

THE PREGNANCY AND LACTATION LABELING RULE (PLLR)

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The speaker has nothing to disclose.

OVERVIEW

- **Introduction**
- **History of Pregnancy Labeling**
- **Overview of PLLR Labeling Changes**
- **Summary/Conclusion**



INTRODUCTION

Pregnancy and Medication Use

- Six million pregnancies in US every year
- 50% of pregnant women reported taking at least one medication
- Pregnant women take an average of 2.6 medications at any time during pregnancy
- First trimester use of prescription medications has increased by more than 60%
- Use of 4 or more medications in the first trimester has tripled (9.9% to 27.6%)

Mitchell AA, Gilboa SM, Werler MM, et al., Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol. 2011;205(1):51.e1-8.

Pregnancy and Medication Use

- Only a small percentage of drugs are contraindicated for use in pregnancy or while breast feeding.
 - e.g., isotretinoin, mycophenolates
- For the majority of drugs, labeling should provide what is known in a way that enables decisions for treatment.

The question is HOW?

HISTORY OF PREGNANCY LABELING

Timeline of the PLLR

1979

1994

1997- 2003

2008 - 2013

2014

Pregnancy Categories established by regulation

Pregnancy Labeling initiative begins

Proposed Rule written with new labeling format

Draft PLLR issued; revised after public comment

PLLR published December 4



2006

Expert input; Advisory Committees, focus groups

Physician Labeling Rule (PLR); revises content and format of entire labeling

The Problem with Letters

A

- Pregnancy letter category system was overly simplistic
- Misinterpreted as a grading system
- A drug with adverse information in animals could be labeled as the same category as a drug with no animal information

B
C

- Pregnancy Category C

D

X

- Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, BUT the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks
- Studies in pregnant women and animals are not available

Intent of PLLR

- Provide the prescriber with relevant information for critical decision-making when treating pregnant or lactating women
- More complete statement of the known risks based on the available data
- Considerations of medical/disease factors
- Animal data put in context of human exposure
- Human data added when available
- Explicitly states when no data are available

PLLR

- Effective date **June 30, 2015**.
- **ALL** prescription drugs to remove pregnancy letter categories over the next 3-5 years
- Prescription drugs approved on or after June 30, 2001 have additional content and formatting requirements
- Reorganizes information in prescription drug labeling to more clearly describe available data to aid decisions and counseling of patients using prescription drugs.

Challenge Question 1

The PLLR completes the content and format changes that began with the 2006 Physician Labeling Rule?

- A. True
- B. False

OVERVIEW OF PLLR LABELING CHANGES

Prescription Drug Labeling Sections 8.1 – 8.3 USE IN SPECIFIC POPULATIONS

CURRENT LABELING

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

NEW LABELING

(effective June 30, 2015)

8.1 Pregnancy
includes Labor and Delivery

8.2 Lactation
includes Nursing Mothers

NEW
8.3

Females and Males of
Reproductive Potential

8.1 Pregnancy

- Four headings
 - Pregnancy Exposure Registry
 - Risk Summary*
 - Clinical Considerations
 - Data



*Required heading

8.1 Pregnancy- Pregnancy Exposure Registry

- Pregnancy Exposure Registry

“There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to TRADENAME during pregnancy.”
- Includes specific contact information
 - Phone
 - Website

8.1 Pregnancy- Risk Summary*

- No drug systemic absorption

“[TRADENAME] is not absorbed systemically following (route of administration) and maternal use is not expected to result in fetal exposure to the drug.”

*Required heading(s)

8.1 Pregnancy- Risk Summary*

- Drugs with systemic absorption
 - When use of a drug is contraindicated during pregnancy, that information must be stated first in the Risk Summary
 - Risk statement based on human data*
 - Risk statement based on animal data*
 - Risk statement based on pharmacology
 - Background risk information in general population*
 - Background risk information in disease population

*Required

Example:

8.1 Pregnancy – Risk Summary - Risk Based on Animal Data

Risk Summary

There are no adequate and well-controlled studies of [TRADENAME] in pregnant women. The limited available information on [TRADENAME] use during pregnancy is not sufficient to inform a drug-associated risk of major birth defects or miscarriage. In animal reproduction studies, oral administration of [drugname] to pregnant rats and rabbits during the period of organogenesis at doses up to 40 and 20 times the maximum recommended human dose (MRHD), respectively, resulted in decreased fetal body weight gain and delayed skeletal ossification but no teratogenic effects were observed. Decreased fetal body weight and delayed skeletal ossification were not observed at doses up to 10 and 5 times the MRHD in rats and rabbits, respectively *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15- 20%, respectively.

Example: Old Labeling

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C

[Drugname] caused some developmental toxicity in rats, but was not teratogenic in rats or rabbits. There are no adequate and well-controlled studies of [TRADENAME] in pregnant women. When treating pregnant women with [TRADENAME], carefully consider whether the potential benefits outweigh the potential risks of treatment.

No teratogenic effects were observed when [drugname] was given to pregnant rats or rabbits during the period of organogenesis at oral doses up to 200 and 36 mg/kg/day, respectively. These doses are 48 and 17 times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 40 mg on a mg/m² basis. Fetal body weight gain was reduced, and skeletal ossification was delayed in both rats and rabbits at these doses; . . .

Example: Old Labeling, continued

8.1 Pregnancy

Nonteratogenic Effects

Neonates exposed to [TRADENAME] and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin Syndrome [see Warnings and Precautions (5.2)].

Example: Old Labeling, continued

8.1 Pregnancy

Nonteratogenic Effects (continued)

Physicians should also note the results of a prospective longitudinal study of pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy.

When treating a pregnant woman with [TRADENAME] , the physician should carefully consider both the potential risks of taking an SSRI, along with the established benefits of treating depression with an antidepressant. This decision can only be made on a case by case basis.

Example:

8.1 Pregnancy – Risk Summary - Risk Based on Animal Data

Risk Summary

There are no adequate and well-controlled studies of [TRADENAME] in pregnant women. The limited available information on [TRADENAME] use during pregnancy is not sufficient to inform a drug-associated risk of major birth defects or miscarriage. In animal reproduction studies, oral administration of [drugname] to pregnant rats and rabbits during the period of organogenesis at doses up to 40 and 20 times the maximum recommended human dose (MRHD), respectively, resulted in decreased fetal body weight gain and delayed skeletal ossification but no teratogenic effects were observed. Decreased fetal body weight and delayed skeletal ossification were not observed at doses up to 10 and 5 times the MRHD in rats and rabbits, respectively *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15- 20%, respectively.

Example:

8.1 Pregnancy – Risk Summary -

Risk Summary

There are no adequate and well-controlled studies of [TRADENAME] in pregnant women. The limited available information on [TRADENAME] use

Required: In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

ossification were not observed at doses up to 10 and 5 times the MTD in rats and rabbits, respectively [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15- 20%, respectively.

8.1 Pregnancy- Clinical Considerations

- Clinical Considerations (five optional subheadings)
 - Disease-Associated Maternal and/or Embryo/Fetal Risk
 - Dose Adjustments During Pregnancy and the Post-Partum Period
 - Maternal Adverse Reactions
 - Fetal/Neonatal Adverse Reactions
 - Labor or Delivery

8.1 Pregnancy – Clinical Considerations

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

In pregnant women with poorly or moderately controlled asthma, there is an increased risk of preeclampsia in the mother and prematurity, low birth weight and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

8.1 Pregnancy – Clinical Considerations

Clinical Considerations

Maternal Adverse Reactions

[TRADENAME] may increase hyperglycemia in pregnant women with diabetes. Monitor maternal blood glucose levels regularly and adjust insulin dosages as needed [see *Warnings and Precautions (5.x)*].

8.1 Pregnancy – Clinical Considerations

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Exposure to SSRIs and SNRIs, including [TRADENAME] , in late pregnancy may lead to an increased risk for neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding, and/or persistent pulmonary hypertension of the newborn (PPHN).

Monitor neonates who were exposed to [TRADENAME] in the third trimester of pregnancy for PPHN and drug discontinuation syndrome *[see Data]*.

8.1 Pregnancy – Clinical Considerations

Clinical Considerations

Dose Adjustments During Pregnancy and the Postpartum Period

- Dosage adjustments mentioned here with cross references to Dosage and Administration (2.x) and Clinical Pharmacology (12.3)]

Labor or Delivery

- New position for information from old format 8.2 Labor and Delivery

8.1 Pregnancy- Data

- Data
 - Detailed description of the data that provide the scientific basis for the summary information presented in the Risk Summary and Clinical Considerations headings
 - Human Data
 - Animal Data

8.2 Lactation

- Three headings:
 - Risk Summary*
 - Clinical Considerations
 - Data



*Required heading

8.2 Lactation- Risk Summary*

- No drug systemic absorption

“[TRADENAME] is not absorbed systemically by the mother following (route of administration) and breastfeeding is not expected to result in exposure of the infant to [drugname].”

*Required heading

8.2 Lactation – Risk Summary

- Systemic drug absorption
 - Presence of drug in milk*
 - Concentration in milk
 - Actual or estimated infant daily dose
 - Effects of drug on the breastfed infant*
 - Effects of the drug on milk production*
 - Risk/Benefit Statement

*if unknown, must state so.

Example:

8.2 Lactation- Risk Summary

Risk Summary

Limited published literature based on breast milk sampling from five mothers, reports that [drugname] is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal

Required: The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed child from TRADENAME or from the underlying maternal condition.

maternal condition.

Example:

8.2 Lactation- Risk Summary- Safety Concerns

Risk Summary

[Drugname] is present in human milk. A published lactation study reports variable levels of [Drugname] in human milk. The highest levels were measured in breast

milk when the drug was taken during the last 24 hours of lactation. Because of the potential for serious adverse reactions, including . . . , advise patients that breastfeeding is not recommended during treatment with

TRADENAME.

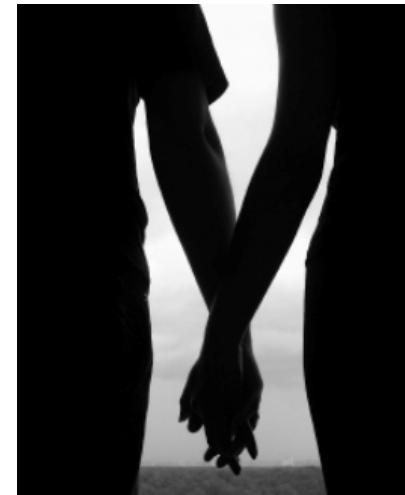
produced. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with [TRADENAME].

8.2 Lactation - Clinical Considerations and Data

- Clinical Considerations
 - Minimizing exposure to the breastfed infant
 - Monitoring the breastfed infant for Adverse Reactions
- Data - Include only when information are available
 - Description of clinical lactation study/data
 - Description of animal lactation study (only if there are no human data)

8.3 Females and Males of Reproductive Potential

- Include when there are requirements or recommendations for pregnancy testing and/or contraception and/or when human and/or animal data suggest drug effects on fertility
- Three headings
 - Pregnancy Testing
 - Contraception
 - Infertility



8.3 Females and Males of Reproductive Potential

- Dedicated labeling subsection consolidates information from other areas of labeling
 - Moves recommendations for contraception and pregnancy testing from section 8.1, Pregnancy and section 13, Nonclinical Toxicology
 - Moves human fertility study descriptions and infertility considerations from section 13, Nonclinical Toxicology
 - Animal fertility study descriptions remain in section 13, Nonclinical Toxicology

Example:

8.3 Females and Males of Reproductive Potential

Based on its mechanism of action, TRADENAME can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

Pregnancy Testing

Female patients of reproductive potential should have a negative pregnancy test ...

Contraception

Females: Advise female patients of reproductive potential to use effective contraception during treatment and for at least 2 weeks after the last dose of TRADENAME. Advise patients that TRADENAME can reduce the effectiveness of oral contraceptives and to use alternative effective contraception during treatment with TRADENAME [*see Warnings and Precautions (5.x), Drug Interactions (7.x), Clinical Pharmacology (12.x)*].

Infertility

Females: Decreased fertility and ovarian toxicity were observed in female rats treated with DRUGNAME. Advise female patients of reproductive potential ...

Males: Effects on spermatogenesis have been observed in animals treated with DRUGNAME. Advise male patients of the potential risk...

Challenge Question 2

A young woman is concerned about a newly prescribed drug. You review the labeling for the drug product to find that the drug can cause embryofetal toxicity if used during pregnancy. The labeling is in PLLR format. Where in the drug labeling would you look for information about potential risks to the fetus with maternal use of the drug and important patient management recommendations?

- A. Highlights
- B. Section 5. Warnings and Precautions
- C. Section 8.1. Pregnancy
- D. Section 8.3. Females and Males of Reproductive Potential
- E. All of the above

Challenge Question 3

You are treating a male patient who is concerned about the effects of a drug on fertility. You review the drug labeling that is in the PLLR format. Where in drug labeling might you find data from human fertility studies?

- A. Section 6. Adverse Reactions
- B. Section 8.3. Females and Males of Reproductive Potential
- C. Section 13. Nonclinical Toxicology
- D. A and B
- E. B and C

SUMMARY/CONCLUSION

PLLR Summary

- PLLR implementation is a gradual process that has started and will take another **2 to 4 years**.
- **ALL** prescription drug labeling will be required to remove pregnancy letter categories.
- PLLR provides clearer communication of available data to assist the prescriber with critical decision-making when treating pregnant or lactating women
- PLLR notes when there is no available data

PLLR – Changes to Labeling

8. USE IN SPECIAL POPULATIONS

8.1 Pregnancy*

Pregnancy Registry
Risk Summary*
Clinical Considerations
Data

8.2 Lactation*

Risk Summary*
Clinical Considerations
Data

8.3 Females and Males of Reproductive Potential

Pregnancy Testing
Contraception
Infertility

*Required heading

[See draft guidance: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.](#)

Conclusion

- The PLLR provides a more structured approach to labeling to help **more clearly describe available data** that can be used to aid in complex risk/benefit discussions between prescribers and their patients.
- PLLR includes required statements when data are not available. Hopefully, all stakeholders will work together to proactively seek information to fill the gaps.

Thank you



RESOURCES

PLLR Website



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Drugs



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Development & Approval Process (Drugs)

Development Resources

Labeling

▶ **Pregnancy and Lactation Labeling Final Rule**

Pregnancy and Lactation Labeling Final Rule

[12/3/14] The FDA published the *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, referred to as the "[Pregnancy and Lactation Labeling Rule](#)" (PLLR or final rule).

The PLLR requires changes to the content and format for information presented in prescription drug labeling in the Physician Labeling Rule (PLR) format to assist health care providers in assessing benefit versus risk and in subsequent counseling of pregnant women and nursing mothers who need to take medication, thus allowing them to make informed and educated decisions for themselves and their children. The PLLR removes pregnancy letter categories – A, B, C, D and X. The PLLR also requires the label to be updated when information becomes outdated.

Below is a comparison of the current prescription drug labeling with the new PLLR labeling requirements.

Prescription Drug Labeling Sections 8.1 – 8.3 USE IN SPECIFIC POPULATIONS

CURRENT LABELING

8.1 Pregnancy

NEW LABELING

(effective June 30, 2015)

8.1 Pregnancy

includes Labor and Delivery

8.2 Labor and Delivery

8.2 Lactation

includes Nursing Mothers

Pregnancy Registry Website

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Women's Health Research
OWH Research and Development Program
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OWH Presentations and Publications
Understanding Sex Differences
Women in Clinical Trials
Pregnancy Registries

Pregnancy Registry Information for Health Professionals



Find a Registry

Sign Up Your Patients

Enrolling your patients in a pregnancy exposure registry can help improve safety information for medicines used during pregnancy and can be used to update drug labeling.

1. **Check the [list of registries](#).** The list includes the website and phone number for you to contact each registry.
2. **Encourage your patients to enroll.**
Remind your patients that they will not be given an experimental drug. Pregnancy registries collect information on pregnancy outcomes in women who are already taking medication.

Buttons



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Copy this code to add the small size
Pregnancy Registry Buttons to your site:
(150X150 pixels)

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/guidancecomplianceandregulatoryinformation/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>



Questions



Back-up slides

Pregnancy Categories

Category	Definition
A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, or animal studies demonstrate a risk and AWC studies in pregnant women have not been done during the first trimester (and there is no evidence of risk in later trimesters)

Pregnancy Categories

Category	Definition
C	<p>Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, And the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.</p> <p>Or animal studies have not been conducted and there are no AWC studies in humans</p>
D	<p>There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, But the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (e.g., if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).</p>

Pregnancy Categories

Category	Definition
X	Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (e.g., safer drugs or other forms of therapy are available).