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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Tipranavir (Aptivus, TPV)

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

Tipranavir is classified as Food and Drug Administration Pregnancy Category C.

Animal Studies

Carcinogenicity

Tipranavir was neither mutagenic nor clastogenic in a battery of five in vitro and animal in vivo screening tests. Long-term carcinogenicity studies in mice and rats have been conducted with tipranavir. Mice were administered 30, 150, or 300 mg/kg/day tipranavir, 150/40 mg/kg/day tipranavir/ritonavir (TPV/r) in combination, or 40 mg/kg/day ritonavir. Incidence of benign hepatocellular adenomas and combined adenomas/carcinomas was increased in females of all groups except females given the low dose of tipranavir. Such tumors also were increased in male mice at the high dose of tipranavir and in the TPV/r combination group. Incidence of hepatocellular carcinoma was increased in female mice given the high dose of tipranavir and in both sexes receiving TPV/r. The combination of tipranavir and ritonavir caused an exposure-related increase in the same tumor type in both sexes. The clinical relevance of the carcinogenic findings in mice is unknown. Systemic exposures in mice (based on area under the curve [AUC] or maximum plasma concentration) at all dose levels tested were below those in humans receiving the recommended dose level. Rats were administered 30, 100, or 300 mg/kg/day tipranavir, 100/26.7 mg/kg/day TPV/r in combination, or 10 mg/kg/day ritonavir. No drug-related findings were observed in male rats. At the highest dose of tipranavir, an increased incidence of benign follicular cell adenomas of the thyroid gland was observed in female rats. Based on AUC measurements, exposure to tipranavir at this dose level in rats is approximately equivalent to exposure in humans at the recommended therapeutic dose. This finding is probably not relevant to humans because thyroid follicular cell adenomas are considered a rodent-specific effect secondary to enzyme induction.

Reproduction/Fertility

Tipranavir had no effect on fertility or early embryonic development in rats at exposure levels similar to human exposures at the recommended clinical dose (500/200 mg of TPV/r BID).

Teratogenicity/Developmental Toxicity

No teratogenicity was detected in studies of pregnant rats and rabbits at exposure levels approximately 1.1-fold and 0.1-fold human exposure. 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 were seen at levels of 40 mg/kg/day (~0.2-fold human exposure), but at 400 mg/kg/day (~0.8-fold human exposure), growth inhibition in pups and maternal toxicity were seen.

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 passage of tipranavir through the placenta or breast milk occurs 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.

Teratogenicity/Developmental Toxicity

The four first-trimester exposures to tipranavir that have been monitored to date in the Antiretroviral Pregnancy Registry are insufficient to allow conclusions to be drawn regarding risk of birth defects.
### References


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**Excerpt from Table 8**

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tipranavir (TPV)</td>
<td>Aptivus</td>
<td>Capsules:</td>
<td><strong>Standard Adult Dose:</strong></td>
<td>Moderate placental transfer to fetus reported in one patient.\a</td>
</tr>
<tr>
<td>Note: Must be combined with RTV for PK boosting</td>
<td>• 250 mg</td>
<td>• TPV 500 mg plus RTV 200 mg twice daily</td>
<td></td>
<td>Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.</td>
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<tr>
<td></td>
<td>Oral Solution:</td>
<td>• Take with food.</td>
<td></td>
<td>Must be given as low-dose RTV-boosted regimen.</td>
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<tr>
<td></td>
<td>• 100 mg/mL</td>
<td><strong>With RTV Tablets:</strong></td>
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<tr>
<td></td>
<td></td>
<td>• Take without regard to food; however, administering with food may help make the dose more tolerable.</td>
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<td></td>
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<td><strong>PK in Pregnancy:</strong></td>
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<tr>
<td></td>
<td></td>
<td>• Limited PK data in human pregnancy.</td>
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<td><strong>Dosing in Pregnancy:</strong></td>
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<tr>
<td></td>
<td></td>
<td>• Insufficient data to make dosing recommendation.</td>
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<td></td>
</tr>
</tbody>
</table>

\a Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Adult Guidelines, Appendix B, Table 7).

\b 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:** PK = pharmacokinetic; RTV = ritonavir; TPV = tipranavir