Regulatory Education for Industry (REdI): PRESCRIPTION DRUG LABELING - CHALLENGES AND ISSUES

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Challenges and Issues with Safety-Related Information in the Prescribing Information

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Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.

The labeling examples included in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended labeling templates.

Prescribing Information (PI)

- Contains a summary of the essential information needed for the safe and effective use of the drug*
- Primary tool for communicating drug risk information and management
- Information is directed to the healthcare provider

- The term *drug* as used in this presentation refers to both human prescription drug and biological products

Full Prescribing Information (FPI)

Many Sections Include Safety Information

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTH
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

Focus of Discussion

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
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Important for All Sections of Labeling

Must be updated when new information becomes available that causes the labeling to be inaccurate, false, or misleading.*

*21 CFR 201.56 (a)(2)

Also Important……

Unapproved indications or uses or dosing regimens must not be implied or suggested in other sections of labeling.*

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

ADVERSE REACTIONS

- 21 CFR 201.57(c)(7)
- FDA Guidance: *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products-Content and Format*

Adverse Reaction: Definition*

- An undesirable effect, reasonably associated with the use of a drug that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.
- Does not include all adverse events observed during use of drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

* 21 CFR 201.57 (c) (6)

Labeling Adverse Reactions

Because only adverse reactions are listed for which there is **some basis for a causal relationship** between the drug and adverse event; avoid text that suggests there is no relationship such as:

Although the events reported occurred during treatment with DRUG, they were not necessarily attributed to dosing of DRUG.

Labeling Adverse Reactions

- Use the term “adverse reactions”
  - Avoid other terms such as “adverse events” or “treatment-emergent adverse events”
- Omit events where there is no reasonable evidence of association with drug (e.g., incidence greater in placebo group than study group)
- Avoid terms that are not clinically meaningful to healthcare provider such as “investigations”
- Avoid referencing “MedDRA” or “COSTART” because they are not clinically relevant for prescribers

Adverse Reactions Subsections

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in labeling:

- Myelosuppression *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

6.2 Immunogenicity (if pertinent)

6.3 Postmarketing Experience

Clinical Trials Experience Data

1. Description of clinical trials database (e.g., population, exposure)

2. Identify most common adverse reactions and those that lead to significant rate of discontinuation

3. Presentation of common adverse reactions
   - Adverse Reactions that occurred at or above a specified rate appropriate to database
   - Pool studies as appropriate
   - Data derived from best available data (e.g., placebo-controlled)

4. Presentation of less common adverse reactions

5. Commentary on reactions with clinical implications (e.g., nature, frequency, and severity of reaction)

Database Description

Only provide key elements necessary for describing safety database (i.e., many study details are more appropriate for the Clinical Studies section)

The data described below reflect exposure to drug X in [n] patients, including [n] exposed for 6 months and [n] exposed for greater than one year. Drug X was studied primarily in placebo and active-controlled trials (n = __, and n = ___, respectively),and in one year follow up studies. The population was [age range], [gender distribution], [race distribution] and had [diseases/conditions]. Most patients received doses [describe range, route of administration, frequency, duration, as appropriate].*

N= those exposed to drug and not control

Common Adverse Reactions

Use best data source:

1. Placebo-controlled or dose ranging studies
2. Active-controlled studies
3. Single-arm studies

Common Adverse Reactions Table Example

Table 1. Adverse Reactions in Disease Y that Occurred in ≥ 3% of DRUG Treated Patients (either 25 once or twice daily) and Greater Incidence than Placebo

	Placebo (n=450)	Drug 25 mg once daily (n=449)	DRUG 25 mg twice daily (n=446)
Abdominal Pain	7%	12%	21%
Diarrhea	5%	6%	12%
Nausea	5%	7%	9%
Flatulence	3%	3%	10%
Vomiting	3%	5%	5%
Headache	<1%	3%	4%
Nasopharyngitis	<1%	3%	4%

Common Adverse Reactions Table Example

Table 1. Adverse Reactions that Occurred in Disease Y ≥ 3% of DRUG Treated Patients (either 25 mg once or twice daily) and Greater Incidence than Placebo

	Placebo (n=450)	Drug 25 mg once daily (n=449)	DRUG 25 mg twice daily (n=446)
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		6%	12%
	%	7%	9%
Flatulence	3%	3%	10%
Vomiting	3%	5%	5%
Headache	<1%	3%	4%
Nasopharyngitis	<1%	3%	3%

If DRUG is only approved for 25 mg twice daily, omit 25 mg once daily data

Comparative Safety Claims in Active Control Studies

- Avoid including comparator rates that imply a safety claim (i.e., frequency, severity, or character of adverse reaction) that is unsubstantiated or misleading.
  - Safety claims must be based on adequate and well-controlled studies*, unless the requirement is waived.
  - If requirement is waived (e.g., because the identity of the rates of adverse reactions for the active comparator are important to know) the comparator rates should be qualified by a disclaimer indicating that the data are not an adequate basis for comparison of rates between study drug and active control

*See 21CFR 314.126

Open-Label Extension Studies

- Primarily conducted as part of safety database for drugs intended for long-term treatment
- Usually one year duration
- Follow (roll-over) controlled studies
- Not designed to test scientific hypothesis; generally lack randomization
- Less rigorous and lack characteristics of adequate and well controlled studies*

*21CFR 314.126

Open-Label Extension Studies

- Provide useful information concerning
  - New adverse reactions not observed during controlled studies
  - More severe adverse reactions
  - Greater frequency of adverse reactions
- Generally not adequately designed to support safety claims

Adverse Reactions/ Postmarketing Experience

- Must list adverse reactions identified from domestic and foreign spontaneous reports
- Must be a separate list from clinical trial adverse reactions
- Avoid listing adverse reactions already discussed in Clinical Trials Experience

Adverse Reactions/ Postmarketing Experience

Even for new molecular entities, list foreign spontaneous reports in Postmarketing Experience

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval of use of DRUG **outside of the United States**. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

PLR Converting Old Drug Labeling

If the source of adverse reactions cannot be determined (e.g., an older drug) consider omitting numbered subsections (i.e., only include an ADVERSE REACTIONS section)

6 ADVERSE REACTIONS

The following adverse reactions associated with the use of DRUG were identified in **clinical trials or postmarketing reports**. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure**.**

CONTRAINDICATIONS

- 21 CFR 201.57(c)(5)
- FDA Guidance: *Warnings and Precautions, Contraindications, and Boxed Warnings Section of Labeling for Human Prescription Drug and Biological Products-Content and Format*

Contraindications

- Any situation in which the drug should not be used because the **risk** (e.g., certain potential fatal adverse reaction) **clearly outweighs any possible therapeutic benefit**
- Described in precise language: “DRUG is contraindicated in..”
- Includes description of anticipated consequence

Examples of Contraindicated Situations

- Population: pediatric patients <6 years of age
- Another Drug: strong CYP3A4 inhibitors
- Food: alcohol
- Concomitant State: patients with severe hepatic impairment

Contraindications Frequently Cross-Reference to Warnings and Precautions

4 CONTRAINDICATIONS

DRUG is contraindicated in patients with:

- Pregnancy *[see Warnings and Precautions (5.1)]*
- Severe hypersensitivity reactions *[see Warnings and Precautions (5.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

DRUG can cause harmful effects to a fetus….

5.2 Hypersensitivity Reactions

DRUG can cause severe hypersensitivity reactions including anaphylaxis. Hypersensitivity reactions may occur immediately or several hours after administration……

Contraindications: Before and After

Before:

4 CONTRAINDICATIONS

DRUG should not be given to a patient with a history of coronary artery disease because DRUG causes vasospasm *[see Warnings and Precautions (5.1)]*.

DRUG is contraindicated in patients with severe hepatic impairment *[see Use in Specific Populations (8.6)]*. DRUG can only be administered in patients with moderate hepatic impairment if the physician determines that the benefit outweighs the risks.

After:

4 CONTRAINDICATIONS

Drug is contraindicated in patients with:

- A history of coronary spasm because DRUG causes vasospasm *[see Warnings and Precautions (5.1)]*
- Severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

WARNINGS AND PRECAUTIONS

- 21 CFR 201.57(c)(6)
- FDA Guidance: *Warnings and Precautions, Contraindications, and Boxed Warnings Section of Labeling for Human Prescription Drug and Biological Products-Content and Format*

Warnings and Precautions

- Clinically significant adverse reactions or risks with use of drug.
- Consider elevating adverse reaction to a warning and precaution
  - Serious adverse reaction (such as death)
  - Otherwise clinically significant adverse reaction based on
    - Indication
    - Incidence
  - Anticipated adverse reaction
  - Adverse reactions with unapproved use
- Risks or other hazards
  - Laboratory test interference
  - Drug interactions
  - Need to monitor for safety

Components of a Warning and Precaution Subsection

- Subsection Title: characterizes risk
- Concise summary of clinically significant risk/adverse reaction including
  - Incidence if known and necessary for safe and effective use
  - Risk factors
  - Outcome (e.g., sequelae)
- Steps to prevent, monitor, mitigate, and/or manage adverse reaction

Warning and Precaution Example

5.1 Hemorrhage

Severe and fatal hemorrhagic events can occur with DRUG.
In clinical studies, 30% of patients treated with DRUG experienced a hemorrhage or bleeding event and 2% of patients experienced a fatal event *[see Adverse Reactions (6.1)]*.

Monitor blood counts and coagulation parameters during treatment with DRUG, especially patients treated with anticoagulants or other concomitant medications that increase the risk of bleeding.
If severe bleeding develops, consider permanently discontinuing DRUG.

Common Review Issue

Including information between the 5 and 5.1…..

5 WARNINGS AND PRECAUTIONS

DRUG should be administered only by individuals experienced in oncology drug administration.

5.1 Myelosupression

Myelosuppression occurs in 30% of patients treated with DRUG…..

Common Review Issue

Title and Text Don't Adequately Define Risk

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Effect

Abnormalities of liver function tests, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin, have been observed in 5 patients treated with DRUG. Severe liver function test abnormalities (Grade 3 to 4) and hepatic dysfunction with clinical manifestations (including fatal outcomes) have been reported in a **small proportion of patients** *[see Adverse Reactions (6.1)]*…….

Common Review Issue

Providing insufficient information about methods to monitor, mitigate, prevent, and/or manage the adverse reaction

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension

Drug can cause hypertension. In clinical studies 20% of patients in experienced hypertension *[see Adverse Reactions (6.1)]*.

Other Special Care Precautions

- Include a warning and precaution regarding any special care to be exerted by the healthcare provider for safe and effective use of the drug (previously called precautions)
- Useful for describing important information that doesn't quite fit the description of a risk or adverse reaction

Warnings and Precautions
"Other Special Precautions" Example

5.7 Acute Critical Illness

Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of growth hormone. DRUG has not been studied in patients with acute critical illness. Since DRUG stimulates growth hormone production, careful consideration should be given to discontinuing DRUG in critically ill patients.

Discussing Risks Associated with an Unapproved Use

1 INDICATIONS AND USAGE

DRUG is indicated for the treatment of rheumatoid arthritis.

5 WARNINGS AND PRECAUTIONS

5.3 Congestive Heart Failure

In a trial of DRUG in patients with asthma, there was a greater Incidence of congestive heart failure leading to hospitalization in DRUG-treated patients compared to control-treated patients (12% versus 2%). The safety and efficacy of DRUG in the treatment of asthma have not been established with DRUG and DRUG is not indicated for the treatment of asthma.

Avoid the use of DRUG in patients with congestive heart failure.

BOXED WARNING

- 21 CFR 201.57(c)(1)
- FDA Guidance: *Warnings and Precautions, Contraindications, and Boxed Warnings Section of Labeling for Human Prescription Drug and Biological Products-Content and Format*

Boxed Warnings

- Certain contraindications or serious warnings, particularly those that may lead to death or serious injury
- Usually based on clinical data, but may be based on serious animal toxicity in absence of clinical data

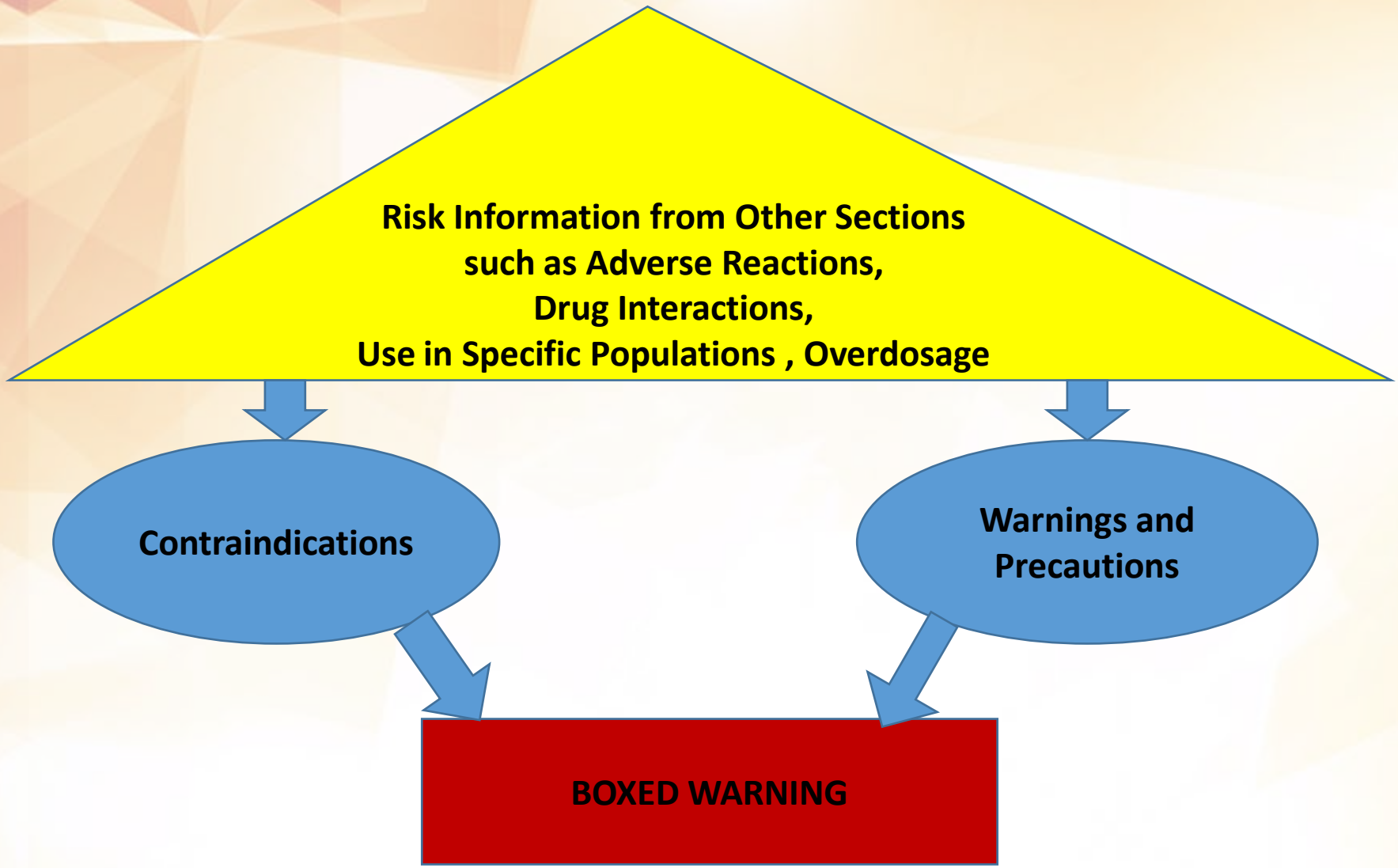
When to Include a Boxed Warning

- Adverse reaction is so serious in proportion to potential benefit of drug (e.g., fatal)
- Serious adverse reaction can be prevented or reduced in frequency or severity by appropriate use (e.g., patient selection)
- Approval with Risk Evaluation and Mitigation Strategies (elements) to assure safe use (REMS-ETASU)

Boxed Warning

Must briefly explain the risk and refer to the **Contraindications** or **Warnings and Precautions** sections for more detailed information

Developing a Boxed Warning



Components of a Boxed Warning (Title and Text in Bold Print)

- Title:
  - **“WARNING”**
  - Focus of Box: most commonly the same title as warning and precaution (i.e., risk or adverse reaction) that boxed warning is based on
- Text:
  - Concise summary of risk as described in Contraindications/Warnings and Precautions
  - Summary of key steps to prevent, monitor, mitigate, and/or manage risk
  - Cross-reference to Contraindications, Warnings and Precautions, and other sections as necessary

Boxed Warning Example

WARNING: SERIOUS INFECTIONS

Patients treated with DRUG are at increased risk for developing serious infections that may lead to hospitalization and death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral and parasitic organisms have occurred *[see Warnings and Precautions (5.1)]*.

Drug is not recommended in patients with an active infection. Discontinue DRUG in patients who develop a serious infection *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with DRUG are at an increased risk for developing a serious infection that may lead to hospitalization and death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, and parasitic pathogens have occurred. In the controlled portion of 12 DRUG clinical studies, the rate of serious infections was 8 per 100 patient-years in 2500 DRUG-treated patients versus a rate of 1 per 100 patient-years in 2400 control-treated patients. Serious infections observed included pneumonia, septic arthritis, diverticulitis, and pyelonephritis.

DRUG is not recommended in patients with an active infection.
Discontinue DRUG in patients who develop a serious infection.

Boxed Warning: Before and After

WARNING: ABUSE AND DEPENDENCE

DRUG is a Schedule II controlled substance. Stimulants, such as amphetamines are subject to abuse *[see Abuse (9.2)]*. Abuse of DRUG may cause severe cardiovascular adverse events including sudden death *[see Overdosage (10)]*.

WARNING: SERIOUS CARDIOVASCULAR ADVERSE REACTIONS WITH ABUSE AND DEPENDENCE

Abuse of stimulants, including DRUG, may cause serious cardiovascular adverse reactions including sudden death. Overdosage of DRUG has been associated with serious cardiovascular events including arrhythmia and severe hypertension. Assess the risk of abuse prior to prescribing and monitor for signs of abuse while on therapy *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2), and Overdosage (10)]*.

Boxed Warning for REMS-ETASU

- Discuss risk(s) that the REMS program intends to mitigate
- Includes concise statement that the product is only available through a REMS

WARNING: EMBRYO-FETAL TOXICITY

DRUG can cause fetal harm and is contraindicated for use in pregnancy. Exclude pregnancy before starting treatment…..[*see Contraindications (4) and Warnings and Precautions (5.1)].*

DRUG is available only through a restricted program called the TASU Program [*see Warnings and Precautions (5.2)].*

Warning and Precaution for REMS-ETASU

- A specific subsection(s) that describes the risk(s) that the REMS is trying to mitigate is followed immediately by the subsection that discusses the REMS
- The subsection that describes the REMS includes high-level elements of the program

Warning and Precaution REMS-ETASU Example

5.1 Embryo-Fetal Toxicity

DRUG can cause major congenital malformations, spontaneous abortions. Drug has been…… *[see Contraindications (4) and Use in Specific Populations (8.1)].*

DRUG is only available through a restricted program under a *REMS [see Warnings and Precautions (5.2)].*

Warning and Precaution REMS-ETASU Example

5.2 TASU Program

Drug is available only through a restricted program under a REMS called the TASU Program, because of the risk of embryo-fetal toxicity *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

Notable requirements of the TASU Program include the following:

- Prescribers must be certified with the program by enrolling and completing training
- Patients must sign a Patient-Prescriber agreement form and comply with following requirements
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.3)]*

Further information is available at www.tasu.com or 888-123-1234

Summary

When developing safety sections of labeling, ensure that the information is:

- Clear and concise
- Easy to access, read, and use
- Directed at the appropriate target audience: the healthcare provider

Thank You!