

FDA Briefing Document

Risk Communication Advisory Committee Meeting

March 5-6, 2018

Communicating Information about Risks in Pregnancy in Product Labeling for Patients and Providers to Make Informed Decisions about the Use of Drugs during Pregnancy

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Divisions or Office. We have brought the issue of how best to communicate the benefits and risks of drugs and biological products to this Advisory Committee to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendations and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered. Final determinations may be affected by issues not discussed at the advisory committee meeting.

Risk Communication Advisory Committee

Communicating Information about Risks in Pregnancy in Product Labeling for Patients and Providers to Make Informed Decisions about the Use of Drugs during Pregnancy

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Food and Drug Administration

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Pediatric and Maternal Health

Division of Bone, Reproductive, and Urologic Products

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: February 16, 2018

From: Division of Pediatric and Maternal Health
Division of Bone, Reproductive, and Urologic Products
Office of New Drugs, CDER, FDA
Center for Biologics Evaluation and Research

To: Members, Risk Communication Advisory Committee

RE: Background Reading Materials, March 5-6, 2018

The reference documents listed below provide background for this meeting:

- FDA Draft Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (December 2014)
- Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling, Final Rule (79 FR 72063, December 4, 2014).

- Meena Pole, Adrienne Einarson, Nicholas Pairaudeau, Tom Einarson, and Gideon Koren. Drug Labeling and Risk Perceptions of Teratogenicity: A Survey of Pregnant Canadian Women and Their Health Professionals. *J Clin Pharmacol* 2000;40:573-577.
- Conover Elizabeth, Polifka Janine. The Art and Science of Teratogen Risk Communication. *Amer J of Medical Genetics*. 2011;157:227.233.

1. Introduction

The implementation of the Pregnancy and Lactation Labeling Rule (PLLR) beginning in 2015 has re-invigorated efforts to improve communication on available evidence on risks associated with drug¹ exposure in pregnancy. Most pregnant women in the United States will take at least one drug during pregnancy, and certain vaccinations are recommended in pregnant women. Considerations for benefit-risks of treatment are unique for pregnant women and their providers. Currently, reliable clinical evidence informing safe drug use in pregnancy is generally lacking, but labeling regulation under PLLR requires the inclusion of available data about use of the medication during pregnancy.

At this Advisory Committee meeting, you will be asked to discuss factors that are meaningful to pregnant women's and healthcare providers' interpretation of risk messages and how those factors affect treatment decisions. You will also be asked to comment on the effectiveness of communications to inform about risks in product labeling under PLLR to date. Lastly, we seek your input on approaches to effectively communicate risk in a manner helpful to prescribers and pregnant women in their treatment decision making, and identify potential unintended adverse consequences of risk communication and strategies for minimizing such unintended consequences.

We thank you for your participation in this meeting and for providing your expertise and insight. We hope that discussions at this meeting will assist us in determining effective approaches to convey safety information in pregnancy in the product labeling.

2. Background

Pregnant women and those who may become pregnant represent an important segment of the population, with more than 60 million females of reproductive age in the United States, and approximately 4 million live births per year. Pregnant women may have chronic conditions, such as diabetes, seizure disorders, or asthma, that need to be treated during pregnancy, or may develop acute medical conditions during pregnancy that require treatment. In addition, nearly half of all pregnancies in the United States are unplanned, resulting in potential inadvertent drug exposure to the developing fetus. Based on published data, 50-70% of pregnant women report taking at least one medication during pregnancy (excluding vitamins/ minerals), and use of medications during pregnancy has been increasing over the last three decades.²

¹ For this document, all references to *drugs* and *medications* include both human drug and biological products.

² Mitchell AA et al. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. *Am J Obstet Gynecol* 2011;205(1):51.

During clinical development of most drug products, pregnant women are actively excluded from trials. Therefore, at the time of FDA approval of a new drug, data on the effects of exposure to a drug during pregnancy are usually limited to animal data. Thus, there is often an absence of evidence-based clinical information for providers to use when prescribing or counseling pregnant women. Obtaining human pregnancy safety data to inform product labeling is usually performed post-approval. Sponsors are required to report adverse drug and vaccine events, including birth defects, to the FDA Adverse Event Reporting System (FAERS) and to the Vaccine Adverse Event Reporting System (VAERS). In addition, sponsors often maintain a pharmacovigilance database of pregnancy-related cases that are reported to them. These reports include both normal and abnormal outcomes. However, spontaneous reporting has inherent and important limitations, including underreporting, reporting biases, missing information on clinical details and other important exposures that hinder a reliable assessment of drug causality. More importantly, interpretation of risk based on spontaneous reporting is impossible because incidence rates cannot be calculated when data on overall exposures during pregnancy are lacking. Therefore, routine pharmacovigilance methods alone are usually insufficient to conclusively determine the drug-related risks to a pregnant woman and her fetus.

Observational studies are an important source of data to help provide information about the safety of drugs in pregnancy. Examples of these studies are pregnancy registries, retrospective cohort studies, and case control studies conducted by industry, academia, government, and surveillance networks. When warranted, FDA may require drug sponsors to conduct post-approval pregnancy safety studies. Sponsors are also responsible for reviewing the available published literature and updating labeling as new data that inform the safety in pregnancy become available. Some of the difficulties in drawing conclusions based on observational data include small sample sizes and inconsistent findings among studies. Methodologic limitations of observational studies include confounding due to the underlying disease and other differences between exposure and comparator cohorts (or cases and controls), variations in birth defect outcome classification systems, recall bias in case control studies, and exposure and outcome misclassification in retrospective cohort studies. These limitations often preclude the ability to draw clear conclusions regarding product safety in pregnant women.

3. Prescription Drug Product Labeling

The objective of drug product labeling is to communicate a summary of the information needed for the safe and effective use of the drug. Prescription drug product labeling is intended for healthcare providers and must, among other requirements³ :

- Contain a summary of the essential scientific information needed for the safe and effective use of the drug,

³ See 21 CFR 201.56 (a)

- Be informative and accurate and neither promotional in tone nor false or misleading
- Be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.

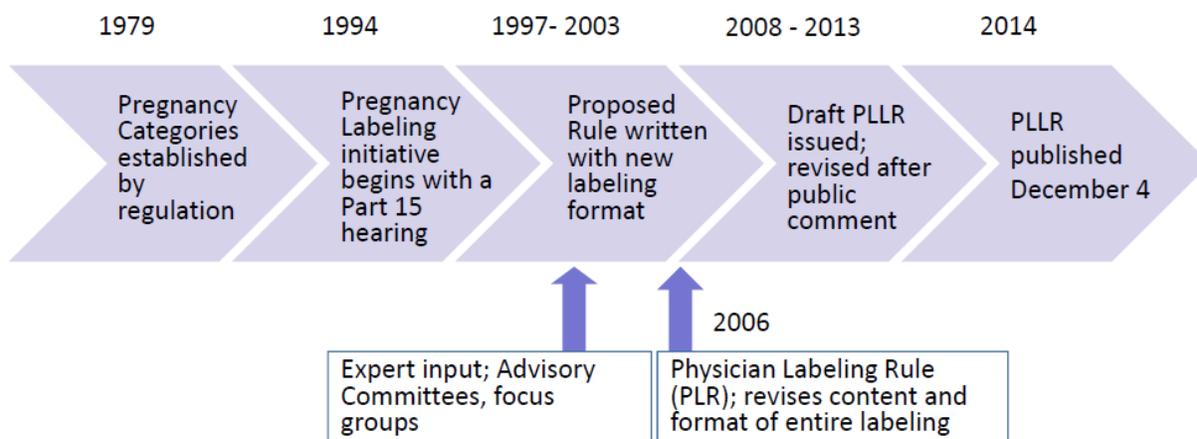
The goal of labeling is to communicate a summary of data on effectiveness and safety of a product that prescribers can use in making treatment decisions. Compared to other adult populations, however, communicating risk information for the pregnant patient can be particularly challenging. In pregnancy, the benefit-risk considerations are not confined to the patient, and there may be a complex interplay of expectations from the pregnant woman, her family, and society in exposing her fetus to medications.

There are three important aspects of drug product labeling that are often not readily apparent to healthcare providers or patients. Firstly, labeling does not specify clinical practice guidelines, but rather, includes a concise summary of information needed for the safe and effective use of drugs. Secondly, absent a contraindication, use of an approved drug product in a pregnant woman is not considered an “off-label” use. Off-label use is defined as a use of an approved product for an indication for which the product has not been approved. Pregnant women are considered a sub-population of the adult population; and, therefore, are not excluded from the approved population if a drug has been approved for use in adults. Lastly, labeling must follow regulations as specified in the Code of Federal Regulations. For example, certain sections of labeling describe only risks, while other sections describe effectiveness of a drug for its approved use (s).

On June 30, 2015, the Final Rule, “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,” also known as the Pregnancy and Lactation Labeling Rule (PLLR), took effect.⁴ The PLLR completes the process of improving the content and format of drug product labeling as implemented by the Physician Labeling Rule in 2006. As illustrated in Figure 1 below, the PLLR was finalized only after input from stakeholders was carefully considered.

⁴ Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling, Final Rule (79 FR 72063, December 4, 2014).

Figure 1: Development Timeline of the Pregnancy and Lactation Labeling Rule



The PLLR called for a narrative summary instead of the pregnancy letter category system (A, B, C, D, and X) because FDA determined the category system was often confusing and did not accurately or consistently communicate risks of a drug when used during pregnancy. Because risk-benefit decisions regarding use of a drug during pregnancy are more complex than the category designations suggest, reliance on this system by healthcare providers was often misinterpreted and could result in incorrect clinical decision making. Now, under PLLR, a narrative summary of the risks of a drug during pregnancy and a summary of the data used to support this narrative are required in labeling.

Under PLLR, the *Pregnancy* subsection of labeling is presented under the following headings and subheadings:

Pregnancy Exposure Registry

If a pregnancy registry is available, this section includes the contact information for enrollment.

Risk Summary

The Risk Summary provides a narrative summary of available human, animal, and pharmacologic data that is intended to describe the risk of adverse developmental outcomes for the drug during pregnancy. Animal data are described in context of human dose exposure. When there are no human and/or animal data, statements are included that state that there are no data to inform the risk. The Risk Summary must state when available human data do not establish the presence or absence of drug-associated risk. In addition, the percentage range of live births in the United States with a major birth defect

and the percentage range of pregnancies in the United States that end in miscarriage, regardless of drug exposure, must be included.⁵ If such information is available for the population(s) for which the drug is labeled, it must also be included.

Clinical Considerations (Included only if data are available)

- Disease-associated maternal and/or embryo/fetal risk
Information on the potential impact of the disease is included with the intent of providing a balanced picture of benefit-risk considerations.
- Dose adjustments during pregnancy and the postpartum period
Summary of dose adjustment recommendations based on pharmacokinetic data is included, if applicable.
- Maternal adverse reactions
Information on drug-associated adverse reactions that are unique to pregnancy and recommendations on how to monitor or mitigate risks are included.
- Fetal/Neonatal adverse reactions
Information on drug-associated fetal/neonatal adverse reactions that are not developmental abnormalities are included.
- Labor or delivery
Information on drug-associated labor or delivery effects is included.

Data

- Human Data
A concise summary of the human data that support the Risk Summary and Clinical Considerations is included.
- Animal Data
A concise summary of the animal data that support the Risk Summary is included.

Pursuant to the PLLR implementation schedule, all prescription drug product labeling must be in compliance with PLLR requirements by June 30, 2020. In the past two years, over 500

⁵ Review of available data suggest that major birth defects occur in 2-4% of the general population and that miscarriage occurs in 15-20% of clinically recognized pregnancies.

product labels were converted to comply with PLLR. This total represents a small proportion of labeling that must be converted to PLLR format by June 30, 2020. Following the PLLR implementation schedule, the Agency anticipates about 450 PLLR labeling conversions in 2018; 800 in 2019; and 300 in 2020.⁶

As mentioned above, the Agency recognizes the challenges in providing the risk information as intended with the PLLR when there are limited available human data to inform about the risk-benefit of the use of a drug during pregnancy. Of the over 500 products that have been converted to PLLR format, fewer than 25% include human data. To demonstrate the limitations of available data, and challenges with providing a clear conclusion based on available human data, labeling examples are listed below in Table 1 and excerpts of their *Pregnancy* subsections are provided as [Attachments](#).

Table 1: Examples of PLLR Labeling*

Example	Human Data	Animal Data
1. Solosec (secnidazole)	Limited data from cases reported in pharmacovigilance database	No adverse developmental outcomes
2. Xenazine (tetrabenazine)	Limited data from published case report	Adverse developmental outcomes
3. Segluromet (ertugliflozin, metformin hydrochloride)	Human data with metformin hydrochloride component from observational studies	Adverse developmental outcomes due to ertugliflozin component
4. Zofran (ondansetron)	Data from observational studies; inconsistent findings	No adverse developmental outcomes
5. Enbrel (etanercept)	Data from pregnancy registry and an observational study	No adverse developmental outcomes
6. Trizivir (abacavir/lamivudine/zidovudine)	Data from pregnancy registry	Inconsistent findings between animal species
7. Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine]	Limited data from pregnancy registry	No adverse developmental outcomes

*See [Attachments](#) for labeling excerpts.

⁶ Note: These estimates do not include the PLLR conversion of labeling of numerous generic drugs or labeling of prescription drugs not already in the Physician Labeling Rule format.

4. Published Literature on Risk Perception of Drugs in Pregnancy

Treatment decisions in pregnancy involve complex maternal, fetal, and obstetrical benefit-risk considerations. Ideally, the considerations involved in the decision to use a drug should balance the risks and benefits of treatment versus the risks to the pregnant woman and fetus, either direct or indirect, if the condition is left untreated or is treated in a different way. However, such a benefit-risk approach is challenging in pregnancy due to various factors, such as societal and familial expectations and personal maternal desire to do what is best for her pregnancy. In reality, the decision to receive treatment is considerably influenced by *perceived* risks of the treatment, which play an important role in prescribers' decision to recommend treatment and pregnant women's acceptance of such treatment.

This section summarizes select available published literature on risk perception of drugs in pregnancy. These publications were chosen on the basis that they were conducted in the US (influenza vaccine) or in regions of the world where the attitudes of those surveyed may be applicable to those of pregnant women in the US (prescription and over-the-counter drugs).

Vaccination: Influenza vaccine

Influenza infection during pregnancy can cause significant morbidity in pregnant women. Influenza vaccination is one of the most important strategies to prevent influenza infection and its severe complications, and to mitigate the impact of influenza epidemics. The World Health Organization (WHO) and the Advisory Committee on Immunization Practices (ACIP) at the Centers for Disease Control and Prevention (CDC) recommend influenza vaccination for pregnant women any time during pregnancy. Despite these recommendations, uptake is still suboptimal. According to the CDC, uptake of flu vaccine among pregnant women in 2012-2015 was only approximately 50%.⁷

Studies that evaluated reasons for the low vaccine uptake have identified some consistent reasons. A 2014 literature review⁸ found that lack of awareness of the need for vaccination and misconception about the influenza vaccine were barriers to acceptance. The review cited a study where 45 % of pregnant women believed that the vaccine was unsafe and nearly 80% thought it could cause birth defects. The review also found that most pregnant women were not aware that they are at high risk for influenza infection, and if they were aware, they underestimated that risk. A study looking at the Influenza A (H1N1) 2009 Monovalent Vaccine acceptance among pregnant women found almost all participants were concerned about the vaccine being untested and lack of information about potential adverse effects, especially the long-term effects on the

⁷ Accessed 1/30/18: https://www.cdc.gov/flu/fluview/pregnant-coverage_1516estimates.htm

⁸ Carol Yuet Sheung Yuen*, Marie Tarrant. Determinants of uptake of influenza vaccination among pregnant women – A systematic review. *Vaccine* 32 (2014): 4602-4613.

developing fetus.⁹ Those opting against vaccination expressed an unwillingness to accept the uncertainty of the safety of the vaccine in pregnancy; the safety of the infant was a key factor in the pregnant women's motivation whether to adopt vaccine recommendations. Another study evaluating Influenza A (H1N1) 2009 Monovalent Vaccine uptake among 1400 pregnant women found that 35% believed that all vaccines should be avoided in pregnancy, and 42% indicated that the Influenza A (H1N1) 2009 Monovalent Vaccine should be avoided during pregnancy.¹⁰ Almost 30% believed that the Influenza A (H1N1) 2009 Monovalent Vaccine increased the risk of miscarriage or birth defects, 35% indicated the vaccine could cause fetal harm, and 29% of women believed that the Influenza A (H1N1) 2009 Monovalent Vaccine could increase the risks of miscarriages or birth defects. The women expressed these beliefs despite the fact that 94% of them recognized the potential seriousness of influenza caused by pandemic (H1N1) 2009 virus during pregnancy, stating that the virus could cause hospitalization or death. Of note, the women's knowledge that influenza disease caused by pandemic (H1N1) 2009 virus was a serious, potentially fatal illness did not influence the decision to receive the vaccine.

Prescription and over-the-counter (OTC) drugs:

A 2016 cross-sectional, web-based study in the United Kingdom sought to describe medication use, and risk perception for common acute conditions in pregnancy among pregnant and postpartum mothers.¹¹ In total, approximately 75% of women reported OTC/prescription medication use in pregnancy. Although a significant proportion of women reported acute conditions in pregnancy, relatively few of them used medication for the conditions. Among those with urinary tract infections (UTI), 65% took prescribed antibiotics. Women who took antibiotics for UTI reported a lower perceived risk score with respect to antibiotics compared to women who were untreated. Almost 75% of women expressed that they deliberately avoided using certain OTC medications in pregnancy. The most common reasons for avoiding OTC medications were fear of harming the fetus, medication not recommended, or that they would not take any medication in pregnancy or would endure as much as possible before taking medications. A 2015 large-scale multinational Internet survey of pregnant and postpartum women evaluated their perception of risks of various substances, including drugs, in pregnancy.¹² Except for thalidomide, the teratogenic risk for the drugs surveyed was considered

⁹ Molly M. Lynch, Elizabeth W. Mitchell, Jennifer L. Williams, et al. Pregnant and Recently Pregnant Women's Perceptions about Influenza A Pandemic (H1N1) 2009: Implications for Public Health and Provider Communication. *Matern Child Health J* (2012) 16:1657–1664.

¹⁰ Dlugacz Y, Fleischer A, Carney MT, et al. 2009 H1N1 vaccination by pregnant women during the 2009-10 H1N1 influenza pandemic. *Am J Obstet Gynecol* 2012; 206:339. e1-8.

¹¹ M. J. Twigg, A. Lupattelli, H. Nordeng. Women's beliefs about medication use during their pregnancy: a UK perspective. *Int J Clin Pharm* (2016) 38:968–976.

¹² Petersen I, McCrea RL, Lupattelli A, et al. Women's perception of risks of adverse fetal pregnancy outcomes: a large-scale multinational survey. *BMJ Open* 2015;5:e007390.

less than 5%. While most women correctly identified that baseline risk of birth defect was less than 5%, they believed that the risk was increased with all medications queried. From a range of 0 (no increased risk) to 10 (definite teratogenic risk), women perceived risk scores of 2 for acetaminophen, 4 for OTC anti-nausea drugs, 6 for swine flu vaccine, 8 for antidepressants, and 10 for thalidomide. A 2010 Internet survey of Norwegian pregnant women and mothers assessed perception of risk of commonly used drugs and other substances in pregnancy.¹³ Numeric rating scales ranged from 0 (no increased risk) to 10 (fetal malformation following each exposure). Similar to the aforementioned 2015 survey, most women estimated correctly a baseline risk of major malformation to be $\leq 5\%$. Women assigned the highest perceived risks (listed in increasing order of risk) to the following medications/substances (median score from 7 to 8): thalidomide, antidepressants, sedatives/anxiolytics, alcohol, and cigarette. Sedatives/anxiolytics and antidepressants were deemed slightly riskier than thalidomide. Many women (70%) reported that they had chosen not to use certain drugs because they were pregnant; the most common reason for not doing so was fear of fetal harm. A 2001 Spanish study examining perceived risks with 14 medications showed that perceived risk was higher than the actual risks for all medications.¹⁴ Also, physician's estimations of risks were closer to the available scientific evidence, but they, too, over assigned risks to many of the drugs queried.

A study examined the perception of risk among healthcare providers and pregnant women based on the information and certain language provided in the drug label of a drug approved to treat a pregnancy-related condition.¹⁵ The drug was labeled to convey (1) the baseline teratogenic risk in the general population and (2) that the drug does not increase this baseline rate. The authors tested the original, but de-identified, drug label and its modified versions on pregnant women and healthcare providers' interpretation of risk. The participants rated the safety of the drug, based on the different versions of the label, on a scale of 1 (*safe*) to 5 (*unsafe*). Pregnant women had the highest risk perception score (average score 2.9-3.3 on a scale of 0-5), followed by pharmacists/nurses/hospital staff (average score 2.0-2.3), with physicians having the lowest risk perception score (average score 1.7-1.8). Of those surveyed, 40% assigned different risks to various modifications of the drug label. A lower risk score was assigned to drug label version that did not repeat the term "congenital malformations"; furthermore, plainly stating that the drug does not cause adverse pregnancy outcomes appeared to be more reassuring to the participants. The authors concluded that pregnant women believed that a drug was harmful even after it was

¹³ Nordeng H, Ystrom E, Einarson A. Perception of risk regarding the use of medications and other exposures during pregnancy. *Eur J Clin Pharmacol* 2010;66:207–14.

¹⁴ Sanz E, Gómez-López T, Martínez-Quintas MJ. Perception of teratogenic risk of common medicines. *Eur J Obstet Gynecol Reprod Biol* 2001;95:127–31.

¹⁵ Meena Pole, Adrienne Einarson, Nicholas Pairedeau, Tom Einarson, and Gideon Koren. Drug Labeling and Risk Perceptions of Teratogenicity: A Survey of Pregnant Canadian Women and Their Health Professionals. *J Clin Pharmacol* 2000;40:573-577

described to them in scientific terms as safe in the drug label. Similarly, but to a lesser extent, all health professionals rated the drug as having some risk, as their mean scores were higher than the correct score of 1.

A review of the literature by teratogen information specialists who provide counseling to pregnant women on the risks of drug exposure in pregnancy, found that a substantial number of physicians and patients have difficulty understanding and interpreting numeric medical data.¹⁶ To facilitate the understanding of teratology data, these experts recommend comparing the risk information to the baseline risk, and providing information in terms of absolute risk.

5. Summary

Many women may need medications for treatment of acute or chronic medical conditions in pregnancy. Pregnant women and their healthcare providers rely on information in the prescription product labeling to guide the safe and effective use of these products. The PLLR replaced the letter category system with a summary of risk information in the context of background risk, to more clearly communicate the available data for prescribers and patients. However, the data available to inform about the risks of use during pregnancy are often limited and difficult to interpret. The lack of interpretable human data combined with potential risk misperceptions can impact appropriate risk-benefit decisions about the use of a drug during pregnancy.

6. Points for Advisory Committee Discussion

We seek input from the Risk Communication Advisory Committee on the following discussion points:

1. Discuss how the factors below impact healthcare provider decision-making and patient counseling
 - A. Risk perception
 - B. Interpretation of uncertainties of available data on drug use in pregnant women
 - C. Context of drug-associated risks in relation to the background risk information on major birth defects and miscarriage
 - D. Benefit-risk considerations
 - E. Medicolegal considerations

2. A. Discuss your interpretation of the following phrases currently used in the PLLR Risk

¹⁶ Conover Elizabeth, Polifka Janine. The Art and Science of Teratogen Risk Communication. Amer J of Medical Genetics. 2011;157:227.233.

Summary, and provide any suggestions for improvement, if applicable: “adverse developmental outcome”, “limited data”, “available data are not sufficient to inform the risk”, and “available data have not reported a clear association”.

B. Discuss how language affects the following:

- i. Patient decision-making and adherence to treatment
- ii. Physician willingness to treat pregnant patients
- iii. Pregnancy planning and prevention (for example, need for pregnancy testing before prescribing a medicine)

C. Discuss intended and unintended consequences that may occur with certain language or communication approaches.

3. A. Discuss how effective PLLR has been in conveying safety evidence in pregnancy that is useful to benefit-risk decision making. Include in your discussion the following:

- i. Interpretability of safety evidence in drug labeling
- ii. Interpretability and impact of animal data on decision-making when there are no human data
- iii. Information that has been unhelpful or has led to unintended adverse consequences (e.g., avoidance of needed treatment)

If appropriate, recommend strategies to improve risk communication that comply with PLLR requirements.

B. Consider the following situations and discuss best practices to communicate the following in drug product labeling, if appropriate:

- i. Observational study data where inconsistent study findings preclude a clear conclusion
- ii. Observational study data where the weight of evidence show no increased risk for major malformations, but some data suggest an increased risk
- iii. Observational study data where there are methodologic limitations (i.e., when to include or not to include these data)
- iv. When there are no study data, but cases reported in the pharmacovigilance safety database are available

4. When the potential for adverse effects in pregnancy exists, discuss communication strategies (e.g., drug safety communication) that FDA can use to maintain a balanced assessment of

the benefit and risk and to minimize unintended adverse consequences.

ATTACHMENTS

Attachment 1- Drug Labeling 1 (no human data or limited data from few pregnancy cases, animal data with no adverse developmental outcomes) – *Solosec (secnidazole), a nitroimidazole antimicrobial indicated for the treatment of bacterial vaginosis in adult women (most recent labeling version approved 9/2017).*

8.1 Pregnancy

Risk Summary

Limited available data with SOLOSEC use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. In animal reproduction studies, there were no adverse developmental outcomes when secnidazole was administered orally to pregnant rats and rabbits during organogenesis at doses up to 4 times the clinical dose (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In animal reproduction studies, pregnant rats were dosed orally with secnidazole during organogenesis (gestational days 6-17) at 100, 300 and 1000 mg/kg/day, up to 4 times the clinical dose based on AUC comparisons. Animals showed no evidence of adverse developmental outcomes, but maternal toxicity (including reduced body weight gain) was observed at and above 300 mg/kg/day. In rabbits, no evidence of adverse developmental outcomes was observed when oral doses of secnidazole were administered to dams during organogenesis (gestational days 7-20) at doses up to 100 mg/kg/day (about 0.1 times the clinical dose, based on AUC comparisons). Secnidazole was associated with maternal toxicity (reduced food consumption and markedly reduced body weight gain) in dams at 100 mg/kg/day.

In a peri- and post-natal development study in rats, secnidazole was administered at 30, 100 and 300 mg/kg/day from Day 6 of gestation through Day 20 of lactation. Secnidazole was not associated with any adverse effects on gestation, parturition, lactation or on subsequent development of first generation (F1) and second generation (F2) offspring at these doses, equivalent to up to 1.4 times the clinical dose based on AUC comparisons. Maternal toxicity (reduced gestational body weight gain) was evident at doses of 100 mg/kg and above (about 0.3 times the clinical dose based on AUC comparisons).

Attachment 2- Drug Labeling 2 (limited human data from case report, animal data with adverse developmental outcomes) – Xenazine (tetrabenazine), a vesicular monoamine transporter 2 (VMAT) inhibitor indicated for the treatment of chorea associated with Huntington's disease (most recent labeling version approved 9/2017).

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of XENAZINE in pregnant women. Administration of tetrabenazine to rats throughout pregnancy and lactation resulted in an increase in stillbirths and postnatal offspring mortality. Administration of a major human metabolite of tetrabenazine to rats during pregnancy or during pregnancy and lactation produced adverse effects on the developing fetus and offspring (increased mortality, decreased growth, and neurobehavioral and reproductive impairment). The adverse developmental effects of tetrabenazine and a major human metabolite of tetrabenazine in rats occurred at clinically relevant doses [see Data].

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

Data

Animal Data

Tetrabenazine had no clear effects on embryofetal development when administered to pregnant rats throughout the period of organogenesis at oral doses up to 30 mg/kg/day (or 3 times the maximum recommended human dose [MRHD] of 100 mg/day on a mg/m² basis). Tetrabenazine had no effects on embryofetal development when administered to pregnant rabbits during the period of organogenesis at oral doses up to 60 mg/kg/day (or 12 times the MRHD on a mg/m² basis).

When tetrabenazine (5, 15, and 30 mg/kg/day) was orally administered to pregnant rats from the beginning of organogenesis through the lactation period, an increase in stillbirths and offspring postnatal mortality was observed at 15 and 30 mg/kg/day and delayed pup maturation was observed at all doses. A no-effect dose for pre- and postnatal developmental toxicity in rats was not identified. The lowest dose tested (5 mg/kg/day) was less than the MRHD on a mg/m² basis.

Because rats dosed orally with tetrabenazine do not produce 9-desmethyl- β -DHTBZ, a major human metabolite of tetrabenazine, the metabolite was directly administered to pregnant and lactating rats. Oral administration of 9-desmethyl- β -DHTBZ (8, 15, and 40 mg/kg/day) throughout the period of organogenesis produced increases in embryofetal mortality at 15 and 40 mg/kg/day and reductions in fetal body weights at 40 mg/kg/day, which was also maternally toxic. When 9-desmethyl- β -DHTBZ (8, 15, and 40 mg/kg/day) was orally administered to

pregnant rats from the beginning of organogenesis through the lactation period, increases in gestation duration, stillbirths, and offspring postnatal mortality (40 mg/kg/day); decreases in pup weights (40 mg/kg/day); and neurobehavioral (increased activity, learning and memory deficits) and reproductive (decreased litter size) impairment (15 and 40 mg/kg/day) were observed. Maternal toxicity was seen at the highest dose. The no-effect dose for developmental toxicity in rats (8 mg/kg/day) was associated with plasma exposures (AUC) of 9-desmethyl- β -DHTBZ in pregnant rats lower than that in humans at the MRHD.

Attachment 3- Drug Labeling 3 (human data with metformin hydrochloride component from observational studies, animal data with adverse developmental outcomes) -- *Segluromet* (metformin hydrochloride -ertugliflozin), a combination of ertugliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, and metformin, a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing ertugliflozin or metformin, or in patients who are already treated with both ertugliflozin and metformin (most recent labeling version approved 12/2017).

8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, from ertugliflozin, SEGLUROMET is not recommended during the second and third trimesters of pregnancy. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk (*see Data*).

The limited available data with SEGLUROMET in pregnant women are not sufficient to determine a drug- associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (*see Clinical Considerations*).

In animal studies, adverse renal changes were observed in rats when ertugliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13 times the maximum clinical dose caused renal pelvic and tubule dilatations and renal mineralization that were not fully reversible. There was no evidence of fetal harm in rats or rabbits at exposures of ertugliflozin approximately 300 times higher than the maximal clinical dose of 15 mg/day when administered during organogenesis (*see Data*).

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was

used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Ertugliflozin

When ertugliflozin was orally administered to juvenile rats from PND 21 to PND 90, increased kidney weight, renal tubule and renal pelvis dilatation, and renal mineralization occurred at doses greater than or equal to 5 mg/kg (13- fold human exposures, based on AUC). These effects occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development, and did not fully reverse within a 1-month recovery period.

In embryo- fetal development studies, ertugliflozin (50, 100 and 250 mg/kg/day) was administered orally to rats on gestation days 6 to 17 and to rabbits on gestation days 7 to 19. Ertugliflozin did not adversely affect developmental outcomes in rats and rabbits at maternal exposures that were approximately 300 times the human exposure at the maximum clinical dose of 15 mg/day, based on AUC. A maternally toxic dose (250 mg/kg/day) in rats (707 times the clinical dose) was associated with reduced fetal viability and a higher incidence of a visceral malformation (membranous ventricular septal defect). In the pre- and post -natal development study in pregnant rats, ertugliflozin was administered to the dams from gestation day 6 through lactation day 21 (weaning). Decreased post -natal growth (weight gain) was observed at maternal doses \geq 100 mg/kg/day (greater than or equal to 331 times the human exposure at the maximum clinical dose of 15 mg/day, based on AUC).

Metformin hydrochloride

Metformin did not adversely affect development outcomes when administered to rats and rabbits at doses up to 600 mg /kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human dose of 2,000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Attachment 4- Drug Labeling 4 (*observational studies show inconsistent findings, animal data with no adverse developmental outcomes*) – Zofran (ondansetron), a 5-HT₃ receptor antagonist indicated for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy, nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen, postoperative nausea and/or vomiting, (most recent labeling version approved 10/2016).

8.1 Pregnancy

Risk Summary

Available data do not reliably inform the association of ZOFRAN and adverse fetal outcomes. Published epidemiological studies on the association between ondansetron and fetal outcomes have reported inconsistent findings and have important methodological limitations hindering interpretation [see Data]. Reproductive studies in rats and rabbits did not show evidence of harm to the fetus when ondansetron was administered during organogenesis at approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, based on body surface area, respectively [see Data].

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

Data

Human Data

Methodological limitations of the epidemiology studies preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of ondansetron in pregnancy.

Two large retrospective cohort studies of ondansetron use in pregnancy have been published. In one study with 1,349 infants born to women who reported the use of ondansetron or received an ondansetron prescription in the first trimester, no increased risk for major congenital malformations was seen in aggregate analysis. In this same study, however, a sub-analysis for specific malformations reported an association between ondansetron exposure and cardiovascular defect (odds ratio (OR) 1.62 [95% CI (1.04, 2.14)]) and cardiac septal defect (OR 2.05 [95% CI (1.19, 3.28)]). The second study examined 1970 women who received ondansetron prescription during pregnancy and reported no association between ondansetron exposure and major congenital malformations, miscarriage or stillbirth, and infants of low birth weight or small for gestational age. Important methodological limitations with these studies include the uncertainty of whether women who filled a prescription actually took the medication, the concomitant use of other medications or treatments, and other unadjusted confounders that may account for the study findings.

A case-control study evaluating associations between several common non-cardiac malformations and multiple antiemetic drugs reported an association between maternal use of

ondansetron and isolated cleft palate (reported adjusted OR = 2.37 [95% CI (1.18, 4.76)]). However, this association could be a chance finding, given the large number of drugs-birth defect comparisons in this study. It is unknown whether ondansetron exposure in utero in the cases of cleft palate occurred during the time of palate formation (the palate is formed between the 6th and 9th weeks of pregnancy) or whether mothers of infants with cleft palate used other medications or had other risk factors for cleft palate in the offspring. In addition, no cases of isolated cleft palate were identified in the aforementioned two large retrospective cohort studies. At this time, there is no clear evidence that ondansetron exposure in early pregnancy can cause cleft palate.

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal exposure margin was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area.

In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal exposure margin was approximately 6 times the maximum recommended human oral dose of 24 mg/day, based on body surface area.

Attachment 5- Drug Labeling 5 (*human data from pregnancy registry and observational study, animal data with no adverse developmental outcomes*) – *Enbrel (etanercept), a tumor necrosis factor (TNF) blocker indicated for the treatment of Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, and Plaque Psoriasis (most recent labeling version approved 11/2017).*

8.1 Pregnancy

Risk Summary

Available studies with use of etanercept during pregnancy do not reliably support an association between etanercept and major birth defects. Clinical data are available from the Organization of Teratology Information Specialists (OTIS) Enbrel Pregnancy Registry in women with rheumatic diseases or psoriasis and a Scandinavian study in pregnant women with chronic inflammatory disease. Both the OTIS Registry and the Scandinavian study showed the proportion of liveborn infants with major birth defects was higher for women exposed to etanercept compared to diseased etanercept unexposed women. However, the lack of pattern of major birth defects is reassuring and differences between exposure groups (e.g. disease severity) may have impacted the occurrence of birth defects (*see Data*). In animal reproduction studies with pregnant rats and rabbits, no fetal harm or malformations were observed with subcutaneous administration of etanercept during the period of organogenesis at doses that achieved systemic exposures 48 to 58 times the exposure in patients treated with 50 mg Enbrel once weekly (*see Data*).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the United States, about 2-4% of liveborn babies have a major birth defect and about 15-20% of pregnancies end in miscarriage, regardless of drug exposure.

Clinical Considerations

Fetal/Neonatal adverse reactions

The risk of fetal/neonatal adverse reactions with in utero exposure to Enbrel is unknown. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to Enbrel in utero [*see Use in Specific Populations (8.4)*].

Data

Human Data

A prospective cohort pregnancy registry conducted by OTIS in the US and Canada between 2000 and 2012 compared the risk of major birth defects in liveborn infants of women with rheumatic diseases or psoriasis exposed to etanercept in the first trimester. The proportion of major birth defects among liveborn infants in the etanercept-exposed (N = 319) and diseased etanercept unexposed cohorts (N = 144) was 9.4% and 3.5%, respectively. The findings showed no statistically significant increased risk of minor birth defects and no pattern of major or minor birth defects.

A Scandinavian study compared the risk of major birth defects in liveborn infants of women with chronic inflammatory disease (CID) exposed to TNF-inhibitors during early pregnancy. Women

were identified from the Danish (2004-2012) and Swedish (2006-2012) population based health registers. The proportion of major birth defects among liveborn infants in the etanercept-exposed (N=344) and CID etanercept unexposed cohorts (N = 21,549) was 7.0% and 4.7%, respectively.

Overall, while both the OTIS Registry and Scandinavian study show a higher proportion of major birth defects in etanercept-exposed patients compared to diseased etanercept unexposed patients, the lack of pattern of birth defects is reassuring and differences between exposure groups (e.g. disease severity) may have impacted the occurrence of birth defects.

Three case reports from the literature showed that cord blood levels of etanercept at delivery, in infants born to women administered etanercept during pregnancy, were between 3% and 32% of the maternal serum level.

Animal Data

In embryofetal development studies with etanercept administered during the period of organogenesis to pregnant rats from gestation day (GD) 6 through 20 or pregnant rabbits from GD 6 through 18, there was no evidence of fetal malformations or embryotoxicity in rats or rabbits at respective doses that achieved systemic exposures 48 to 58 times the exposure in patients treated with 50 mg Enbrel once weekly (on an AUC basis with maternal subcutaneous doses up to 30 mg/kg/day in rats and 40 mg/kg/day in rabbits). In a peri-and post-natal development study with pregnant rats that received etanercept during organogenesis and the later gestational period from GD 6 through 21, development of pups through post-natal day 4 was unaffected at doses that achieved exposures 48 times the exposure in patients treated with 50 mg Enbrel once weekly (on an AUC basis with maternal subcutaneous doses up to 30 mg/kg/day).

Attachment 6-Drug Labeling 6 (*human data from pregnancy registry, inconsistent findings between animal species*) – Trizivir (abacavir/lamivudine/zidovudine), nucleoside analogue HIV-1 reverse transcriptase inhibitors indicated for treatment HIV-1 infection (most recent labeling version approved 3/2017).

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to TRIZIVIR during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Available data from the APR show no difference in the overall risk of birth defects for abacavir, lamivudine, or zidovudine compared with the background rate for birth defects of 2.7% in the Metropolitan Atlanta Congenital Defects Program (MACDP) reference population [*see Data*]. The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks gestation. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The background risk for major birth defects and miscarriage for the indicated population is unknown.

In animal reproduction studies, oral administration of abacavir to pregnant rats during organogenesis resulted in fetal malformations and other embryonic and fetal toxicities at exposures 35 times the human exposure (AUC) at the recommended clinical daily dose. However, no adverse developmental effects were observed following oral administration of abacavir to pregnant rabbits during organogenesis, at exposures approximately 9 times the human exposure (AUC) at the recommended clinical dose. Oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryolethality at systemic exposure (AUC) similar to the recommended clinical dose; however, no adverse development effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (C_{max}) 35 times the recommended clinical dose. Administration of oral zidovudine to female rats prior to mating and throughout gestation resulted in embryotoxicity at doses that produced systemic exposure (AUC) approximately 33 times higher than exposure at the recommended clinical dose. However, no embryotoxicity was observed after oral administration of zidovudine to pregnant rats during organogenesis at doses that produced systemic exposure (AUC) approximately 117 times higher than exposures at the recommended clinical dose. Administration of oral zidovudine to pregnant rabbits during organogenesis resulted in embryotoxicity at doses that produced systemic exposure (AUC) approximately 108 times higher than exposure at the recommended clinical dose. However, no embryotoxicity was observed at doses that produced systemic exposure (AUC) approximately 23 times higher than exposures at the recommended clinical dose [*see Data*].

Data

Human Data

Abacavir: Based on prospective reports to the APR of over 2,000 exposures to abacavir during pregnancy resulting in live births (including over 1,000 exposed in the first trimester), there was no difference between the overall risk of birth defects for abacavir compared with the background birth defect rate of 2.7% in a U.S. reference population of the MACDP. The prevalence of defects in live births was 2.9% (95% CI: 2.0% to 4.1%) following first trimester exposure to abacavir-containing regimens and 2.7% (95% CI: 1.9% to 3.7%) following second/third trimester exposure to abacavir-containing regimens.

Abacavir has been shown to cross the placenta and concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery [*see Clinical Pharmacology (12.3)*].

Lamivudine: Based on prospective reports to the APR of over 11,000 exposures to lamivudine during pregnancy resulting in live births (including over 4,500 exposed in the first trimester), there was no difference between the overall risk of birth defects for lamivudine compared with the background birth defect rate of 2.7% in a U.S. reference population of the MACDP. The prevalence of birth defects in live births was 3.1% (95% CI: 2.6% to 3.6%) following first trimester exposure to lamivudine-containing regimens and 2.8% (95% CI: 2.5% to 3.3%) following second/third trimester exposure to lamivudine-containing regimens.

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of lamivudine were 3.9 (1.2 to 12.8)-fold greater compared with paired maternal serum concentration (n = 8).

Zidovudine: Based on prospective reports to the APR of over 13,000 exposures to zidovudine during pregnancy resulting in live births (including over 4,000 exposed in the first trimester), there was no difference between the overall risk of birth defects for zidovudine compared with the background birth defect rate of 2.7% in a U.S. reference population of the MACDP. The prevalence of birth defects in live births was 3.2% (95% CI: 2.7% to 3.8%) following first trimester exposure to zidovudine-containing regimens and 2.8% (95% CI: 2.5% to 3.2%) following second/third trimester exposure to zidovudine-containing regimens.

A randomized, double-blind, placebo-controlled trial was conducted in HIV-1-infected pregnant women to determine the utility of zidovudine for the prevention of maternal-fetal HIV-1 transmission. Zidovudine treatment during pregnancy reduced the rate of maternal-fetal HIV-1 transmission from 24.9% for infants born to placebo-treated mothers to 7.8% for infants born to mothers treated with zidovudine. There were no differences in pregnancy-related adverse events between the treatment groups. Of the 363 neonates that were evaluated, congenital abnormalities occurred with similar frequency between neonates born to mothers who received zidovudine and neonates born to mothers who received placebo. The observed abnormalities included problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of trial drug. See full prescribing information for RETROVIR (zidovudine) and COMBIVIR® (lamivudine and zidovudine).

Zidovudine has been shown to cross the placenta and concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery [*see Clinical Pharmacology (12.3)*].

Animal Data

Abacavir: Abacavir was administered orally to pregnant rats (at 100, 300, and 1,000 mg per kg per day) and rabbits (at 125, 350, or 700 mg per kg per day) during organogenesis (on gestation Days 6 through 17 and 6 through 20, respectively). Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) or developmental toxicity (decreased fetal body weight and crown-rump length) were observed in rats at doses up to 1,000 mg per kg per day, resulting in exposures approximately 35 times the human exposure (AUC) at the recommended daily dose. No developmental effects were observed in rats at 100 mg per kg per day, resulting in exposures (AUC) 3.5 times the human exposure at the recommended daily dose. In a fertility and early embryo-fetal development study conducted in rats (at 60, 160, or 500 mg per kg per day), embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) or toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at doses up to 500 mg per kg per day. No developmental effects were observed in rats at 60 mg per kg per day, resulting in exposures (AUC) approximately 4 times the human exposure at the recommended daily dose. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. In pregnant rabbits, no developmental toxicities and no increases in fetal malformations occurred at up to the highest dose evaluated, resulting in exposures (AUC) approximately 9 times the human exposure at the recommended dose.

Lamivudine: Lamivudine was administered orally to pregnant rats (at 90, 600, and 4,000 mg per kg per day) and rabbits (at 90, 300, and 1,000 mg per kg per day and at 15, 40, and 90 mg per kg per day) during organogenesis (on gestation Days 7 through 16 [rat] and 8 through 20 [rabbit], respectively). No evidence of fetal malformations due to lamivudine was observed in rats and rabbits at doses producing plasma concentrations (C_{max}) approximately 35 times higher than human exposure at the recommended daily dose. Evidence of early embryoletality was seen in the rabbit at systemic exposures (AUC) similar to those observed in humans, but there was no indication of this effect in the rat at plasma concentrations (C_{max}) 35 times higher than human

exposure at the recommended daily dose. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. In the pre- and postnatal development study in rats, lamivudine was administered orally at doses of 180, 900, and 4,000 mg per kg per day (from gestation Day 6 through postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, was not affected by maternal administration of lamivudine.

Zidovudine: A study in pregnant rats (at 50, 150, or 450 mg per kg per day starting 26 days prior to mating through gestation to postnatal Day 21) showed increased fetal resorptions at doses that produced systemic exposures (AUC) approximately 33 times higher than exposure at the recommended daily human dose (300 mg twice daily). However, in an oral embryo-fetal development study in rats (at 125, 250, or 500 mg per kg per day on gestation Days 6 through 15), no fetal resorptions were observed at doses that produced systemic exposure (AUC) approximately 117 times higher than exposures at the recommended daily human dose. An oral embryo-fetal development study in rabbits (at 75, 150, or 500 mg per kg per day on gestation Days 6 through 18) showed increased fetal resorptions at the 500-mg-per-kg-per-day dose which produced systemic exposures (AUC) approximately 108 times higher than exposure at the recommended daily human dose; however, no fetal resorptions were noted at doses up to 150 mg per kg per day, which produced systemic exposure (AUC) approximately 23 times higher than exposures at the recommended daily human dose. These oral embryo-fetal development studies in the rat and rabbit revealed no evidence of fetal malformations with zidovudine. In another developmental toxicity study, pregnant rats (dosed at 3,000 mg per kg per day from Days 6 through 15 of gestation) showed marked maternal toxicity and an increased incidence of fetal malformations at exposures greater than 300 times the recommended daily human dose based on AUC. However, there were no signs of fetal malformations at doses up to 600 mg per kg per day.

Attachment 7- Vaccine Labeling (limited human data from pregnancy registry, animal data with no adverse developmental outcomes) – Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] , vaccine indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135 (most recent labeling version approved 9/2016).

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Menactra during pregnancy. To enroll in or obtain information about the registry, call Sanofi Pasteur at 1-800-822-2463.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. There are no adequate and well-controlled studies of Menactra administration in pregnant women in the US. Available data suggest that rates of major birth defects and miscarriage in women who received Menactra 30 days prior to pregnancy or during pregnancy are consistent with estimated background rates.

A developmental toxicity study was performed in female mice given 0.1 mL (in divided doses) of Menactra prior to mating and during gestation (a single human dose is 0.5 mL). The study revealed no evidence of harm to the fetus due to Menactra [*see Animal Data (8.1)*]

Data

Human Data

A pregnancy registry spanning 11 years (2005-2016) included 222 reports of exposure to Menactra from 30 days before or at any time during pregnancy. Of these reports, 87 had known pregnancy outcomes available and were enrolled in the pregnancy registry prior to the outcomes being known. Outcomes among these prospectively followed pregnancies included 2 major birth defects and 6 miscarriages.

Animal Data

A developmental toxicity study was performed in female mice. The animals were administered 0.1 mL of Menactra (in divided doses) at each of the following time points: 14 days prior to mating, and on Days 6 and 18 of gestation (a single human dose is 0.5 mL). There were no vaccine-related fetal malformations or variations, and no adverse effects on pre-weaning development observed in the study.