Tipranavir (TPV, APTIVUS)  (Last updated April 27, 2017; last reviewed April 27, 2017)

For additional information see Drugs@FDA:  http://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Oral Solution: 100 mg tipranavir/mL, with 116 International Units (IU) vitamin E/mL
Capsules: 250 mg

Dosing Recommendations

**Note:** Tipranavir must be used with ritonavir boosting. The ritonavir boosting dose used for tipranavir is higher than that used for other protease inhibitors.

**Pediatric Dose (Aged <2 Years):**
- Not approved for use in children aged <2 years.

**Pediatric Dose (Aged 2–18 Years):**
- Note: Not recommended for treatment-naive patients

**Body Surface Area Dosing:**
- Tipranavir 375 mg/m² plus ritonavir 150 mg/m², both twice daily (maximum tipranavir 500 mg plus ritonavir 200 mg, both twice daily)

**Weight-Based Dosing:**
- Tipranavir 14 mg/kg plus ritonavir 6 mg/kg, both twice daily (maximum tipranavir 500 mg plus ritonavir 200 mg, both twice daily)

**Adult Dose:**
- Note: Not recommended for treatment-naive patients
- Tipranavir 500 mg (two 250-mg capsules) plus ritonavir 200 mg, both twice daily

Selected Adverse Events

- Rare cases of fatal and non-fatal intracranial hemorrhage
- Skin rash (more common in children than adults)
- Nausea, vomiting, diarrhea
- Hepatotoxicity: elevated transaminases; clinical hepatitis
- Hyperlipidemia
- Hyperglycemia
- Elevated creatine phosphokinase

Special Instructions

- Administer tipranavir and ritonavir together with food.
- Tipranavir oral solution contains 116 IU vitamin E/mL, which is significantly higher than the reference daily intake for vitamin E. Patients taking the oral solution should avoid taking any form of supplemental vitamin E that contains more vitamin E than found in a standard multivitamin.
- Tipranavir contains a sulfonamide moiety and should be used with caution in patients with sulfonamide allergy.
- Store tipranavir oral solution at room temperature, 25°C (77°F); do not refrigerate or freeze. Oral solution must be used within 60 days after the bottle is first opened.
- Store unopened bottles of oral tipranavir capsules in a refrigerator at 2°C to 8°C (36°F to 46°F). Once bottle is opened, capsules can be kept at room temperature (maximum of 77°F or 25°C) if used within 60 days.
- Use tipranavir with caution in patients who may be at increased risk of intracranial
• Tipranavir has the potential for multiple drug interactions. Co-administration of tipranavir/ritonavir (TPV/r) with drugs that are highly dependent on CYP3A for clearance or are potent CYP3A inducers is contraindicated.

• Before tipranavir is administered, a patient’s medication profile should be carefully reviewed for potential drug interactions.

• TPV/r is a potent enzyme inducer and has the potential to decrease plasma concentrations of other antiretroviral drugs. TPV/r significantly decreases plasma concentrations of etravirine. Etravirine and TPV/r should not be coadministered.

• Tipranavir should be used with caution in patients who are receiving medications known to increase the risk of bleeding, such as antiplatelet agents, anticoagulants, or high doses of supplemental vitamin E.

**Metabolism/Elimination**

- Cytochrome P450 3A4 (CYP3A4) inducer and substrate; P-glycoprotein substrate;
- Dosing in patients with renal impairment: No dose adjustment required
- Dosing in patients with hepatic impairment: No dose adjustment required for mild hepatic impairment; use contraindicated for moderate-to-severe hepatic impairment.

**Drug Interactions** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and [http://www.hiv-druginteractions.org/](http://www.hiv-druginteractions.org/))

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**Major Toxicities**

- *More common:* Diarrhea, nausea, fatigue, headache, rash (more frequent in children than in adults), and vomiting. Elevated transaminases, cholesterol, and triglycerides. Elevated creatine phosphokinase.

- *Less common (more severe):* Lipodystrophy. Hepatotoxicity: clinical hepatitis and hepatic decompensation, including some fatalities. Patients with chronic hepatitis B or hepatitis C coinfection or elevations in transaminases are at increased risk of developing further transaminase elevations or hepatic decompensation (approximately 2.5-fold risk). Epistaxis which is more common with oral solution than capsule formulation.

- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs. Increased risk of intracranial hemorrhage. Tipranavir should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other medical conditions.
Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

Pediatric Use

Approval and General Considerations

Tipranavir is approved for use in children as young as 2 years and is available in a liquid formulation. Its indication is limited to those patients who are treatment-experienced and infected with HIV strains resistant to more than one protease inhibitor (PI). The use of tipranavir is limited by the high pill burden imposed on patients taking tipranavir capsules, including the need for a higher dose of boosting ritonavir than is required with other PIs. This increased dose of ritonavir is associated with greater potential for drug interactions and increased toxicity. In addition, tipranavir is associated with serious adverse events (AEs) that limit its use to patients with few treatment options.

Efficacy

Food and Drug Administration approval of tipranavir was based on a multicenter, pediatric study of the safety, efficacy, and pharmacokinetics (PKs) of TPV/r in children with HIV infection (PACTG 1051/BI-1182.14). This study enrolled 110 treatment-experienced children (with the exception of 3 treatment-naive patients) aged 2 to 18 years (median age 11.7 years). Patients were randomized to receive two different dosing regimens. The higher dose of TPV/r (375 mg/150 mg/m² body surface area twice daily) plus optimized background therapy was associated with better virologic responses at 48 weeks, particularly in the older, more heavily pretreated patients when compared to the lower dose that was studied. The 5-year, long-term follow-up study to evaluate safety, efficacy, and tolerability of patients enrolled in PACTG 1051 was reported. At week 288, most children were no longer receiving TPV/r. Reasons for discontinuation included AEs, virologic failure, and non-adherence. The youngest patients who were stable at week 48 were more likely to still be on treatment after 5 years with continued efficacy.

Pharmacokinetics

PK evaluation of the liquid formulation at steady state in children was assessed. In children aged 2 to <12 years, at a dosage of TPV/r 290/115 mg/m² body surface area, tipranavir trough concentrations were consistent with those achieved in adults receiving standard TPV/r 500 mg/200 mg dosing. However, children aged 12 to 18 years required a higher dose (375/150 mg/m² body surface area, 30% higher than the directly scaled adult dose) to achieve drug exposure similar to that in adults receiving the standard TPV/r dose. Based on these studies, the final dose of TPV/r 375/150 mg/m² body surface area twice daily is recommended.

Toxicity

AEs were similar between treatment groups in the multicenter, pediatric study. Twenty-five percent of children experienced a drug-related serious AE, and 9% of patients discontinued study drugs because of AEs. The most common AEs were gastrointestinal disturbances: 37% of participants had vomiting and 24% had diarrhea. The most common Grade 3 through 4 laboratory abnormalities were increases in CPK (11%), alanine aminotransferase (6.5%), and amylase (7.5%). In the long-term follow-up report for PACTG 1051, incidence of AEs defined as drug-related was 55% to 65% regardless of age at entry, with higher discontinuation rates due to AEs in the older age groups.

Vitamin E is an excipient in the tipranavir oral solution, with a concentration of 116 IU of vitamin E and 100 mg tipranavir/mL of solution. The recommended dose of tipranavir (14 mg/kg body weight) results in a vitamin E dose of 16 IU/kg body weight per day, significantly higher than the reference daily intake for vitamin E (10 IU) and close to the upper limit of tolerability for children. In PACTG 1051, bleeding events were reported more commonly in children receiving tipranavir oral capsules (14.3%) than in children.
taking tipranavir oral solution (5.75%). Overall, the incidence of bleeding episodes (primarily epistaxis) in pediatric patients observed in clinical trials was 7.5%.

References


