

<b>TIPRANAVIR (TPV)</b> (Updated April 2010)	
<b>Trade Name</b>	Aptivus
<b>Classification</b>	Protease Inhibitor
<b>Form</b>	250-mg capsules; 100 mg/ml solution
<b>Dosing Recommendations</b>	Must be co-administered with ritonavir (RTV) – TPV 500 mg + RTV 200 mg twice daily (+/- EFV or NVP)
<b>Hepatic Impairment Dosing</b>	Should not be administered in patients with moderate to severe hepatic impairment (Child-Pugh Class B and C). Discontinue TPV/RTV in patients who: develop asymptomatic elevations in AST/ALT >10 x ULN  <i>or</i> show elevations in AST/ALT between 5-10 x ULN + increases in total bilirubin >2.5 x ULN
<b>Food Effect</b>	Take with food. Bioavailability is increased with a high-fat meal
<b>Oral Bioavailability</b>	Absolute bioavailability is not known but is increased with fatty meals
<b>Serum Half-life</b>	4.8-6.0 hours
<b>Route of Metabolism</b>	Hepatic enzyme CYP 3A4; CYP 3A inhibitor
<b>Storage</b>	Capsules should be stored in a refrigerator 2°-8°C (36°-46°F) prior to opening the bottle. After opening the bottle, the capsules may be stored at room temperature and must be used within 60 days
<b>Adverse Events</b>	Fatal and nonfatal intracranial bleeding. PI class adverse effect that includes GI intolerance (N/V/D; abdominal pain), lipodystrophy syndrome, hyperglycemia, increased triglycerides and/or cholesterol, and transaminase elevation. Rash was observed in 8-14% of pts in phase 2/3 trials. TPV contains a sulfonamide moiety; therefore, should be used with caution in patients with severe sulfa allergy. TPV resulted in higher incidence of grade 2-4 LFTs elevation (17.5% vs. 9.9% in LPV/r, APV/r, SQV/r, and IDV/r comparator)
<b>FDA Pregnancy Category</b>	C
<b>Long-Term Animal Carcinogenicity Studies</b>	Currently underway
<b>Animal Teratogen Studies</b>	Conflicting animal studies. Not teratogenic in rats and rabbits studies or a decreased sternebrae ossification and body weight when given 0.1-fold to 1.1-fold human exposure
<b>Black Box Warnings</b>	Aptivus co-administered with 200 mg ritonavir has been associated with reports of both fatal and non-fatal intracranial hemorrhage and clinical hepatitis and hepatic decompensation including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity.

<b>Drugs to Avoid</b>	<p><b>As part of the ARV regimen:</b>  Etravirine  Fosamprenavir  Lopinavir  Saquinavir  Or any other PIs</p> <p>Alfuzosin, amiodarone, astemizole, bepridil, cisapride, ergot derivatives, flecainide, lovastatin, midazolam, pimozone, propafenone, quinidine, ranolazine, rifampin, high-dose sildenafil, simvastatin, St. John's wort, terfenadine, triazolam</p>
<b>Cautious Use or Dose Adjustment</b>	
<b>Antiretrovirals</b>	<p><b>Abacavir:</b> ABC AUC ↓ 40% – Clinical significance unknown; no dose adjustment recommended at this time</p> <p><b>Didanosine (EC):</b> ddI AUC ↓ by 33% – Clinical significance unknown, but take ddI-EC at least 2 hours before or after TPV/r</p> <p><b>Ritonavir:</b> TPV AUC ↑, Cmax ↑, Cmin ↑. Use TPV/r 500/200 mg twice daily</p> <p><b>Zidovudine:</b> ZDV AUC ↓ 35% – Clinical significance unknown; no dose adjustment recommended at this time</p>
<b>Antacids</b>	TPV AUC ↓ by approximately 30% – Avoid co-administration or separate administration time by 2 hours
<b>Antialcoholics</b>	<b>Disulfiram/metronidazole:</b> TPV capsules contain alcohol, which can produce disulfiram-like reactions
<b>Anticoagulants</b>	<b>Warfarin:</b> Monitor INR. Use with caution in patients who may be at risk for increased bleeding or who are receiving medications known to increase the risk of bleeding
<b>Anticonvulsants</b>	<b>Carbamazepine, phenobarbital, phenytoin:</b> May ↑ or ↓ anticonvulsants – Monitor levels; TPV may ↓ – use with caution. Consider alternate
<b>Antidepressants</b>	<b>Desipramine:</b> Desipramine ↑ or ↓ – ↓ desipramine dose and monitor concentration
<b>Antifungals</b>	<p><b>Fluconazole:</b> TPV AUC ↑ 50% – Do not use fluconazole doses &gt;200 mg/day</p> <p><b>Itraconazole:</b> Use with caution; do not use itraconazole doses &gt;200 mg/day</p> <p><b>Ketoconazole:</b> Use with caution; do not use ketoconazole doses &gt;200 mg/day</p> <p><b>Voriconazole:</b> Voriconazole levels may be ↓ – Use with caution</p>
<b>Antigout</b>	<p><b>Colchicine:</b> For treatment of gout flares – 0.6 mg (1 tablet) x 1 dose, then 0.3 mg (½ tablet) 1 h later. Do not repeat dose before 3 days.</p> <p>For prophylaxis of gout flares – adjust dose to ¼ original regimen</p> <p>For treatment of familial Mediterranean fever (FMF) – Max: 0.6 mg daily</p> <p>Do not co-administer in patients with hepatic or renal impairment</p>
<b>Antimycobacterials</b>	<p><b>Clarithromycin:</b> TPV AUC ↑ 66%; CL AUC ↑ 19%; 14-hydroxy-CL metabolite ↓ – No dose adjustment necessary for patients with normal renal function; Clarithromycin dose with CrCl 30-60 mL/min=50% of dose. CrCl &lt;30mL/min=25% of dose</p> <p><b>Rifabutin:</b> RFB ↑; desacetyl-RFB ↑ – RFB 150 mg qod; monitor patients for adverse events</p>

<b>Bronchodilators</b>	<b>Salmeterol:</b> Co-administration not recommended. Consider formoterol
<b>Calcium Channel Blockers</b>	Clinical monitoring of patients is recommended
<b>Erectile Dysfunction Agents</b>	<p><b>Sildenafil:</b> May ↑ sildenafil – Use cautiously, start with reduced dose of 25 mg q48h and monitor for adverse effects</p> <p><b>Tadalafil:</b> May ↑ tadalafil – Start with a 5-mg dose; do not exceed a single 10-mg dose of tadalafil in 72 hours</p> <p><b>Vardenafil:</b> May ↑ vardenafil – Start with a 2.5-mg dose, and do not exceed a single 2.5-mg dose in 72 hours</p>
<b>H2 Blocker and Proton Pump Inhibitor</b>	No data. TPV absorption may be ↓ – Use with caution
<b>Immunosuppressants</b>	<b>Cyclosporine, sirolimus, tacrolimus:</b> May ↑ or ↓ immunosuppressants – Monitor immunosuppressant concentrations closely
<b>Lipid-Lowering Agents</b>	<b>Atorvastatin:</b> ATO AUC ↑ by 8-fold – Use lowest possible starting dose of ATO with careful monitoring (consider pravastatin or rosuvastatin with close monitoring)
<b>Narcotic Analgesics</b>	<b>Meperidine:</b> Meperidine ↓; normeperidine (metabolite) ↑ – Dosage increase and long-term use of meperidine with TPV are not recommended
<b>Oral Contraceptives</b>	<b>Ethinyl estradiol:</b> EE ↓ 50% – Use alternative or additional method of contraception
<b>Pulmonary Hypertension Agents</b>	<p><b>Bosentan:</b> In patients already taking TPV/r for ≥10 days, co-administer bosentan at a reduced dose of 62.5 mg once daily or qod based on tolerability. If patient is already taking bosentan, discontinue bosentan for ≥36 hrs prior to initiating TPV/r. After TPV/r has been given for &gt;10 days, once daily or qod bosentan can be reintroduced.</p> <p><b>Tadalafil:</b> In patients already taking TPV for ≥1 wk, co-administer tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability. In patients already taking tadalafil, avoid use of tadalafil during initiation of TPV. Stop tadalafil ≥24 h prior to starting TPV. At least ≥1 wk after initiating TPV, resume tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability.</p>
<b>Synthetic Narcotics</b>	<b>Methadone:</b> Methadone ↓ 50% – Clinical significance unknown. May need to ↑ methadone dose