Overview of Pregnancy and Lactation Subsection Content and Sample Labels

Pregnancy subsection: Overview

General Information

Contact information if pregnancy registry available

General statement about background risk

Fetal Risk Summary

Based on all available data, this section characterizes the likelihood that the drug increases the risk of developmental abnormalities in humans and other relevant risks. More than one risk conclusion may be needed.

For drugs that are not systemically absorbed, there is a standard statement that states that maternal use is not expected to result in fetal exposure.

For drugs that are systemically absorbed include:

- When there are human data, a statement about the likelihood of increased risk based on this data. This statement is followed by a description of findings.
- A standard statement about likelihood of increased risk based on animal data.

Clinical Considerations

This section provides information on the following topics:

- Inadvertent exposure:
  Known or predicted risk to the fetus from inadvertent exposure to drug early in pregnancy
- Prescribing decisions for pregnant women:
  - Describe any known risk to the pregnant woman and fetus from the disease or condition the drug is intended to treat.
  - Information about dosing adjustments during pregnancy.
  - Maternal adverse reactions unique to pregnancy or increased in pregnancy.
  - Effects of dose, timing, and duration of exposure to drug during pregnancy.
  - Potential neonatal complications and needed interventions

Data

Human and animal data are presented separately with human data presented first.

- Describe study type, exposure information (dose, duration, timing), any identified fetal developmental abnormality or other adverse effects
- For human data, include positive and negative experiences, number of subjects, and duration of study.
- For animal data, include species studied and describe doses in terms of human dose equivalents (provide basis for calculation).

Pregnancy Subsection: Labeling Examples

1. Drug for which only animal data are available; with developmental toxicity findings:

All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes ALPHATHON's potential to increase the risk of developmental abnormalities above the background risk.

Fetal Risk Summary
Based on animal data, the likelihood that ALPHATHON increases the risk of developmental abnormalities is predicted to be high (see Data).

Clinical Considerations
Asthma complicates approximately 1% of all pregnancies resulting in higher perinatal mortality, low birth weight infants, preterm births, and pregnancy-induced hypertension compared to outcomes for nonasthmatic women. Because of the risks of even mild maternal hypoxia to the developing fetus, asthma should be clinically well-controlled during pregnancy. There are no human studies evaluating ALPHATHON use in pregnant women. The time of gestation at which risk may be greatest is unknown; therefore, risks of inadvertent exposure in early gestation cannot be evaluated. Animal data suggest that ALPHATHON exposure may result in early fetal loss and anomalies of major organ systems. There are no data regarding dose adjustment needs in pregnancy. Given the lack of human data and the risks suggested by animal data, prescribers should consider alternative treatments for asthma for pregnant women when possible (especially during the first trimester) and women planning pregnancy.

Data
Human data.

- There are no data on human pregnancies exposed to ALPHATHON.

Animal Data.

- Reproductive studies performed during early pregnancy in rats at oral doses 0.75 to 1.0 times the recommended human dose (adjusted for body surface area) showed implantation loss, fetal resorptions, and major congenital anomalies of the cardiac, skeletal and renal systems without signs of maternal toxicity.
- Reproductive studies performed in early pregnancy in rabbits at doses approximately 0.33 to 1.0 times the recommended human dose (adjusted for body surface area) showed increased post-implantation loss. Studies at 3 times the human dose showed significant fetal loss without signs of maternal toxicity.
- The effects of ALPHATHON on fetal growth, labor, or post-natal complications were not evaluated in the animal studies.

2. Drug for which only animal data are available; lack of developmental toxicity findings:

All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes GAMMAZINE's potential to increase the risk of developmental abnormalities above the background risk.

Fetal Risk Summary
Based on animal data, GAMMAZINE is not predicted to increase the risk of developmental abnormalities.

Clinical Considerations
Infection of the urinary tract in pregnant women carries a higher risk of morbidity than in the general population and is associated with an increased incidence of preterm delivery, low birth weight, and progression to pyelonephritis. It is not known whether the dose of GAMMAZINE requires adjustment during pregnancy.

Data
Human Data.

- There are no data on human pregnancies exposed to GAMMAZINE.

Animal Data.

- No teratogenic effects were seen when pregnant rats and rabbits were treated throughout pregnancy with doses equivalent to 1.5 times the maximum recommended human dose adjusted for body surface area. There were no findings of increased fetal loss, mortality or resorptions, reductions in body weights in fetuses, or other developmental abnormalities.

3. Drug for which animal and some human (insufficient) data are available:

All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes KAPPAATE's potential to increase the risk of developmental abnormalities above the background risk.

Fetal Risk Summary
Based on limited human data from one retrospective cohort study and postmarketing adverse event reporting, the likelihood that KAPPAATE increases the risk of major congenital abnormalities or spontaneous abortions is low. Short term (less than 3 weeks), first trimester exposure to 5 to 10mg/day of KAPPAATE did not result in an increase in major congenital abnormalities or spontaneous abortions over the background rate. The limited number of pregnant women that were exposed to KAPPAATE during the second and third trimesters delivered infants with no major congenital abnormalities. Based on animal data, the likelihood that KAPPAATE increases the risk of developmental abnormalities is predicted to be moderate.

Clinical Considerations
Symptoms of heartburn and gastroesophageal reflux disease (GERD) are common during pregnancy, occurring in about 50% of women in the third trimester. During pregnancy,

untreated GERD can lead to reflux esophagitis and can increase nausea and asthma exacerbations in asthmatics. Based on limited human data, inadvertent exposure to KAPPAATE in early pregnancy is unlikely to be associated with major congenital abnormalities or spontaneous abortions; however, animal data suggest that early fetal loss may result from KAPPAATE exposure. Pharmacokinetic studies have shown that no dose adjustment of KAPPAATE is needed for pregnant women in the third trimester (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY). Pharmacologically similar drugs have demonstrated delayed parturition in animal studies, but the relevance of this finding in humans is not known.

Data

Human Data.

- A retrospective cohort study reported on 400 pregnant women who used 5 to 10 mg/day of KAPPAATE in the first trimester.[1] The majority of use (90%) was short term (less than 3 weeks). The overall malformation rate for first trimester exposure to KAPPAATE was 3.4% (95% CI 1.3-7.2) compared to 4.1% (95% CI 1.6-6.2) in the comparator group. The study could effectively rule out a relative risk greater than 2.0 for overall malformations. Rates of spontaneous abortions did not differ between the groups.
- Postmarketing reports on 125 women exposed to 5 to 10 mg/day of KAPPAATE during pregnancy did not suggest an increased risk of major congenital malformations compared to the background rate in the general population. However, gestational ages and durations of exposure were not available for all cases. Interpretation of these results are limited by the voluntary nature of postmarketing adverse event reporting and underrreporting.
- No change in pharmacokinetics were seen in pregnant women at 32 to 36 weeks gestation given a single dose of KAPPAATE (see CLINICAL PHARMACOLOGY).

Animal Data.

- In rats, no teratogenic or embryocidal effects were observed when KAPPAATE was administered at doses up to 7 times the human dose on a body surface area basis).
- In rabbits, KAPPAATE at maternal doses about 5 to 50 times the human dose on a body surface area basis produced dose-related increases in embryo-lethality, fetal resorptions, pregnancy disruptions, and fetal growth impairment.
- No effects were seen on parturition.

[1] Smith J.D., M.R. Perkins, "Retrospective study on pregnant women exposed to Kappaate," Some Medical Journal, 121(55):123-134, 2002.

4. Drug for which sufficient human data are available:

All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes Deltaman's potential to increase the risk of developmental abnormalities above the background risk.

Fetal Risk Summary

Human data do not indicate that DELTAMAN increases the overall risk of congenital malformations or neural tube defects. The majority of reported human exposures to DELTAMAN are first trimester exposures. Epidemiology studies adequate to detect a 2.5-fold increase in the rate of major malformations and a 10-fold increase in the rate of neural tube defects did not detect a risk. Based on animal data, the likelihood that DELTAMAN increases the risk of other developmental abnormalities is predicted to be low.

Clinical Considerations

About 1 in 100 women of childbearing age has diabetes. During pregnancy, diabetic women have increased risks of miscarriage, preterm labor, stillbirth, macrosomia, and congenital malformations, including heart defects and neural tube defects. Neonates born to women with poorly controlled diabetes are at increased risk of breathing difficulties, low blood sugar levels and jaundice. Based on human data, inadvertent exposure to DELTAMAN in early pregnancy is not associated with an increased risk of major congenital abnormalities or neural tube defects. There are no data regarding whether dosing adjustments are needed when DELTAMAN is used in pregnancy.

Data

Human Data.

- The DELTAMAN Pregnancy Exposure Registry, a population-based prospective cohort epidemiological study, has collected data since January 2000. As of December 2007, the registry documented outcomes on 1,055 infants exposed to DELTAMAN during pregnancy (997 exposed during the first trimester and 58 exposed after the first trimester) have been documented. *In utero* exposure to DELTAMAN was not associated with an increased risk of major congenital malformations at birth (odds ratio 0.93, 95% CI 0.52-1.39). The number of infants born with neural tube defects was similar in the DELTAMAN exposed infants and controls. The sample size in this study had 90% power to detect a 2.5-fold increase in the rate of major malformation and 80% power to detect a 10-fold increase in the rate of neural tube defects.
- A retrospective cohort study reported on 869 pregnant women exposed to either DELTAMAN or pharmacologically similar drugs in the first trimester (245 exposed to DELTAMAN).[2] The overall major malformation rate was 4.1% (95% CI 3.2-5.1) and the malformation rate for first trimester exposure to DELTAMAN was 3.4% (95% CI 1.3-7.8). The relative risk of major malformations associated with first trimester exposure to DELTAMAN compared with nonexposed women was 0.92 (95% CI 0.34-2.3). The sample size in this study had 80% power to detect a 4-fold increase in the rate of major malformations.

[2] Jones A.B. and C.D. Smith, "Exposure to Deltaman during pregnancy," Medical Journal, 98:56-68, 2000.

Animal Data.

- Exposure of pregnant rats or mice to DELTAMAN at doses comparable to the maximum recommended human dose (based on body surface area) resulted in embryonic death and malformations in the offspring. Skeletal abnormalities were the most common malformations observed in rats and cardiac, skeletal and urinary tract abnormalities were seen most often in mice. Neural tube defects were observed in pregnant mice and rats at doses of 15 to 25 and 5 to 20 times the human dose (based on body surface area), respectively. Behavioral alterations and poor weight gain were seen among the offspring of rats treated with DELTAMAN during pregnancy at doses > 15 times the maximum human dose (based on body surface area).
- Studies in cynomolgus monkeys at 1 to 10 times the maximum recommended human dose (based on a body surface area) demonstrated a dose dependent increase in neural tube and skeletal anomalies.