

# FDA Pregnancy Categories

## FDA Pregnancy Risk Information: An Update

In 2015 the FDA replaced the former pregnancy risk letter categories (see below) on prescription and biological drug labeling with new information to make them more meaningful to both patients and healthcare providers. The FDA received comments that the old five-letter system left patients and providers ill-informed and resulted in false assumptions about the actual meaning of the letters.

The new labeling system allows better patient-specific counseling and informed decision making for pregnant women seeking medication therapies. While the new labeling improves the old format, it still does not provide a definitive “yes” or “no” answer in most cases. Clinical interpretation is still required on a case-by-case basis.

The **Pregnancy and Lactation Labeling Final Rule (PLLR)** went into effect on June 30, 2015; however, the timelines for implementing this new information on drug labels (also known as the package insert) is variable.

Prescription drugs submitted for FDA approval after June 30, 2015 will use the new format immediately, while labeling for prescription drugs approved on or after June 30, 2001 will be phased in gradually. Medications approved prior to June 29, 2001 are not subject to the PLLR rule; however, the pregnancy letter category must be removed by June 29, 2018. For generic drugs, if the labeling of a reference listed drug is updated as a result of the final rule, the abbreviated new drug application (ANDA) labeling must also be revised. Labeling for over-the-counter (OTC) medicines will not change, as OTC drug products are not affected by the new FDA pregnancy labeling.

The A, B, C, D and X risk categories, in use since 1979, are now replaced with narrative sections and subsections to include:

### **Pregnancy** (includes Labor and Delivery):

- Pregnancy Exposure Registry
- Risk Summary
- Clinical Considerations
- Data

## **Lactation** (includes Nursing Mothers)

- Risk Summary
- Clinical Considerations
- Data

## **Females and Males of Reproductive Potential**

- Pregnancy Testing
- Contraception
- Infertility

The **Pregnancy** subsection will provide information about dosing and potential risks to the developing fetus and registry information that collects and maintains data on how pregnant women are affected when they use the drug or biological product. Information in drug labeling about the existence of any pregnancy registries has been previously recommended but not required until now. Contact information for the registries will also be included, and pregnant women are encouraged to enroll to help provide data on the effects of drug use or biologics in pregnancy.

If information for the subsections of Pregnancy Exposure Registry, Clinical Considerations, and Data is not available, these subsections will be excluded. The Risk Summary subheadings are always required, even if no data is available.

The **Lactation** subsection will replace the “Nursing Mothers” subsection of the old label. Information will include drugs that should not be used during breastfeeding, known human or animal data regarding active metabolites in milk, as well as clinical effects on the infant. Other information may include pharmacokinetic data like metabolism or excretion, a risk and benefit section, as well as timing of breastfeeding to minimize infant exposure.

In the subsection entitled **Females and Males of Reproductive Potential**, relevant information on pregnancy testing or birth control before, during or after drug therapy, and a medication’s effect on fertility or pregnancy loss will be provided when available.

## **Why Did the FDA Make This Change?**

Clinically, many women require drug treatment during pregnancy due to chronic conditions such as epilepsy, diabetes, hypertension (high blood pressure), or asthma. To withhold drug treatment would be dangerous for both mother and baby. In addition, women are having babies at a later age, which can boost the number of women with chronic conditions. Accessible and understandable pregnancy and

lactation information is important for women and their health care provider's to assess risk versus benefit.

The FDA has received requests to improve the decades-old content and format of pregnancy prescription drug labeling since 1992. According to the Drug Information Division at the FDA, they obtained input from many affected groups and held public hearings, advisory committee meetings, and focus groups to assess the changes. In 2008, the FDA issued the proposed rule and then opened a docket for public comments.

Clinicians and patients were often confused by the meaning of the pregnancy risk categories because, according to the FDA, it was overly simplistic, led to misinformation, and did not adequately address the available information.

Examples of drugs approved since June 30th, 2015 showing various new pregnancy and lactation subsections in their labels:

- Addyi (flibanserin) - indicated for generalized hypoactive sexual desire disorder (HSDD) in premenopausal women.
- Descovy (emtricitabine and tenofovir alafenamide fumarate) - indicated for HIV-1 infection.
- Entresto (sacubitril and valsartan) - indicated for heart failure.
- Harvoni (ledipasvir and sofosbuvir) - indicated for chronic viral hepatitis C infection (HCV).
- Praluent (alirocumab) - indicated for heterozygous familial hypercholesterolemia, or patients with atherosclerotic heart disease who require additional lowering of LDL-cholesterol.

## **FDA Pregnancy Risk Categories Prior to 2015**

In 1979, the FDA established five letter risk categories - A, B, C, D or X - to indicate the potential of a drug to cause birth defects if used during pregnancy. The categories were determined by assessing the reliability of documentation and the risk to benefit ratio. These categories did not take into account any risks from pharmaceutical agents or their metabolites in breast milk. In the drug product label, this information was found in the section "Use in Specific Populations".

The former pregnancy categories, which still may be found in some package inserts, were as follows:

### **Category A**

Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Example drugs or substances: levothyroxine, folic acid, liothyronine

## Category B

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Example drugs: metformin, hydrochlorothiazide, cyclobenzaprine, amoxicillin

## Category C

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Example drugs: gabapentin, amlodipine, trazodone

## Category D

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Example drugs: losartan

## Category X

Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Example drugs: atorvastatin, simvastatin, methotrexate, finasteride

## Related Slideshows

- Breastfeeding & OTC Medication: Safety Tips That You Need To Know
- OTC Medication Use In Pregnancy: Wise or Worrisome?

### Sources:

1. FDA/CDER SBIA Chronicles. Drugs in Pregnancy and Lactation: Improved Benefit-Risk Information. Accessed August 1, 2019 at <https://www.fda.gov/files/drugs/published/%22Drugs-in-Pregnancy-and-Lactation--Improved-Benefit-Risk-Information%22-January-22--2015-Issue.pdf>
2. FDA Consumer Articles. Pregnant? Breastfeeding? Better Drug Information Is Coming. Accessed August 1, 2019 at <https://www.fda.gov/consumers/consumer-updates/pregnant-breastfeeding-better-drug-information-coming>

3. FDA News Release. FDA issues final rule on changes to pregnancy and lactation labeling information for prescription drug and biological products. Accessed August 1, 2019 at <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>
4. Mospan C. New Prescription Labeling Requirements for the Use of Medications in Pregnancy and Lactation. CE for Pharmacists. The Ohio Pharmacist Foundation. Accessed August 1, 2019 at [https://cdn.ymaws.com/www.wsparx.org/resource/resmgr/CE\\_Magazine/WA\\_0416\\_State\\_CE\\_Lesson.pdf](https://cdn.ymaws.com/www.wsparx.org/resource/resmgr/CE_Magazine/WA_0416_State_CE_Lesson.pdf)

## **See also**

- Pregnancy Support Group
- Medicine use during Pregnancy
- Breastfeeding Support Group
- Safe Medicine use while Breastfeeding