Drug Labeling 1

DRUGMNO (drugmno), injection

- Indicated for chronic inflammatory disease (CID).
- Inhibits binding of tumor necrosis factor (TNF) molecules to cell surface TNF receptors, reduces inflammation and can affect host defenses against infections.
- Serious adverse events associated with the drug include: worsening congestive heart failure, serious infections, neurologic reactions, hematologic reactions, allergic reactions, immunosuppression.

EXCERPT OF FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

NO RISK IDENTIFIED
Major Birth Defects/Miscarriage: • No findings of concern in large cohort or case-control studies, or pregnancy exposure registry study. • No findings of concern observed in animal studies across species

Risk Summary

Clinical data available from the DRUGMNO Pregnancy Registry in women with rheumatic diseases or psoriasis, and a published study in pregnant women with chronic inflammatory disease, do not reliably support an association between drugmno and major birth defects. Despite that both studies showed the proportion of liveborn infants with major birth defects was higher for women exposed to DRUGMNO compared to diseased DRUGMNO unexposed women, the lack of pattern of major birth defects is reassuring and the differences in disease severity between exposure groups may have impacted the occurrence of birth defects (*see Data).* In animal reproduction studies with pregnant rats and rabbits, no adverse developmental effects were observed with subcutaneous administration of DRUGMNO during the period of organogenesis at doses that achieved systemic exposures 48 to 58 times the exposure in patients treated with 50 mg DRUGMNO once weekly (*see Data*).

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

The risk of fetal/neonatal adverse reactions with in utero exposure to DRUGMNO is unknown. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to DRUGMNO in utero *[see Drug Interactions (7.1)]*.

Data

Human Data

A prospective cohort pregnancy registry conducted 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 DRUGMNO in the first trimester. The proportion of major birth defects among liveborn infants in the DRUGMNO -exposed (N = 319) and diseased DRUGMNO unexposed cohorts (N = 144) was 9.4% and 3.5%, respectively. The findings showed no increased risk of minor birth defects and no pattern of major or minor birth defects.
A published 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 DRUGMNO-exposed (N=344) and CID DRUGMNO unexposed cohorts (N = 21,549) was 7.0% and 4.7%, respectively.
Overall, while both the DRUGMNO Registry and published study show a higher proportion of major birth defects in DRUGMNO-exposed patients compared to diseased DRUGMNO 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 DRUGMNO at delivery, in infants born to women administered DRUGMNO during pregnancy, were between 3% and 32% of the maternal serum level.

Animal Data

In embryofetal development studies with DRUGMNO 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 DRUGMNO 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 DRUGMNO 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 DRUGMNO once weekly (on an AUC basis with maternal subcutaneous doses up to 30 mg/kg/day).

7 DRUG INTERACTIONS

7.1 Vaccines

Most patients receiving DRUGMNO were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and fewer patients had 2-fold rises in titers compared to patients not receiving DRUGMNO. The clinical

significance of this is unknown. Patients receiving DRUGMNO may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving DRUGMNO.
Patients with a significant exposure to varicella virus should temporarily discontinue DRUGMNO therapy and be considered for prophylactic treatment with varicella zoster immune globulin.

Drug Labeling 2

DRUGAMZ (drugamz)

- Indicated for nausea and vomiting.
- Selectively blocks the serotonin 5-HT3 receptor.
- Serious adverse events associated with the drug include: hypersensitivity reactions, QT prolongation, serotonin syndrome, phenylketonuria.

EXCERPT OF FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

INSUFFICIENT TO IDENTIFY RISK
Major Birth Defects: • Inconsistent findings of concern in large cohort or case-control studies. • No findings of concern observed in animal studies across species

Risk Summary

Available data do not reliably inform the association of DRUGAMZ and adverse fetal outcomes. Published epidemiological studies on the association between DRUGAMZ 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 DRUGAMZ 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 DRUGAMZ in pregnancy.

Two large retrospective cohort studies of DRUGAMZ use in pregnancy have been published. In one study with 1,349 infants born to women who reported the use of DRUGAMZ or received a DRUGAMZ 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 DRUGAMZ 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 DRUGAMZ prescription during pregnancy and reported no association between DRUGAMZ 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 DRUGAMZ 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 DRUGAMZ 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 DRUGAMZ 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 DRUGAMZ 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 DRUGAMZ 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 DRUGAMZ 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.

Drug Labeling 3

DRUGEFG (drugefg)

- Indicated for treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder.
- Non-selectively activates melanocortin receptors.
- Serious adverse events associated with the drug include: elevated blood pressure, hyperpigmentation, and intentional misuse.

EXCERPT OF FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

POTENTIAL RISK IDENTIFIED
Major Birth Defects/Miscarriage: Potential concern; requires further study • Findings of risk from animal studies in at least one species at clinically relevant exposures • Pregnancies that occurred during clinical development did not indicate risk
Risk Reduction Strategies *(see Risk Summary)*

Pregnancy Exposure Registry

There will be a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DRUGEFG during pregnancy. Pregnant women exposed to DRUGEFG and healthcare providers are encouraged to contact the DRUGEFG Pregnancy Exposure Registry at 1-800-xxx-xxxx or www.pregnancyregistrywebsite.com.

Risk Summary

The few pregnancies in women exposed to DRUGEFG in clinical trials are insufficient for determining whether there is a drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes.

Based on findings in animal studies, the use of DRUGEFG in pregnant women may be associated with the potential for fetal harm. In animal reproduction and development studies, daily subcutaneous administration of DRUGEFG to pregnant dogs during the period of organogenesis at exposures equal to or greater than the maximum recommended human dose

produced post-implantation loss. In mice subcutaneously dosed with DRUGEFG during pregnancy and lactation, developmental effects were observed in the offspring at greater than or equal to 12-times the maximum recommended dose (*see Data*). However, the lowest DRUGEFG dose associated with fetal harm has not been identified for either species. For this reason, women should use effective contraception while taking DRUGEFG and discontinue DRUGEFG if pregnancy is suspected.

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

There were 7 pregnancies reported in the clinical trials of more than 1057 patients treated with DRUGEFG for up to 12 months. Among these 7 pregnancies, no major congenital anomalies were reported. There was one spontaneous abortion (miscarriage), five full-term live births, and one outcome was unknown due to loss to follow-up.

Animal Data

An embryofetal development study was conducted in the dog and a pre-and postnatal development study was conducted in the mouse to inform developmental risk. These two species are not routinely used for reproductive toxicity assessment but were the only two species that could be successfully dosed by the subcutaneous route during gestation.

DRUGEFG was administered subcutaneously to pregnant dogs (8/dose) at 2, 8, or 20 mg/kg from gestation day (GD) 18-35, corresponding to the period from implantation to late embryogenesis in the dog. Embryofetal toxicity, as measured by post-implantation loss, was elevated approximately 3 to 8-fold compared to controls across all treated groups but was not dose-dependent. A developmental no-observed-effect level (NOEL) was not set. At the low dose of 2 mg/kg/day in the dog, exposure was approximately equal to the human exposure based on AUC.

In a pre-and postnatal development study, female mice (30/dose) were dosed subcutaneously at 0, 30, 75, and 150 mg/kg/day from GD 6 through lactation day (LD) 28, and two generations of offspring were assessed (F1 and F2). There were no effects on reproductive parameters in parental (F0) or F1 generation animals at doses up to 150 mg/kg/day (approximately 70 times the human AUC). However, developmental delays were observed in the F1 generation mice at ≥ 30 mg/kg/day (approximately 12 times the human AUC). For that reason, a developmental NOEL was not set. There were no significant effects on the growth and development of F2 generation pups.

Vaccine Labeling

VACCINERST (drugrst)

- Indicated for prevention of dengue disease in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.
- Elicits dengue-specific immune responses against the four dengue virus serotypes.
- Serious adverse events associated with the drug include: increased risk of severe disease following vaccination if person not previously infected by virus, allergic reactions, syncope.

EXCERPT OF FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

POTENTIAL RISK IDENTIFIED
Vaccine viremia and miscarriage: Potential concern; requires further study • Insufficient human data • Inconsistent animal data
INSUFFICIENT TO IDENTIFY RISK
Major Birth Defects: • Insufficient human data insufficient to determine risk • No findings of concern in animal studies across species
Risk Reduction Strategies *(see Clinical Considerations)*

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to VACCINERST during pregnancy. Women who receive VACCINERST during pregnancy are encouraged to contact directly or have their healthcare professional contact Drug Manufacturer at 1-800-xxx-xxxx or www.pregnancyregistrywebsite.com. to enroll in or obtain information about the registry.

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.

No specific studies of VACCINERST have been performed among pregnant women. A limited number of cases of inadvertent exposure during pregnancy were reported during clinical studies. Isolated adverse pregnancy outcomes (e.g., stillbirth, intrauterine death, spontaneous abortion, blighted ovum) have been observed for these exposed pregnancies, with similar frequency and nature in the vaccinated individuals compared to the control group, and with risk factors identified for all cases. Available data in pregnant women are not sufficient to determine the effects of VACCINERST on pregnancy, embryo-fetal development, parturition and post-natal development.

In two developmental toxicity studies, the effect of VACCINERST on embryo-fetal and post-natal development was evaluated in pregnant rabbits and mice. A developmental toxicity study was performed in female rabbits given a 5 $\log_{10}$50% cell culture infectious dose ($CCID_{50}$) of VACCINERST (full human dose ranging from 4.5 $\log_{10}$ to 6.0 $\log_{10}$ $CCID_{50}$) by intravenous injection prior to mating and during gestation. The study revealed no evidence of harm to the fetus due to VACCINERST. In another study, female mice were administered a single dose of 5 $\log_{10}$ $CCID_{50}$, 6.5 $\log_{10}$ $CCID_{50}$ (about 3 times the highest human dose) or 8 $\log_{10}$ $CCID_{50}$ (about 100 times the highest human dose) of VACCINERST by intravenous injection during gestation. Fetal toxicities were observed at maternally toxic doses *(see Data)*.

Clinical Considerations

Disease-associated Maternal and/or Embryo/fetal Risk

Pregnant women are at increased risk of complications associated with dengue infection compared to non-pregnant women. Pregnant women with dengue may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery. Vertical transmission of dengue virus from mothers with viremia at delivery to their infants has been reported.

Fetal/neonatal Adverse Reactions

Vaccine viremia can occur 7 to 14 days after vaccination with a duration of <7 days *[See Pharmacokinetics (12.3).]*. The potential for transmission of the vaccine virus from mother to infant is unknown.

Data

Animal Data

In two developmental toxicity studies, the effect of VACCINERST on embryo-fetal and post-natal development was evaluated in pregnant rabbits and mice.

Rabbits were administered a full human dose [0.5 mL (5 $\log_{10}$ $CCID_{50}$/animal/occasion)] of VACCINERST by intravenous injection 30 and 10 days before mating and on Days 6, 12 and 27 during gestation. No vaccine-related fetal malformation or variations and adverse effects on female fertility or pre-weaning development were reported in this study. Pregnant mice were administered a single dose of either 5 $\log_{10}$ $CCID_{50}$ (full human dose ranging from 4.5 $\log_{10}$ to 6.0 $\log_{10}$ $CCID_{50}$), 6.5 $\log_{10}$ $CCID_{50}$ (about 3 times the highest human dose) or 8 $\log_{10}$ $CCID_{50}$ (about 100 times the highest human dose) of VACCINERST by intravenous injection on Day 6, 9 or 12 of gestation. At doses of 6.5 $\log_{10}$ $CCID_{50}$ or 8 $\log_{10}$ $CCID_{50}$ of VACCINERST, maternal toxicity was observed which was associated with increased post-implantation loss and at doses of 8 $\log_{10}$ $CCID_{50}$ with reduced fetal body weight. The significance of this observation for humans is

unknown, especially considering the different route of administration (the human route of administration is subcutaneous) and dose levels which exceeded the intended human dose. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Viremia

In studies that evaluated the occurrence of vaccine viremia systematically at pre-specified timepoints, vaccine viremia (measured by genomic amplification methods) was observed following vaccination with VACCINERST in 5.6% of subjects, with 90% of these occurrences documented after the first injection. Vaccine viremia was observed 7 to 14 days after VACCINERST vaccination with a duration of <7 days.