

Medication Use During Pregnancy and Lactation: Introducing the Pregnancy and Lactation Labeling Rule

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On June 30, 2015, the U.S. Food and Drug Administration implemented the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR was issued to address the shortcomings of pregnancy and lactation information in prescription drug and biological product labeling. The new labeling format under PLLR is structured to better help providers communicate important information about the risks and benefits of taking a specific medication to their pregnant or breastfeeding patients.

Keywords: pregnancy, lactation, breastfeeding, Pregnancy and Lactation Labeling Rule, PLLR

THERE ARE SIX million pregnancies in the United States every year,¹ and over 50% of pregnant women report taking at least one medication.² Regarding lactation, 81% of women will breastfeed at some point during their infant's first year of life with 52% of women still breastfeeding at 6 months postpartum and 31% of women still breastfeeding at 12 months postpartum.³ Often, prescribing decisions during pregnancy and lactation are individualized and involve complex maternal, fetal, and infant risk–benefit considerations.

On June 30, 2015, the U.S. Food and Drug Administration implemented the Pregnancy and Lactation Labeling Rule (PLLR).^{4,5} The rule was issued to address the shortcomings of pregnancy and lactation information in prescription drug and biological product labeling. Based on input from key stakeholders through advisory committees and focus groups, the U.S. Food and Drug Administration determined that the pregnancy letter category system was overly simplistic because it did not capture the complexities of available risk information and risk–benefit considerations. In addition, the pregnancy letter categories were misinterpreted as a grading system that resulted in prescribing decisions that were based on incorrect assumptions for the known risks of the drug.^{6–8} The new labeling format under PLLR is structured to better help providers communicate important information about the risks and benefits of taking a specific medication to their pregnant or breastfeeding patients.

The PLLR requires drugs and biological products approved after June 30, 2001, to reformat the information found in the Pregnancy and Nursing Mothers sections of prescription product labeling, and remove the letter category by June 2020. In addition, the pregnancy letter categories A,

B, C, D, and X are required to be removed from all prescription drug and biological product labeling, including generic labeling and drugs approved before June 30, 2001, by June 30, 2018. The old format and pregnancy letter categories are replaced with integrated narrative summaries of the risks of using a drug or biological product during pregnancy and lactation. Specifically, the new labeling requirements describe, based on available information, a summary of the risks of the prescription drug or biological product for the mother, the fetus, the breastfeeding infant, and females and males of reproductive potential. The new format requires a discussion of data supporting the Risk Summary and relevant information to help healthcare providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation.

When a drug is initially approved, there are often little or no human data to inform the pregnancy and lactation sections of drug or biological product labeling. Information from animal studies may be the only information described in these sections. Therefore, human data collected in the post-marketing setting are often relied upon to provide additional information when the drug is used during pregnancy or lactation. The PLLR depends on the quality of available data and requires drug manufacturers to update drug or biological product labeling when new information becomes available.⁹ To obtain the highest quality data to inform product labeling about risks of use of a product during pregnancy or lactation, all stakeholders, including the academic community, patient and advocacy groups, the pharmaceutical industry, and global regulatory authorities, are encouraged to work together to provide this important information.

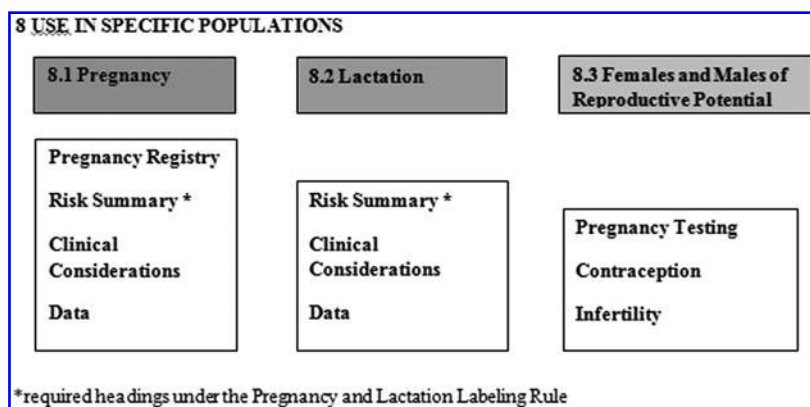


FIG. 1. The Pregnancy and Lactation Labeling Rule and changes to the prescription drug labeling.

Description of the New Labeling Required Under the PLLR¹

Labeling under the PLLR includes three sections: Pregnancy (8.1), Lactation (8.2), and Females and Males of Reproductive Potential (8.3) (Fig. 1).

Pregnancy, Section 8.1

Pregnancy, section 8.1, includes four headings: “Pregnancy Exposure Registry,” “Risk Summary,” “Clinical Considerations,” and “Data.” If a pregnancy exposure registry is available, this section includes contact information on how to enroll. The Risk Summary provides a narrative summary of the human, animal, and pharmacologic data and describes the risk of adverse developmental outcomes for the drug during pregnancy. When there are no human and/or animal data, labeling will explicitly state that there are no data to inform the risk. The Clinical Considerations heading provides information to further inform prescribing and benefit–risk counseling and is divided into five subheadings: Disease-Associated Maternal and/or Embryo/Fetal Risk, Dose Adjustments During Pregnancy and the Postpartum Period, Maternal Adverse Reactions, Fetal/Neonatal Adverse Reactions, and Labor or Delivery. For example, mepolizumab, which is a drug indicated for the treatment of asthma, includes a Clinical Consideration section that provides a description of the effects of poorly controlled asthma in a pregnant woman and its association with an increased risk of preeclampsia, prematurity, low birth weight, and small-for-gestational age.¹⁰ The data section includes a detailed description of the information that provided the scientific basis for the summary information presented in the Risk Summary and Clinical Considerations headings and is divided into two subheadings: Human Data and Animal Data.

Lactation, Section 8.2

Lactation, section 8.2, includes three headings: “Risk Summary,” “Clinical Considerations,” and “Data” and provides information about using the drug while breastfeeding. The Risk Summary section includes information about whether or not the drug is present in breast milk, the amount of drug in breast milk, the potential effects of the drug on the breastfed infant, and the effects of the drug on milk production, if available. Data that inform this section of labeling may be derived, for example, from clinical lac-

tation studies, case series, and/or case reports. The Clinical Considerations section includes information on minimizing exposure to the breastfed infant (relying on pharmacokinetic data from clinical studies) and on monitoring the breastfed infant for adverse reactions, if applicable. For example, hydrocortisone probutate cream, which is a topical corticosteroid cream indicated for the treatment of dermatitis, includes a Clinical Consideration section that provides ways to minimize exposure of the drug to the breastfed infant by using the drug on the smallest area of skin and for the shortest duration while breastfeeding.¹¹

Females and Males of Reproductive Potential, Section 8.3

The Females and Males of Reproductive Potential, section 8.3, is a new section required under PLLR and is included when relevant information is available. This section includes three headings: “Pregnancy Testing,” “Contraception,” and “Infertility.” The recommendations for pregnancy testing and contraception may be based on concerns for potential adverse developmental outcomes associated with drug exposure during pregnancy. In addition, if there are concerns that a drug or biological product may have adverse effects on fertility, a summary of the information and its clinical implications will appear in section 8.3.

Conclusion

The new labeling format under PLLR is structured to better help providers communicate important information about the risks and benefits of taking a specific medication to their pregnant or breastfeeding patients, and, when applicable, to males and females of reproductive potential. Therefore, to obtain the highest quality data to inform product labeling about risks of use of a product during pregnancy or lactation, all stakeholders are encouraged to work together to provide this important information.

Disclaimer

This article reflects the views of the authors and should not be construed to represent the U.S. Food and Drug Administration’s views or policies.

Author Disclosure Statement

No competing financial interests exist.

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