

## **Ritonavir (Norvir, RTV)**

**(Last updated June 7, 2016; last reviewed June 7, 2016)**

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

### **Animal Studies**

#### *Carcinogenicity*

Ritonavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies in mice and rats have been completed. In male mice, a dose-dependent increase in adenomas of the liver and combined adenomas and carcinomas of the liver was observed at levels of 50, 100, or 200 mg/kg/day; based on area under the curve, exposure in male mice at the highest dose was approximately 0.3-fold that in male humans at the recommended therapeutic dose. No carcinogenic effects were observed in female mice with exposures 0.6-fold that of female humans at the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 6% of recommended therapeutic human exposure.!

#### *Reproduction/Fertility*

No effect of ritonavir has been seen on reproductive performance or fertility in rats at drug exposures 40% (male) and 60% (female) of that achieved with human therapeutic dosing; higher doses were not feasible because of hepatic toxicity in the rodents.!

#### *Teratogenicity/Developmental Toxicity*

No ritonavir-related teratogenicity has been observed in rats or rabbits. Developmental toxicity, including early resorptions, decreased body weight, ossification delays, and developmental variations such as wavy ribs and enlarged fontanelles, was observed in rats; however, these effects occurred only at maternally toxic dosages (exposure equivalent to 30% of human therapeutic exposure). In addition, a slight increase in cryptorchidism was also noted in rats at exposures equivalent to 22% of the human therapeutic dose. In rabbits, developmental toxicity (resorptions, decreased litter size, and decreased fetal weight) was observed only at maternally toxic doses (1.8 times human therapeutic exposure based on body surface area).!

#### *Placental and Breast Milk Passage*

Transplacental passage of ritonavir has been observed in rats with fetal tissue-to-maternal-serum ratios >1.0 at 24 hours post-dose in mid- and late-gestation fetuses.

### **Human Studies in Pregnancy**

#### *Pharmacokinetics*

A Phase I/II safety and pharmacokinetic study (PACTG 354) of ritonavir (500 or 600 mg twice daily) in combination with zidovudine and lamivudine in pregnant HIV-infected women showed lower levels of ritonavir during pregnancy than postpartum.<sup>2</sup> Ritonavir concentrations are also reduced during pregnancy versus postpartum when the drug is used at a low dose (100 mg) to boost the concentrations of other protease inhibitors.<sup>3,4</sup>

#### *Placental and Breast Milk Passage*

In a human placental perfusion model, the clearance index of ritonavir was very low, with little accumulation in the fetal compartment and no accumulation in placental tissue.<sup>5</sup> In a Phase I study of pregnant women and their infants (PACTG 354), transplacental passage of ritonavir was minimal, with an average cord blood-to-maternal-delivery concentration ratio of 5.3%.<sup>2</sup> In a study of cord blood samples from 6 women treated with ritonavir during pregnancy, the cord blood concentration was less than the assay limit of detection in 5 of the women and was only 0.38 micrograms/mL in the remaining woman.<sup>6</sup> In contrast, in a study of plasma and hair drug concentration in 51 mother-infant pairs in Uganda receiving lopinavir/ritonavir-based therapy during pregnancy and breastfeeding, infant plasma levels at delivery and hair levels at age 12 weeks suggested *in*

utero transfer of ritonavir: 2% of infants had detectable plasma ritonavir concentrations at birth while mean infant-to-maternal-hair concentration at 12 weeks postpartum was 0.47 for ritonavir.<sup>7</sup> However, transfer during breastfeeding was not observed, with no infant having detectable ritonavir plasma levels at 12 weeks.

### Teratogenicity/Developmental Toxicity

In the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to ritonavir have been monitored to be able to detect at least a **1.5-fold increase** in risk of overall birth defects. No such increase in birth defects has been observed with ritonavir. Among cases of first-trimester ritonavir exposure reported to the APR, the prevalence of birth defects was **2.3%** (**63** of **2,720** births; 95% CI, 1.8% to 3.0%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.<sup>8</sup>

### Excerpt from Table 8<sup>a</sup>

| Generic Name<br>(Abbreviation)<br>Trade Name | Formulation  | Dosing Recommendations   | Use in Pregnancy   |
|--|--|--|--|
| Ritonavir<br>(RTV)<br>Norvir                 | <p><u>Capsules:</u></p> <ul style="list-style-type: none"> <li>• 100 mg</li> </ul> <p><u>Tablets:</u></p> <ul style="list-style-type: none"> <li>• 100 mg</li> </ul> <p><u>Oral Solution:</u></p> <ul style="list-style-type: none"> <li>• 80 mg/mL</li> </ul> | <p><u>Standard Adult Dose as PK Booster for Other PIs:</u></p> <ul style="list-style-type: none"> <li>• 100–400 mg per day in 1–2 divided doses (refer to other PIs for specific dosing recommendations.)</li> </ul> <p><u>Tablet:</u></p> <ul style="list-style-type: none"> <li>• Take with food.</li> </ul> <p><u>Capsule or Oral Solution:</u></p> <ul style="list-style-type: none"> <li>• To improve tolerability, recommended to take with food if possible.</li> </ul> <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• Lower levels during pregnancy compared with postpartum.</li> </ul> <p><u>Dosing in Pregnancy:</u></p> <p>No dosage adjustment necessary when used as booster.</p> | <p>Low placental transfer to fetus.<sup>b</sup></p> <p>No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).</p> <p>Should only be used as low-dose booster for other PIs.</p> <p>Oral solution contains 43% alcohol and therefore may not be optimal for use in pregnancy.</p> |

<sup>a</sup> Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Adult Guidelines, Appendix B, Table 7](#)).

<sup>b</sup> Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

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

**Key to Abbreviations:** PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir

## References

1. Ritonavir (Norvir) [package insert]. Food and Drug Administration. 2015. Available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/020659s062,022417s014lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020659s062,022417s014lbl.pdf). Accessed April 22, 2016.
2. Scott GB, Rodman JH, Scott WA, et al. Pharmacokinetic and virologic response to ritonavir (RTV) in combination with zidovudine (ZDV) and lamivudine (3TC) in HIV-10-infected pregnant women and their infants. Presented at: 9th Conference on Retroviruses and Opportunistic Infections. 2002. Seattle, WA.
3. Best BM, Stek AM, Mirochnick M, et al. Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. *J Acquir Immune Defic Syndr*. 2010;54(4):381-388. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20632458>.
4. Mirochnick M, Best BM, Stek AM, et al. Atazanavir pharmacokinetics with and without tenofovir during pregnancy. *J Acquir Immune Defic Syndr*. 2011;56(5):412-419. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21283017>.

5. Casey BM, Bawdon RE. Placental transfer of ritonavir with zidovudine in the ex vivo placental perfusion model. *Am J Obstet Gynecol*. 1998;179(3 Pt 1):758-761. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9757985>.
6. Mirochnick M, Dorenbaum A, Holland D, et al. Concentrations of protease inhibitors in cord blood after in utero exposure. *Pediatr Infect Dis J*. 2002;21(9):835-838. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12352805>.
7. Gandhi M, Mwesigwa J, Aweeka F, et al. Hair and plasma data show that lopinavir, ritonavir, and efavirenz all transfer from mother to infant in utero, but only efavirenz transfers via breastfeeding. *J Acquir Immune Defic Syndr*. 2013;63(5):578-584. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24135775>.
8. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 Jan 1989–31 July 2015. Wilmington, NC: Registry Coordinating Center. 2015. Available at <http://www.apregistry.com/>.