Approved Dosage (include disclaimer)



2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended DRUG-X dosage is 10 mg once daily.

14 CLINICAL STUDIES

14.1 Clinical Studies in Ulcerative Colitis

Study 1 was a randomized, double-blind, placebo-controlled, 6-week trial in patients with ulcerative colitis in which patients were randomized to receive placebo, DRUG-x 10 mg once daily, or DRUG-X 20 mg once daily. DRUG-X 10 mg once daily demonstrated improved Mayo scores compared to the placebo group at Week 6 (see Table 5).

Compared to DRUG-X 10 mg once daily, DRUG-X 20 mg once daily did not demonstrate significantly greater reductions in Mayo scores and had a greater incidence of adverse reactions. Therefore, DRUG-X 20 mg once daily is not recommended [see *Dosage and Administration (2.1)*].

Table 5: Efficacy Results at Week 6 in Patients with Ulcerative Colitis in Study 1

	Placebo (n=76)	DRUG-X 10 mg once daily (n=80)
Proportion of Patients with Mayo Score ≤ 2	6%	19%
Proportion of patients with a decrease from baseline in the Mayo score by $\geq 30\%$	30%	52%

Unclear Recommended Duration of Use



What is the Recommended Duration of Use?



WARNING: ADVERSE REACTION-Y

Consider the risks of Adverse Reaction-Y and benefits of DRUG-X before using longer than 3 months [see *Warnings and Precautions* (5.1)].

2 DOSAGE AND ADMINISTRATION

If patients do not respond after several months of treatment, increase the dosage to 15 mg once daily.

5 WARNINGS AND PRECAUTIONS

5.1 Adverse Reaction-Y

Adverse Reaction-Y has occurred more commonly after the first 3 months of DRUG-X use. DRUG-X should not be used for longer than 3 months.



Recommended Duration of Use is Clear



WARNING: ADVERSE REACTION-Y

Avoid treatment with DRUG-X for **longer than 3 months** because of the increased risk of developing Adverse Reaction-Y with longer term use [*see Warnings and Precautions (5.1)*].

2 DOSAGE AND ADMINISTRATION

Avoid treatment with DRUG-X for **longer than 3 months** [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Adverse Reaction-Y

The risk of Adverse Reaction-Y increases with longer term use (> 3 months); therefore, **avoid** use of DRUG-X **longer than 3 months**.

Inconsistency Between Strengths and Recommended Dosage



Inconsistency Between Strengths and Recommended Dosage¹



2 DOSAGE AND ADMINISTRATION

- Recommended dosage of DRUG-X is 10 mg once daily.
- Recommended dosage of DRUG-X in patients with severe renal impairment ($\text{Clcr} < 30 \text{ mL/minute}$; renal function estimated by Cockcroft-Gault using ideal body weight) is 5 mg once daily.
- Do not split tablets [*see Warnings and Precautions (5.7)*]

3 DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg (light yellow, round, "Pharma" on one side)

5 WARNINGS AND PRECAUTIONS

5.7 Serious Adverse Reaction-Y with Inappropriate Administration

Serious Adverse-Reaction-Y has occurred in patients who split DRUG-X tablets.

¹ Tablets are not functionally scored. See [Tablet Scoring – Nomenclature, Labeling, and Data for Evaluation](#) guidance



Consistency Between Strengths & Recommended Dosage



2 DOSAGE AND ADMINISTRATION

- Recommended dosage of DRUG-X is 10 mg once daily.
- Do not split tablets [see Warnings and Precautions (5.7)]

3 DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg (light yellow, round, “Pharma” on one side)

5 WARNINGS AND PRECAUTIONS

5.7 Serious Adverse Reaction-Y with Inappropriate Administration

Serious Adverse-Reaction-Y has occurred in patients who split DRUG-X tablets.

8 USE IN SPECIFIC POPULATIONS

8.6 Renal Impairment

The use of DRUG-X in patients with severe renal impairment (Cl_{cr} < 30 mL/minute; renal function estimated by Cockcroft-Gault using ideal body weight) is not recommended [provide a rationale] [see Warnings and Precautions (5.7)].

Unclear Risk Management



What are Prevention/Mitigation Recommendations in Patients with Severe Renal Impairment?

4 CONTRAINDICATIONS

DRUG-X **should not be used** 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

Initiation of DRUG-X in patients with severe renal impairment is **not recommended**. **Discontinue** DRUG-X if creatinine clearance remains persistently below 30 mL/minute.

Labeling Development Steps: Renal Impairment Information



12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics

First: data

8 USE IN SPECIFIC POPULATIONS
8.6 Renal Impairment

Second: clinical implications of differences in response, safety, or recommendations for use

BOXED WARNING
2 DOSAGE AND ADMINISTRATION
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS

Third: Risk management



Step #1: Summarize Data - Severe Renal Impairment



12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Specific Populations

Patients with Renal Impairment

Compared to patients with normal renal function, the AUC of drugoxide was increased by 1.2, 2, and **20 times** in patients with mild renal impairment (Clcr 60 to 90 mL/minute), moderate renal impairment (Clcr 30 to 60 mL/minute), and **severe renal impairment** (Clcr < 30 mL/minute), respectively, following a single 50 mg dose of drugoxide [*see Use in Specific Populations (8.6)*].

Include PK differences in patients with renal impairment compared to patients with normal renal function¹



Step #2 Summarize Risk and Risk Management Information about Severe Renal Impairment¹



8 USE IN SPECIFIC POPULATIONS

8.6 Renal Impairment

DRUG-X is contraindicated in patients with severe renal impairment ($\text{Clcr} < 30 \text{ mL/minute}$) because the use of DRUG-X in patients with severe renal impairment was associated greater blood levels of drugoxide compared to patients with normal renal function (**20 times greater**) [see *Clinical Pharmacology* (12.3)].

Implications of differences in response, safety, or recommendations for use in patients with mild and moderate renal impairment (compared to patients with normal renal function) are included

Clcr = creatinine clearance

¹ draft [Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling](#)

Step #3 Include Risk Management Information¹ (1 of 2)



4 CONTRAINDICATIONS

DRUG-X is contraindicated in patients with severe renal impairment ($\text{Clcr} < 30 \text{ mL/minute}$) [*see Use in Specific Populations (8.6)*].

Clcr = creatinine clearance

¹ 21 CFR 201.57(c)(5); [W&P, Contraindications, and BW Sections of Labeling guidance](#); and draft [Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling](#)



Step #3 Include Risk Management Information¹ (2 of 2)



2 DOSAGE AND ADMINISTRATION

DRUG-X is contraindicated in patients with severe renal impairment ($\text{Clcr} < 30$ mL/minute).

The recommended once daily oral dosage of DRUG-X is (renal function estimated by Cockcroft-Gault using ideal body weight) [*see Use in Specific Populations (8.6)*]:

- 50 mg in patients with normal renal function or mild renal impairment ($\text{Clcr} \geq 60$ mL/minute).
- 25 mg in patients with moderate renal impairment (Clcr 30 to 60 mL/minute)

4 CONTRAINDICATIONS

DRUG-X is contraindicated in patients with severe renal impairment ($\text{Clcr} < 30$ mL/minute) [*see Use in Specific Populations (8.6)*].

Clcr = creatinine clearance

¹ 21 CFR 201.57(c)(3); [Dosage and Administration Section of Labeling guidance](#); and draft [Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling](#)

Topic #2: Labeling Considerations





Labeling Considerations for CLINICAL STUDIES Section

CLINICAL STUDIES Section - To Improve Readability, Recommend



(1 of 2):

- Use one statistical population for efficacy results
- Use mean or median (not both)
- Round when displaying treatment effects in percentages (if appropriate)
- Include results in a table or text (not both)

CLINICAL STUDIES Section - To Improve Readability, Recommend

(2 of 2):



- Define terms not understood
- When subsection heading(s) are used, recommend not including information between Section 14 and subsection 14.1

For Complicated CLINICAL STUDIES Sections Consider Creating an Overview Subsection¹

14 CLINICAL STUDIES

14.1 Description of Clinical Trials

The efficacy of VOSEVI was evaluated in two Phase 3 trials in DAA-experienced subjects with genotype 1, 2, 3, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis, as summarized in Table 8.

Same primary endpoint

Sustained virologic response, defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment, was the primary endpoint in both trials.

Table 8 **Trials Conducted With VOSEVI in DAA-Experienced Subjects With HCV Infection**

Trial	Population	Study Arms and Comparator Groups (Number of Subjects Treated)
POLARIS-1	Genotype 1, 2, 3, 4, 5, or 6 NS5A inhibitor-experienced ^a , without cirrhosis or with compensated cirrhosis	VOSEVI 12 weeks (263) Placebo 12 weeks (152)
POLARIS-4	Genotype 1, 2, 3, or 4 DAA-experienced ^b who have not received an NS5A inhibitor, without cirrhosis or with compensated cirrhosis	VOSEVI 12 weeks (182) SOF/VEL 12 weeks (151)

CLINICAL STUDIES Section: Subsection Titles



- Bold font¹ and Title case²
- Title should reflect information within subsection
 - Instead of “**14.1 Monotherapy**”
 - State “**14.1 Monotherapy Use of DRUG-X in Patients with Disease-Y**”
- Avoid conclusions about results in title
 - Avoid “**Improvement in Mayo Score at 24 Weeks in Study 1**”

¹ 21 CFR 201.57(d)(1); ² [Clinical Studies Section of Labeling Guidance](#)

CLINICAL STUDIES Section:

Subsection Titles

14 CLINICAL STUDIES

- 14.1 Unresectable or Metastatic Melanoma
- 14.2 Metastatic Non-Small Cell Lung Cancer (NSCLC)
- 14.3 Renal Cell Carcinoma
- 14.4 Classical Hodgkin Lymphoma
- 14.5 Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)
- 14.6 Urothelial Carcinoma
- 14.7 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer

CLINICAL STUDIES Section - Titles of Tables and Figures

Should include type of data, time point, patient population, and study name:¹

Change in Bone Mineral Density

Type of data

from Baseline at Month 12

Time point

in Postmenopausal Women with Osteoporosis

in Study 1

Patient population

Study name

¹ [Clinical Studies Section of Labeling guidance](#)

Recommend Including NCT# in CLINICAL STUDIES Section



14 CLINICAL STUDIES

...

MONARCH 2 (NCT02107703) was a randomized, placebo-controlled, multicenter study in women with HR-positive, HER2-negative metastatic breast cancer in combination with fulvestrant in patients with disease progression following endocrine therapy who had not received chemotherapy in the metastatic setting.



Labeling Considerations for Product Quality-Related Information in PI

Highlights: Product Title¹



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 and Medication Guide.

Revised: M/201Y

¹ 21 CFR 201.57(a)(2)

Format of Product Title (PT)



- Must bold text in PT¹
- Proprietary name is in UPPER-CASE and rest of PT is in lower case²
 - **MYDRUG (drugozone) capsules, for oral use**
- If there is no proprietary name, chemical proportion of nonproprietary name (or proper name) is in UPPER-CASE and rest of PT is in lower case (parentheses are omitted)²
 - **DRUGOZONE capsules, for oral use**
- Comma precedes ROA² (if ROA not part of nonproprietary name)

ROA = route of administration

¹ 21 CFR 201.57(d)(5)

² Consider having all items in PT appear in lower case with some limited exceptions (e.g., proprietary name, controlled substance symbol, acronyms for radioisotopes)

Consider Avoiding Following in PT



- Additional descriptors (e.g., avoid film-coated)
- Methods of intravenous infusion (e.g., infusion)
- Abbreviations (e.g., IV for intravenous, HCl for hydrochloride)
- Drug's origin information¹
- Slash marks when displaying name of fixed combination drug products
- Repetition of ROA if ROA precedes dosage form
 - DRUG (drugozide) topical solution, ~~for topical use~~

¹ Consider avoiding including information about drug's origin (e.g., rDNA) unless it is required by regulation, it is part of the nonproprietary name, or it is clinically relevant (e.g., human)

Avoid Use of Following Terminology in PT



- “USP”
- “Powder” as a dosage form for injectable products requiring reconstitution
 - e.g., avoid “lyophilized powder”, instead use “for injection”¹
- “Solution” as a dosage form for injectable drug products²
- “Only” (e.g., for topical use only)

¹ USP General Chapter <1121> Nomenclature for additional information on the nomenclature of injectable drug products

Product Title Examples: Products With a Proprietary Name



CADUET (amlodipine besylate and atorvastatin calcium) tablets, for oral use

LEVITRA (vardenafil hydrochloride) tablets, for oral use

ZOMIG-ZMT (zolmitriptan) orally disintegrating tablets

FENTORA (fentanyl buccal tablets), CII

REVATIO (sildenafil) for oral suspension

OXYTROL (oxybutynin transdermal system)

ADASUVE (loxapine) inhalation powder, for oral inhalation use

SIMPONI (golimumab) injection, for subcutaneous use

BOTOX (onabotulinumtoxin A) for injection, for intramuscular, intradetrusor, or intradermal use

Product Title Examples: Products Without a Proprietary Name



CYCLOPHOSPHAMIDE tablets, for oral use

PHENYLEPHRINE HYDROCHLORIDE injection, for intravenous use

GLUCAGON for injection, for intravenous or intramuscular use

DOXORUBICIN HYDROCHLORIDE for injection, for intravenous use

DOXORUBICIN HYDROCHLORIDE injection, for intravenous use

Format of Elements in PT in Highlights vs. Carton/Container Labeling



Product information in product title and on carton/container labeling should be as consistent as possible, but acceptable differences

	Carton/Container Labeling	Product Title in Highlights of Prescribing Information
Format of proprietary name	Title Case	UPPER CASE
Number of lines	Many lines (e.g., dosage form and ROA can be presented beneath drug name)	Present on one line if space permits
Strength	Strength present	Strength generally should <u>not</u> appear
ROA	May include word “only”	Avoid word “only”
Methods of intravenous administration (e.g., intravenous infusion)	May appear	Avoid

Full Prescribing Information (FPI)

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
9 DRUG ABUSE AND DEPENDENCE
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
13 NONCLINICAL TOXICOLOGY
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION



Considerations for Order¹ of Required² Elements in DOSAGE FORMS AND STRENGTHS (DFS) Section of FPI

Dosage form

Strength

Identifying characteristics

3 DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/2.4 mL (50 mg/mL)

clear to opalescent, colorless to slightly yellow

solution in a single-dose vial

¹ Consider order of elements for consistency across labeling

² 21 CFR 201.57(c)(4)

DFS Section of FPI: Packaging Information



3 DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/2.4 mL (50 mg/mL)

clear to opalescent, colorless to slightly yellow
solution in a single-dose vial



Although not required in this section, may include package term¹ and limited package information

Should include functionally scored when appropriate²

¹ [Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use](#) draft guidance

² [Tablet Scoring – Nomenclature, Labeling, and Data for Evaluation](#) guidance

DFS Section Examples



- For injection: 50 mg, 100 mg, or 200 mg of drugozone as a white lyophilized powder in single-dose vial for reconstitution
- Injection: 90 mg/0.75 mL clear solution in single-patient-use autoinjector
- Injection: 300 mg/3 mL (100 mg/mL) clear solution in multiple-dose vial
- Cream: 70 mg of lidocaine per gram (7%) and 70 mg of tetracaine per gram (7%) of white to off-white cream in 30 gram and 60 gram tubes
- Implant: 68 mg of etonogestrel, pre-loaded in needle of disposable applicator

Alternative Format for DFS Section: Multiple Strengths



3 DOSAGE FORMS AND STRENGTHS

REXULTI tablets are available in 6 strengths (see Table 2).

Table 2: REXULTI Tablet Strengths and Identifying Features

Tablet Strength	Tablet Color/Shape	Tablet Markings
0.25 mg	Light brown; Round; shallow convex; bevel-edged	“BRX” and “0.25”
0.5 mg	Light orange Round; shallow convex; bevel-edged	“BRX” and “0.5”
1 mg	Light yellow Round; shallow convex; bevel-edged	“BRX” and “1”
2 mg	Light green Round; shallow convex; bevel-edged	“BRX” and “2”
3 mg	Light purple Round; shallow convex; bevel-edged	“BRX” and “3”
4 mg	White Round; shallow convex; bevel-edged	“BRX” and “4”

DESCRIPTION Section of FPI Must Include:¹



- Proprietary name
 - Established name or proper name
 - **Dosage form(s)**
 - **Route(s) of administration**
 - **Pharmacologic or therapeutic class**
 - Qualitative and quantitative ingredients
 - Statement product is sterile (if product is sterile)
 - Chemical name and structural formula (for drug products)
 - If radioactive, important nuclear physical characteristics
 - Other important chemical or physical information (e.g., pH)
- Sometimes missing from proposed labeling**
-
- Diagram illustrating items sometimes missing from proposed labeling:
- Arrow pointing to **Dosage form(s)**
 - Arrow pointing to **Route(s) of administration**
 - Arrow pointing to **Pharmacologic or therapeutic class**

¹ 21 CFR 201.57(c)(12)

Information that Generally Does Not Belong in DESCRIPTION Section



- “Drugoxide sublingual tablets are intended to be placed under the tongue where they will **dissolve in about two minutes to allow disintegration and absorption of drugoxide across the oral mucosa**”
- “DRUG contains drugoxide, an inhibitor of transporter X, **the transporter responsible for reabsorbing the majority of glucose filtered by the kidney**”
- “DRUG, a therapy for Condition-Y”

Storage Instructions for Supplied vs. Reconstituted/Diluted Products



Supplied Product

Special handling and storage conditions must be in HOW SUPPLIED/STORAGE AND HANDLING section¹

- Protect from light, do not shake, do not freeze, refrigerate

Reconstituted or Diluted Products

- Detailed description of storage conditions in D&A section²
- May also summarize storage conditions in HOW SUPPLIED/STORAGE AND HANDLING with a cross-reference to D&A section
 - “Store reconstituted solutions of DRUG-X at Y temperature [see *Dosage and Administration (2.x)*].”

D&A = DOSAGE AND ADMINISTRATION

¹ 21 CFR 201.57(c)(17)

² 21 CFR 201.57(c)(3) and [Dosage and Administration Section of Labeling guidance](#)

Topic #3: Quality Check for Format/Appearance of PI



Selected Requirements of Prescribing Information (SRPI)¹



The Selected Requirements of Prescribing Information (SRPI) is a 41-item checklist of important format prescribing information (PI) items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**no deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

2. The length of HL must be one-half page or less unless (the HL Boxed Warning does not count against the one-half page requirement).

Comment:

3. A horizontal line must separate:
 - HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

¹ SRPI on [PLR Requirements for Prescribing Information website](#)

Labeling Finalization During NDA/BLA Review Cycle



- After FDA and firm are close to an agreed-upon PI, remove all annotations from PI:
 - Line numbers
 - Headers and footers
- Ensure two column format for Highlights and Table of Contents; recommend one-column format for FPI

What Can be Improved?



NDA 0123456-S-030
NDA 023456-S-020
NDA 034567-S-18
FDA Draft Labeling Text 8/5/15

1.14.1.3 Page 3 of 20 Confidential

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 and Medication Guide.

Revised: 10/2015

Remove Annotations



NDA 0123456-S-030

NDA 023456-S-020

NDA 034567-S-18

FDA Draft Labeling Text 8/5/15

1.14.1.3 Page 3 of 20 Confidential

HIGHLIGHTS OF PRESCRIBING INFORMATION

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Revised: 10/2015

Annotations Removed¹



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- Text (8.x)

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

Revised: M/201Y

¹ “Sample PLR Template – Highlights, Contents, and Full Prescribing Information” on [PLR Requirements for Prescribing Information website](http://www.fda.gov/oc/ohrt/PLRRequirementsforPrescribingInformationWebsite59)59

Summary



- Ensure a consistent message about conditions of use throughout PI
 - If inconsistent, determine appropriate message
- Labeling considerations
 - CLINICAL STUDIES section
 - Product quality information
- Perform a quality labeling check prior to approval





Extra Slides: Additional Labeling Considerations

General Considerations for All Sections of PI

Abbreviations and Symbols in PI

(1 of 2)



- Institute for Safe Medication Practices: a list of error-prone abbreviations, symbols, and dose designations¹
- Consider whether these items will create potential for prescribing or administration errors in PI
- However, commonly used symbols may be preferable when there is minimal risk for medication error and where replacement of symbols would decrease readability

¹ <http://www.ismp.org/tools/errorproneabbreviations.pdf>

Abbreviations and Symbols in PI

(2 of 2)

Instead of	Consider
ALT greater than 3 times ULN to less than or equal to ALT 5 times ULN	ALT > 3 times ULN to \leq 5 times ULN
CrCl 30 mL per minute to 50 mL per minute	CrCl 30 mL/minute to 50 mL/minute
5 mg per kg per day	5 mg/kg/day

Use of “Studies” vs. “Trials” in PI



- Regulations do not define the terms “studies” and “trials” for use in labeling
- Labeling regulations use these terms inconsistently
 - Title of Section 14 must be “CLINICAL STUDIES”¹
 - Title of one of the Adverse Reaction subsections is “Clinical Trials Experience”²
 - INDICATIONS AND USAGE section regulations uses both terms (e.g., “short term trial” and “adequate and well-controlled studies”)³
- Consider using a consistent use of scientifically appropriate terminology throughout PI

¹ 21 CFR 201.56(d) and 21 CFR 201.57(c)(15); ² 21 CFR 201.57(c)(7)(ii)(A) ³ 21 CFR 201.57(c)(2)

Use of “Subjects” vs. “Patients” in PI



- Regulations do not define the terms “subjects” and “patients” for use in labeling
- Labeling regulations use these terms inconsistently. For example, in the Geriatric Use subsection¹ of the USE IN SPECIFIC POPULATIONS section both terms are used
- Consider using a consistent use of terminology throughout PI if scientifically appropriate

¹ 21 CFR 201.57(c)(9)(v)

Metric System in PI



- Use metric system for dosage instead of British Imperial system. For example, use “kg” instead of “pounds.”
- Avoid use of both “kg” and “pounds” in DOSAGE AND ADMINISTRATION section because this may lead to medication errors

Appropriate Units in PI



Recommend units in labeling are understood by U.S. healthcare providers. For example:

- Instead of LDL = 4.14 mmol/L
- Use LDL = 160 mg/dL

Format of Proprietary Name in PI



- Proprietary name should appear in UPPER CASE letters in ≥ 3 places in PI¹
 - Twice in Highlights Limitation Statement
 - Once in product title
- In other parts of PI, proprietary name can appear in other cases (e.g., UPPER CASE, Title Case)
 - Recommend consistency in use of letter case in other parts of PI (e.g., always UPPER CASE or always Title Case)

Generally Avoid in PI (1 of 3)



- Bold print (unless required by regulation)
- Text with all UPPER CASE letters
- Passive voice (use active voice), especially in DOSAGE AND ADMINISTRATION section
- Arbitrary categories of “mild,” “moderate,” and “severe” that do not have established definitions
- International spelling (e.g., use “hematologic,” not “haematologic”)

Generally Avoid in PI (2 of 3)



Vague, misleading, or promotional terms or terms that may lack meaning to U.S. healthcare providers, e.g.,^{1,2}

- Investigational drug names (e.g., T-20)
- “generally well-tolerated”, avoid “effective dosage” in D&A section because all recommended dosages are effective, instead of “optimal dose” consider using “target dose”
- “few patients” or “rare”

¹ [Clinical Studies Section of Labeling](#) guidance

² [Adverse Reactions Section of Labeling](#) guidance

Generally Avoid in PI^{1,2} (3 of 3)



- “frequent”, “large” “infrequent”, or “small” (instead, use actual amount)
- “mild”
- “potent” (instead give the size of the effect)
- “transient”, “rapid”, “rapid-onset”, or “rapidly absorbed”
- “well-designed” (instead, provide specifics about study design)

¹ [Clinical Studies Section of Labeling](#) guidance

² [Adverse Reactions Section of Labeling](#) guidance

Generally Avoid in PI (1 of 3)



- Bold print (unless required by regulation)
- Text with all UPPER CASE letters
- Passive voice (use active voice), especially in DOSAGE AND ADMINISTRATION section
- Arbitrary categories of “mild,” “moderate,” and “severe” that do not have established definitions
- International spelling (e.g., use “hematologic,” not “haematologic”)

Highlights of Prescribing Information (Highlights)

Periods in Highlights of Prescribing Information



- There is no regulatory requirement or guidance recommendation regarding use of periods in Highlights
- FDA does not recommend any specific style guide for labeling
- Consider using a consistent approach throughout Highlights. For example, include a period:
 - At end of numerical identifier “(2.1).”
 - Before numerical identifier “. (2.1)” or
 - Avoid use periods in Highlights except at end of a complete sentence.

Boxed Warning Heading in Highlights



- Summarize information in a bulleted format. Generally, each bullet should communicate a discrete warning or contraindication¹
 - However, for lengthy risk information, several bullets may be preferable to communicate the discrete warning or contraindication
- Consider including a white space between verbatim statement “***See full prescribing information for complete boxed warning***” and the summary to enhance effective communication of labeling information in Boxed Warning

¹ [Implementing the PLR Content and Format Requirements](#) guidance

Initial U.S. Approval



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

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

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- 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 and Medication Guide.

Revised: M/201Y

Initial U.S. Approval



- On line immediately beneath Product Title¹, “**Initial U.S. Approval:**” in bold type² must be displayed:
 - Followed by four-digit year in which FDA initially approved NME, new biological product, or new combination of active ingredients¹
 - Irrespective of salt, dosage form, ROA, or indication
- Fixed Combination Drug Products (FCDP):
 - First time a new combination is approved, Initial U.S. Approval is 4-digit year of FCDP approval
- First time active moiety is approved alone (previously FCDP approved that contains active moiety), Initial U.S. Approval is 4-digit year of FCDP

¹ 21 CFR 201.57(a)(3); ² 21 CFR 201.57(d)(5)

Highlights: DFS Heading



HIGHLIGHTS OF PRESCRIBING INFORMATION

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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** and Medication Guide.

Revised: M/201Y

Highlights: DFS Heading



- Include a concise summary:¹
 - Dosage form(s) (e.g., tablets, capsules, injection)
 - Strength or potency of dosage form in metric system (e.g., 10 mg)
- Use bullets if a product has more than one dosage form²
- May include limited packaging information to facilitate prescribing (e.g., 15 and 30 gram tubes)²
- Multiple strengths should be listed on one line if possible²
- Should not include identifying characteristics of dosage forms (e.g., tablet color, shape, embossing)²

¹ 21 CFR 201.57(a)(8)

² Implementing the PLR Content and Format Requirements guidance

Highlights: DFS Heading – Examples



-----DOSAGE FORMS AND STRENGTHS-----

- Tablets: 5 mg (functionally-scored) (3)
- Orally disintegrating tablets: 2.5 mg and 5 mg (3)

-----DOSAGE FORMS AND STRENGTHS-----

For injection: 50 mg of drugoxide as a lyophilized powder in a single-dose vial for reconstitution (3)

-----DOSAGE FORMS AND STRENGTHS-----

Injection: 100 mg/2 mL (50 mg/mL) in single-patient use autoinjector (3)

Highlights: Revision Date¹



Month/year of most recent revision of PI (including minor editorial changes)

Type of Labeling Submission	Revision Date
Approval of an NDA, BLA, efficacy supplement, prior approval labeling supplement	Date of application approval
CBE labeling supplement	<ul style="list-style-type: none">• Date of CBE labeling supplement receipt• CBE labeling supplement approval date if labeling text subsequently changed
Annual report labeling	Date of annual report receipt

¹ 21 CFR 201.57(a)(15), [Implementing PLR Content and Format Requirements](#) guidance

Revision Date in PI vs. Revision Date in Patient Labeling



Revision Date at end of Highlights in PI may be different than Revision Date at end of FDA-approved patient labeling because these documents may have been updated at different times:

- Revision Date in PI:
 - Month/year of most recent revision of PI (any change to the PI including minor editorial changes)
- Revision Date at end of Medication Guide²:
 - Date of most recent revision of patient labeling (e.g., Month/Year)

¹ 21 CFR 201.57(a)(15) and [Implementing PLR Content and Format Requirements](#) guidance

² 21 CFR 208.20(b)(8)(iv)

Full Prescribing Information

Format of Headings and Subheadings in Sections/Subsections¹



- Terms “heading” and “subheading” are titles that appear within a section or subsection of PI¹
- Assuming that heading is first level down from a section or subsection, and a subheading is second level down²
- E.g., in Pharmacokinetics subsection, “Drug Interaction Studies” is the heading and “*CYP3A4 Inhibitors*” is the subheading:

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Drug Interaction Studies

CYP3A4 Inhibitors

¹ Terms “heading” and “subheading” are not consistently defined in labeling regulations and guidances

² Headings and subheadings are defined in this slide for the purposes of this presentation

Use Consistent Format for Headings and Subheadings in Sections/Subsections¹



- Use title case and either underlining or *italics* (but not both) for headings and subheadings
- Use a consistent approach (e.g., underlining for headings and *italics* for subheadings)
 - This is especially important for subsections 6.1 Clinical Trials Experience, 8.1 Pregnancy, and 12.3 Pharmacokinetics

¹ [Clinical Pharmacology Section of Labeling](#) guidance

Table and Figure Titles



- Generally titles of tables and graphs should include type of data, time point, important features of patient population, and study name(s)¹
- Should use title case¹ and consider using bold font
- Consider ensuring that titles of tables and figures represent content in table and figures
- Consider including at least one sentence about tables and figures in text, e.g., “Table 1 describes the dosage modifications for DRUG-X in patients with renal impairment”
- If proprietary name is used in labeling, consider using proprietary name in tables and figures

¹ [Clinical Studies Section of Labeling](#) guidance

Additional Subsection Titles



- There are required subsection and subsection headings in PLR format labeling¹
- Additional subsections may be added (e.g., **5.1 Anaphylaxis**)²
- Clearly identify content in subsection:
 - For example, use “**5.3 Heart Failure**” instead of “**5.3 Cardiac Adverse Reactions**” if the warning only describes cases of heart failure and does not describe other types of cardiac adverse reactions
 - Avoid using non-specific terminology such as “General” or “Adults” for title of a subsection

¹ 21 CFR 201.56(d)(1); 21 CFR 201.56(d)(2)

- For weight based dosage, consider identifying if dosage is based on ideal or actual weight
- If dosage adjustments in patients with renal impairment are described, include sufficient information needed to evaluate renal function, e.g., method used to calculate the creatinine clearance such as:¹
 - Cockcroft-Gault or Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate equations for adults
 - Schwartz or Bedside Schwartz equations for pediatric patients

¹ draft guidance: [PK in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling](#)

DOSAGE FORMS AND STRENGTHS

Section



If appearance of a parenteral dosage form (e.g., injection, for injection) is visible to the healthcare provider consider including identifying characteristics:

- Information about color (e.g., colorless to slightly pale yellow solution), and
- Clarity (e.g., clear to slightly cloudy)

W&P Section: Components for Describing a Warning¹

- Description of clinically significant AR or risk
- Risk factors, if known
- Incidence, if known and necessary for safe and effective use of drug
- Outcome (e.g., sequelae, hospitalization or time to resolution)
- Steps to prevent, reduce, or monitor risk
 - Avoid “use with caution”
- Management strategies if occurs

¹ 21 CFR 201.57(c)(6) and [W&P, Contraindications, and BW Sections of Labeling](#) guidance

YERVOY: Embryo-Fetal Toxicity W&P¹

5 WARNINGS AND PRECAUTIONS

5.7 Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, YERVOY can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with a YERVOY-containing regimen and for 3 months after the last dose of YERVOY [see *Use in Specific Populations* (8.1, 8.3)].

¹ YERVOY approved PI (7/21/17)

YERVOY: Embryo-Fetal Toxicity W&P

Generally, subsection W&P title should be a clinically significant AR or risk

Description of warning and outcome

Risk factors

5 WARNINGS AND PRECAUTIONS

5.7 Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, YERVOY can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with a YERVOY-containing regimen and for 3 months after the last dose of YERVOY [see *Use in Specific Populations* (8.1, 8.3)].

Steps to reduce, monitor, or manage risk

ADVERSE REACTIONS Section: When Do You Include AR from Related Drugs?



- According to the AR regulations, ADVERSE REACTIONS section “must list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, **if applicable**”
- Consider including AR from other related drugs (e.g., same active moiety but different dosage form, same class) when safety database for drug is limited

ADVERSE REACTIONS Section: Immunogenicity Statement¹



- Include following standard statement or appropriate modification at beginning of Immunogenicity subsection preceding the immunogenicity data
 - "As with all therapeutic proteins* there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to *[insert product's nonproprietary name]* in the studies described below with the incidence of antibodies in other studies or to other products may be misleading."
- * If product is a peptide, an oligonucleotide, or a heparin, instead of including the words "therapeutic proteins" insert the word "peptides", "oligonucleotides", and "heparins", respectively.

¹ [Labeling for Biosimilar Products](#) draft guidance

Language for Situations When Use Generally Not Recommended



- Contraindications are “situations in which the drug should not be used because the risk of use ... clearly outweighs any possible therapeutic benefit”¹
- For contraindications:²
 - Instead of “DRUG-X should not be used in patients with Condition-Y”
 - State “DRUG-X is contraindicated in patients with Condition-Y”
- **What terminology do you recommend for a subpopulation when use is generally not recommended but is not contraindicated?**

¹ 21 CFR 201.57(c)(5)

² [Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling](#) guidance