

Etravirine (Intelence, ETR)

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Animal Studies

Carcinogenicity

Etravirine (ETR) was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests.¹ ETR was evaluated for carcinogenic potential in mice and rats for up to approximately 104 weeks. Because of intolerance of the formulation, the areas under the curve (AUC) for ETR were 0.6-fold (in mice) and 0.2-fold to 0.7-fold (in rats), compared with the typical AUC in humans receiving standard dosing. In rats and male mice, no significant findings were noted. In female mice, increased incidences of hepatocellular carcinoma and those of hepatocellular adenomas or carcinomas combined were observed. Whether these liver tumor findings in mice are relevant to humans is unclear.¹

Reproduction/Fertility

ETR had no effect on fertility and early embryonic development when tested in pregnant rats at doses that produced systemic drug exposures equivalent to those observed in humans who received the recommended dose of ETR 400 mg per day.¹

Teratogenicity/Adverse Pregnancy Outcomes

Animal reproduction studies in rats and rabbits revealed no evidence of fetal toxicity or altered development at systemic exposures equivalent to those seen in humans who received the recommended dose of ETR 400 mg per day.¹

Human Studies in Pregnancy

Pharmacokinetics

ETR pharmacokinetics (PK) in pregnant women have been reported in two studies. Ramgopal et al. found approximately 1.1-fold to 1.4-fold increases in total ETR AUC, C_{\min} , and C_{\max} during the second (n = 13) and third trimesters (n = 10) compared with the levels in the same women postpartum (n = 10). The differences in unbound ETR concentrations were less pronounced, with least-squares mean ratios of approximately 0.9 to 1.2.² Similarly, Mulligan et al. found 1.3-fold to 1.9-fold increases in total ETR AUC, C_{\min} , and C_{\max} during the third trimester (n = 13) compared with the levels in the same women postpartum (n = 8).³ ETR was well tolerated in both of these studies. ETR is a substrate for cytochrome P450 (CYP) 2C19 metabolism, and the increase in ETR exposure during pregnancy is consistent with the previously observed decrease in CYP2C19 activity during pregnancy.⁴

Placental and Breast Milk Passage

In seven mother–infant pairs, the median ratio of ETR concentration in cord blood to ETR concentration in maternal plasma at delivery was 0.52 (with a range of 0.19–4.25).³ In another study, the median ratio of cord blood to maternal plasma concentration in 10 mother–infant pairs was 0.32 (with a range of 0.19–0.63).² Placental passage of ETR was described in a report on the use of ETR, darunavir/ritonavir, and enfuvirtide in a woman who gave birth to twins. Cord-blood ETR levels were 414 ng/mL in Twin 1 and 345 ng/mL in Twin 2 (maternal plasma ETR concentration at delivery was not reported).⁵

Plasma and breast milk concentrations were measured on postpartum Days 5 and 14 in eight women who began taking ETR on postpartum Day 1.⁶ Plasma PK were similar between Days 5 and 14 and were similar to the published PK parameters of ETR in nonpregnant adults. ETR AUC_{0–12h} in breast milk was higher in mature milk (collected on Day 14) than in colostrum and/or transitional milk (collected on Day 5): 12,954 ± 10,200 ng•h/mL versus 4,372 ± 3,016 ng•h/mL (*P* = 0.046). Median ETR concentrations in plasma and breast milk on Day 5 were 300 ng/mL and 241 ng/mL, respectively (within-subject breast milk concentration/plasma concentration

ratio was 109%). Median plasma and breast milk concentrations on Day 14 were 197 ng/mL and 798 ng/mL, respectively (within-subject breast milk concentration/plasma concentration ratio was 327%). The maximum ETR concentration in breast milk was significantly higher than the maximum concentration in plasma ($1,245 \pm 1,159$ ng/mL vs. 531 ± 336 ng/mL, $P = 0.04$). Two women had detectable HIV RNA in breast milk on Day 14 despite having suppressed plasma viral loads. ETR concentrations in the plasma and breast milk of these women were similar to those observed in women with undetectable HIV RNA in breast milk. ETR penetrates well and may accumulate in breast milk.

Teratogenicity/Adverse Pregnancy Outcomes

In eight reported cases of ETR use in pregnancy, no maternal, fetal, or neonatal toxicities were noted.^{5,7} One infant was born with a small accessory auricle on the right ear but no other malformations, and no birth defects were noted in the other children.⁵ **Seventy-one live births** of infants who were exposed to ETR during the first trimester have been reported to the Antiretroviral Pregnancy Registry; among these infants, only one birth defect has been reported. These data are insufficient to draw conclusions about the risk of birth defects among infants who were exposed to ETR.⁸

Excerpt from Table 10

Generic Name (Abbreviation) <i>Trade Name</i>	Formulation	Dosing Recommendations ^a	Use in Pregnancy
Etravirine (ETR) <i>Intelligence</i>	<p>Tablets:</p> <ul style="list-style-type: none"> • 25 mg • 100 mg • 200 mg <p>For patients who are unable to swallow tablets whole, the tablets may be dispersed in a glass of water.</p>	<p>Standard Adult Doses</p> <ul style="list-style-type: none"> • 200 mg twice daily with food <p>Pregnancy <i>PK in Pregnancy:</i></p> <ul style="list-style-type: none"> • PK data in pregnancy suggest 1.2-fold to 1.6-fold increases in ETR exposure during pregnancy. <p><i>Dosing in Pregnancy:</i></p> <ul style="list-style-type: none"> • No change in dose indicated. 	<p>Placental transfer varies; it is usually in the moderate-to-high categories, ranging 0.19–4.25.^b</p> <p>Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.</p>

^a Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the [Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 10](#)).

^b Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6

Moderate: 0.3–0.6

Low: <0.3

Key: ARV = antiretroviral; ETR = etravirine; PK = pharmacokinetic

References

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