Etravirine (Intelence, ETR)

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Summary

- No dose adjustments are required for etravirine (ETR) during pregnancy.
- Clinical data are insufficient to characterize the risk for congenital anomalies associated with *in utero* exposure to ETR. No reproductive toxicity or teratogenicity concerns were identified in animal studies.

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 area under the curve (AUC), minimum plasma concentration (C_{min}), and maximum plasma concentration (C_{max}) during the second (n = 13) and third (n = 10) trimesters compared with the levels in the same women postpartum (n = 10). The differences in unbound ETR concentrations were less pronounced,[1] with least-squares mean ratios of approximately 0.9 to 1.2. 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).[2] ETR was well tolerated in both 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.[3] There is no evidence that ETR requires dose adjustment in pregnancy.

Placental and Breast Milk Passage

ETR crosses the placenta. In seven mother–infant pairs, the median ratio of ETR concentration in cord blood–to–ETR concentration in maternal plasma at birth was 0.52 (with a range of 0.19–4.25).[2] 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).1 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 birth was not reported).[4]

Plasma and breast milk concentrations were measured on postpartum Days 5 and 14 in eight women who began taking ETR on postpartum Day 1.[5] Plasma PK parameters were similar between Days 5 and 14 and were similar to the published PK parameters of ETR in nonpregnant adults. ETR AUC from 0 to 12 hours post-dose 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–to–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–to–plasma concentration ratio was 327%). The maximum ETR concentration in breast milk was significantly higher than the maximum concentration in plasma (1,245 ± 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

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for ETR and other ARV drugs twice a year through an interim report released in June and December. For the most recent data about ETR, refer to Table 5. Number of Birth Defects by Trimester of Earliest Exposure to Each Drug in the current APR interim report. The most recent data are insufficient to draw conclusions about the risk of birth defects among infants who were exposed to ETR.

Animal Studies

Carcinogenicity

ETR was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests.[6] ETR was evaluated for carcinogenic potential in mice and rats for up to approximately 104 weeks. Because of intolerance of the formulation, the AUCs 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 of hepatocellular adenomas or carcinomas combined were observed. Whether these liver tumor findings in mice are relevant to humans is unclear.[6]

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.[6]

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.[6]

Excerpt From Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines for information about the dosing and safety of individual drug components of the FDC tablet during pregnancy.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
Etravirine (ETR) *Intelence*	**Tablet** • 25 mg • 100 mg[c] • 200 mg[c] For patients who are unable to swallow tablets whole, the tablets may be dissolved in a glass of water.	**Pregnancy** *PK in Pregnancy* • PK data in pregnancy suggest increases in ETR exposure during pregnancy. *Dosing in Pregnancy* • No change in dose is indicated. **Standard Adult Doses** • 200 mg twice daily with food	Placental transfer varies; it is usually in the moderate-to-high category, ranging from 0.19 to 4.25.[b] Insufficient data to assess teratogenicity in humans; no evidence of teratogenicity in rats or rabbits. **Note:** Please see FDA label for full list of drugs with potential interactions and drugs for which administration with ETR is contraindicated.

[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).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio.

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

[c] Generic product is available.

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

References

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5. Spencer L, Liu S, Wang C, et al. Intensive etravirine PK and HIV-1 viral load in breast milk and plasma in HIV+ women receiving HAART. Poster 891. Presented at: Conference on Retroviruses and Opportunistic Infections 2014. Boston, MA. Available at: https://www.croiconference.org/abstract/intensive-etravirine-pk-and-hiv-1-viral-load-breast-milk-and-plasma-hiv-women-receiving.

6. Etravirine (Intelence) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022187s025lbl.pdf.