Tipranavir (Aptivus, TPV)

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Tipranavir is classified as Food and Drug Administration Pregnancy Category C. Tipranavir **should not** be used during pregnancy.

Animal Studies

Carcinogenicity

Tipranavir was neither mutagenic nor clastogenic in a battery of five screening tests, both *in vitro* and, in animals, *in vivo*. Long-term carcinogenicity studies of tipranavir have been conducted in mice and rats. Mice were administered tipranavir doses ranging from 30 to 300 mg/kg/day, with or without ritonavir 40 mg/ kg/day; all doses resulted in systemic exposures below those seen in humans receiving the recommended dose. Incidence of benign hepatocellular adenomas, combined adenomas/carcinomas, and hepatocellular carcinoma was increased in both male and female mice receiving tipranavir/ritonavir (TPV/r). The clinical relevance of the carcinogenic findings in mice is unknown. Rats were administered doses ranging from 30 to 300 mg/kg/day tipranavir, with or without ritonavir. No drug-related findings were observed in male rats. At the highest dose of tipranavir (approximately equivalent to exposure in humans at the recommended therapeutic dose), an increased incidence of benign follicular cell adenomas of the thyroid gland was observed in female rats. This finding is probably not relevant to humans, because thyroid follicular cell adenomas are considered a rodent-specific effect secondary to enzyme induction.[1]

Reproduction/Fertility

Tipranavir had no effect on fertility or early embryonic development in rats at exposure levels that are similar to human exposure levels at the recommended clinical dose (TPV/r 500 mg/200 mg administered twice daily).[1]

Teratogenicity/Adverse Pregnancy Outcomes

No teratogenicity was detected in studies of pregnant rats and rabbits with exposure levels that were approximately 1.1-fold and 0.1-fold human exposure levels. Fetal toxicity (decreased ossification and body weights) was observed in rats exposed to 400 mg/kg/day or more of tipranavir (~0.8-fold human exposure). Fetal toxicity was not seen in rats and rabbits at levels of 0.2-fold and 0.1-fold human exposures. In rats, no adverse effects on development occurred at exposure levels of 40 mg/kg/day (~0.2-fold human exposure), but growth inhibition in pups and maternal toxicity were observed at 400 mg/kg/day (~0.8-fold human exposure).[1]

Placental and Breast Milk Passage

No animal studies of placental or breast milk passage of tipranavir have been reported.

Human Studies in Pregnancy

Pharmacokinetics

No studies of tipranavir have been completed in pregnant women or neonates.

Placental and Breast Milk Passage

It is unknown if tipranavir passes through the placenta or breast milk in humans. A single case report described relatively high levels of tipranavir in the third trimester and relatively high placental transfer (0.41), as measured by cord blood.[2]

Teratogenicity/Adverse Pregnancy Outcomes

The five first-trimester exposures to tipranavir that have been monitored to date in the Antiretroviral Pregnancy Registry are insufficient to draw conclusions regarding the risk of birth defects.[3]

Excerpt From Table 10[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Tipranavir (TPV) *Aptivus* **Note:** Must be combined with RTV for PK boosting	**TPV (Aptivus)** *Capsules* • 250 mg *Oral Solution:* • 100 mg/mL	**Standard Adult Dose:** • TPV/r 500 mg/200 mg twice daily *With RTV Tablets:* • Take with food. *With RTV Capsules or Solution:* • Take without regard to food; however, administering with food may help make the dose more tolerable. **Dosing in Pregnancy:** • Insufficient data to make dosing recommendation **PK in Pregnancy:** • Limited PK data in human pregnancy	TPV **should not** be used during pregnancy. Moderate placental transfer to fetus reported in 1 patient.b Insufficient data to assess teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Must be given as low-dose, RTV-boosted regimen.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[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 to Acronyms: PK = pharmacokinetic; RTV = ritonavir; TPV = tipranavir; TPV/r = tipranavir/ritonavir

References

1. Tipranavir [package insert]. Food and Drug Administration. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021814s016,022292s009lbl.pdf.

2. Weizsaecker K, Kurowski M, Hoffmeister B, Schurmann D, Feiterna-Sperling C. Pharmacokinetic profile in late pregnancy and cord blood concentration of tipranavir and enfuvirtide. *Int J STD AIDS*. 2011;22(5):294-295. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21571982.

3. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.