



**Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States**

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## Entry Inhibitors

### Glossary of Terms for Supplement

**Carcinogenic** = producing or tending to produce cancer

- Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic.
- Genetic mutations and/or chromosomal damage can contribute to cancer formation.

**Clastogenic** = causing disruption of or breakages in chromosomes

**Genotoxic** = damaging to genetic material such as DNA and chromosomes

**Mutagenic** = inducing or capable of inducing genetic mutation

**Teratogenic** = interfering with fetal development and resulting in birth defects

Drugs in this class of antiretroviral (ARV) drugs inhibit viral binding or fusion of HIV to host target cells. Binding of the viral envelope glycoprotein (gp)120 to the CD4 receptor induces conformational changes that enable gp120 to interact with a chemokine receptor such as CCR5 or CXCR4 on the host cell; binding of gp120 to the co-receptor causes subsequent conformational changes in the viral transmembrane gp41, exposing the fusion peptide of gp41, which inserts into the cell membrane. A helical region of gp41, called HR1, then interacts with a similar helical region, HR2, on gp41, resulting in a zipping together of the two helices and mediating the fusion of cellular and viral membranes. Enfuvirtide, which requires subcutaneous (SQ) administration, is a synthetic 36-amino-acid peptide derived from a naturally occurring motif within the HR2 domain of viral gp41, and the drug binds to the HR1 region, preventing the HR1-HR2 interaction and correct folding of gp41 into its secondary structure, thereby inhibiting virus-cell fusion. Enfuvirtide was approved for use in combination with other ARV drugs to treat advanced HIV infection in adults and children aged 6 years or older. Maraviroc interferes with viral entry at the chemokine co-receptor level; it is a CCR5 co-receptor antagonist approved for combination therapy for HIV infection in adults infected with CCR5-tropic virus.

### ***Enfuvirtide (Fuzeon, T-20)***

**(Last updated August 6, 2015; last reviewed August 6, 2015)**

Enfuvirtide is classified as Food and Drug Administration Pregnancy Category B.

#### **Animal Studies**

##### *Carcinogenicity*

Enfuvirtide was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies of enfuvirtide have not been conducted.

##### *Reproduction/Fertility*

Reproductive toxicity has been evaluated in rats and rabbits. Enfuvirtide produced no adverse effects on fertility of male or female rats at doses up to 30 mg/kg/day administered subcutaneously (1.6 times the maximum recommended adult human daily dose on a body surface area basis).

##### *Teratogenicity/Developmental Toxicity*

Studies in rats and rabbits have shown no evidence of teratogenicity or effect on reproductive function with enfuvirtide.<sup>1</sup>

##### *Placental and Breast Milk Passage*

Studies in rats and rabbits revealed no evidence of harm to the fetus from enfuvirtide administered in doses up to 27 times and 3.2 times, respectively, the adult human daily dose (on a body surface area basis). Studies of radiolabeled enfuvirtide administered to lactating rats indicated radioactivity in the milk; however, it is not

known if this reflected radiolabeled enfuvirtide or metabolites (amino acid and peptide fragments) of enfuvirtide.

## Human Studies in Pregnancy

### Pharmacokinetics

Data on the use of enfuvirtide in human pregnancy are limited to case reports of a small number of women treated with the drug.<sup>2-8</sup>

### Placental and Breast Milk Passage

*In vitro* and *in vivo* studies suggest that enfuvirtide does not readily cross the human placenta. Published reports of a total of eight peripartum patients and their neonates and data from an *ex vivo* human placental cotyledon perfusion model demonstrated minimal placental passage of enfuvirtide.<sup>2,5,9-11</sup>

### Teratogenicity/Developmental Toxicity

In the Antiretroviral Pregnancy Registry and in a national cohort of pregnant women with HIV infection in Italy, insufficient numbers of first-trimester exposures to enfuvirtide in humans have been monitored to be able to make a risk determination.<sup>12,13</sup>

## References

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## **Maraviroc (Selzentry, MVC)**

**(Last updated August 6, 2015; last reviewed August 6, 2015)**

Maraviroc is classified as Food and Drug Administration Pregnancy Category B.<sup>1</sup>

### **Animal Studies**

#### *Carcinogenicity*

Maraviroc was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies of maraviroc showed no drug-related increases in tumor incidence.

#### *Reproduction/Fertility*

Reproductive toxicity has been evaluated in rats and rabbits. Maraviroc produced no adverse effects on fertility of male or female rats at doses with exposures (area under the curve [AUC]) up to 20-fold higher than in humans given the recommended 300-mg, twice-daily dose.

#### *Teratogenicity/Developmental Toxicity*

The incidence of fetal variations and malformations was not increased in embryo-fetal toxicity studies in rats at AUC approximately 20-fold higher (and in rabbits at approximately 5-fold higher) than human exposures at the recommended 300-mg, twice-daily dose (up to 1000 mg/kg/day in rats and 75 mg/kg/day in rabbits).

#### *Placental and Breast Milk Passage*

Minimal placental passage was demonstrated in a study of single-dose maraviroc in rhesus macaques that showed poor placental transfer and rapid clearance from infant monkeys' blood.<sup>2</sup> Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk.

### **Human Studies in Pregnancy**

#### *Pharmacokinetics*

Data on the use of maraviroc in human pregnancy are limited to a small pharmacokinetic study that found exposure to maraviroc was 21% lower during the third trimester than postpartum.<sup>3</sup>

#### *Placental and Breast Milk Passage*

An *ex vivo* human placental cotyledon perfusion model demonstrated minimal placental passage of maraviroc.<sup>4</sup> In a study in humans of six mother/infant pairs, the median ratio of cord blood-to-maternal-plasma drug concentrations was 0.33 (0.03–0.56).<sup>3</sup> Whether maraviroc is secreted into human milk is unknown.

#### *Teratogenicity/Developmental Toxicity*

In the Antiretroviral Pregnancy Registry, insufficient numbers of first-trimester exposures to maraviroc in humans have been monitored to be able to make a risk determination.<sup>5,6</sup>

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