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PLLR Labeling and Process Considerations

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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.

OVERVIEW

- Process Considerations
- Content Considerations
- Format Considerations
- Summary

Best Practice for Submission of PLLR Compliant Labeling

- The submitted labeling should:
  - comply with the PLLR format
  - reflect an integrated assessment of known risks relevant to pregnancy, lactation and infertility based on available information/data
  - be accompanied by a summary and review of the available relevant information/data that supports labeling content
- Locate labeling and supportive information in Module 1 of submission

Process Considerations (1)

- Applicant must be aware of requirement for labeling to comply with PLLR format
  - includes new 505 (b)(2) and biosimilar applications
- Agency is informing applicants through pre-BLA/pre-NDA meetings, external conferences, FDA website and other methods of communications
- No waivers of PLLR requirement
- Deferral requests will be reviewed on a case-by-case basis
- Potential Refuse to File issue

Process Considerations (2)

- If submission lacks information/data to support labeling content
  - Review division may issue information request (IR)
  - Applicant should consider the amount of supporting information that needs to be prepared and the time needed to respond to the IR
  - Response to an IR could be considered a major amendment

Supportive Information

- Assessment should generally include (when applicable):
  - a review and summary of available nonclinical information, including published literature
  - a review and summary of all available published literature regarding [drug name] use in pregnant and lactating women and the effects of [drug name] on male and female fertility (include search parameters and a copy of each reference publication)
  - a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present)
  - a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval
  - interim report from an ongoing pregnancy registry or final report from a closed pregnancy registry (if applicable)

Content Considerations (1)

- *Clinical Considerations:*

  Disease-Associated Maternal and/or Embryo/Fetal Risk

  - This subheading should not include an exhaustive textbook review of the untreated disease/condition and pregnancy outcomes
  - Limit information contained in this subheading to a brief description of any serious known or potential risk of the underlying disease/condition on pregnancy outcomes that is well-established

Example of 8.1 Pregnancy, Clinical Considerations

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

…

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia-related morbidity.

Content Considerations (2)

8.2 Lactation

- Required risk and benefit statement unless breastfeeding is not recommended, then required statement may be omitted

  "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for [name of drug] and any potential adverse effects on the breast-fed child from [name of drug] or from the underlying maternal condition"

Example of Subsection 8.2 – When Breastfeeding is Not Recommended

8 USE IN SPECIFIC POPULATIONS

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8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV infection.

There is no information available on the presence of drugname in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. When administered to lactating rats, drugname was present in milk (*see Data*). Because of the potential for (1) HIV transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants) and (3) serious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving TRADENAME.

Content Considerations (3)

8.3 Females and Males of Reproductive Potential

- Use the following headings as required
  - Pregnancy Testing
    - Intent is to determine the woman's pregnancy status in time to prevent or minimize embryo/fetal exposure to a drug with embryo-fetal toxicity.
    - Section 2 Dosage and Administration should identify any specific safety monitoring procedures that should be implemented before initiating therapy (i.e., the need to test to rule out pregnancy).
  - Contraception
    - Intent is to prevent embryo/fetal exposure.
  - Infertility
- If there is embryo-fetal toxicity that supports recommendations for pregnancy testing and contraception use, a Warning & Precaution is generally included
- If there are drug interactions that require the use of alternative contraception methods, these should be included under the heading Contraception and cross-referenced to Section 7 Drug Interactions

Example of 8.3 Females and Males of Reproductive Potential (1)

- When there is embryofetotoxicity:

8 USE IN SPECIFIC POPULATIONS

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8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating TRADENAME treatment.

Contraception

Females

Based on its mechanism of action and animal data, TRADENAME can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)].* Advise females of reproductive potential to use effective contraception during treatment with TRADENAME and for at least X months after the last dose.

Example of 8.3 Females and Males of Reproductive Potential (2)

- When embryofetotoxic drug is present in semen:

8 USE IN SPECIFIC POPULATIONS

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8.3 Females and Males of Reproductive Potential

Contraception

Males

Drugname is present in semen [*see Clinical Pharmacology (12.3)*]. It is not known if the amount of drugname in semen can cause embryo-fetal harm. Advise male patients to use condoms, even after a vasectomy, to avoid potential drug exposure to pregnant partners and female partners of reproductive potential during treatment with TRADENAME and for at least X months after the last dose. Advise males not to donate semen during treatment with TRADENAME and for at least X months after the last dose.

Example of 8.3 Females and Males of Reproductive Potential (3)

- When there are drug-contraceptive interactions

8 USE IN SPECIFIC POPULATIONS

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8.3 Females and Males of Reproductive Potential

Contraception

Use of TRADENAME may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception *[see Drug Interactions (7.3)].*

Example of 8.3 Females and Males of Reproductive Potential (4)

8 USE IN SPECIFIC POPULATIONS

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8.3 Females and Males of Reproductive Potential

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Infertility

Females

Based on findings from animal studies, female fertility may be compromised with TRADENAME *[see Nonclinical Toxicology(13.1)].*

Males

Based on animal studies, TRADENAME can lead to inhibition of spermatogenesis and may impair fertility in males of reproductive potential. The long-term effects of TRADENAME on male fertility have not been studied *[see Nonclinical Toxicology (13.1)].*

Format Considerations

- Formatting of titles for headings and subheadings within subsections should be consistent throughout the labeling
- Combination products must address information known about each individual component, as well as the combined product

Example of Subsection 8.1 Labeling for a Combination Product (1)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with TRADENAME, component1 or component2 in pregnant women to inform a drug associated risk for adverse developmental outcomes. There are clinical considerations of risks [from the underlying disease] in pregnancy *(see Clinical Considerations).*

For component1 , rats and rabbits were exposed in animal reproduction studies at X times (rat) and X times (rabbit) the human exposure of 0.75 U/kg/day. No adverse outcomes were observed for pregnant animals and offspring *(see Data).*

Example of Subsection 8.1 Labeling for a Combination Product (2)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

For component2, animal reproduction studies identified increased adverse developmental outcomes from exposure during pregnancy. Component2 exposure was associated with . . . some fetal abnormalities in pregnant rats administered component2 during organogenesis at doses that approximate clinical exposures at the maximum recommended human dose (MRHD) of 1.8 mg/day. . .*[see Data]*.

The estimated background risk of major birth defects for women . . .

Example of Section 8.1 Labeling for a Combination Product (3)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Data

Animal Data

Component1

Component1 was investigated in studies covering fertility, embryo-fetal development and pre- and post-natal development in rats and during the period of embryofetal development in rabbits. . . .

Component2

Female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day component2 beginning 2 weeks before mating, during mating and the period of organogenesis, through gestation day 17 had estimated systemic exposures 0.X, X, and XX-times the human exposure at the MRHD based on plasma AUC comparison. . . .

Summary

- The submitted labeling should comply with PLLR requirements and be accompanied by a summary and review of the available relevant information/data
- Additional Recommendations:
  - Refer to the Draft Guidance for Industry
  - Refer to the Selected Requirements of Prescribing Information (SRPI)
  - Review recent PLLR conversions, especially those in similar drug class or for similar patient population

PLLR Resources

- Draft Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425398.pdf
- Pregnancy and Lactation Labeling Final Rule http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
- Physician's Labeling Rule Requirements for Prescribing Information http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

Where to find product labeling and other resources

- Drugs @FDA
  http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
- Daily Med (National Library of Medicine)
  http://dailymed.nlm.nih.gov/dailymed/about.cfm
- LactMed (National Library of Medicine)
  http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
- CDC (Centers for Disease Control)
  http://www.cdc.gov/pregnancy/meds/index.html
- FDA Office of Women's Health Pregnancy Registry Website
  https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm251314.htm

THANK YOU