Selected Properties of Tipranavir

Other names	Aptivus®, TPV, PNU-140690
Manufacturer	Boehringer Ingelheim
Pharmacology/Mechanism of Action	non-peptidic protease inhibitor
Molecular Weight	602.68
Activity	In vitro EC50 0.03-0.07 uM, EC90 0.07-0.18 uM. In vivo EC90 0.28-0.72 uM.
Resistance - genotypic	Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations): Major: L33I/F, V82L/T, I84V Minor: L10V, I13V, K20M/R, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, N83D, L90M **as major & minor mutations accumulate, susceptibility to PIs decreases*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): 32, 33, 45, 82, 84: 14-fold ↑ Approx. 3-fold ↑ IC90 after serial passage of virus in presence of tipranavir
Cross-Resistance	Only mild (6-fold ↑) in IC90 with ritonavir-resistance virus that is highly cross-resistant to indinavir, nelfinavir, and saquinavir.
Oral Bioavailability	
Effect of Food	Bioavailability of older formulation of tipranavir increased 2-fold with high-fat meal. Tipranavir capsules: When tipranavir 500 mg/ritonavir 200 mg BID was administered with food, tipranavir bioavailability was not altered compared to when TPV/r was administered in a fasting state.[1] Tipranavir oral solution: When tipranavir 500 mg/ritonavir 200 mg BID as oral solution was administered with food, tipranavir Cmax ↑ 21% relative to fasting, with no change in AUC or Cmin. [1] Tipranavir/ritonavir may be taken with or without food. May take with food to decrease potential for nausea and vomiting.
Protein Binding	>99.9%
Vd	
Tmax	2.9-3 hours
serum T ½	5.5-6 hours
Drug Concentrations	Median steady-state tipranavir plasma concentrations with 500/200mg ritonavir BID: Ctrough 21.01-29.1 uM, Cmax 123.4 uM, AUC 855.6 h.uM.

	Peak RNA reduction is correlated with Cmin. Significantly higher tipranavir Ctrough and lower inter-individual variability observed in women versus men (Solas et al. 2007).
Minimum target trough concentrations (for wildtype virus)	20 uM (preliminary target)
CSF (% of serum)	2010 CNS Penetration Effectiveness (CPE) Score: 1 [Letendre S et al. 2010]
Metabolism	Substrate of CYP3A4 and P-gp. Inducer of CYP3A4, P-gp, glucuronyl transferase, slight inducer of CYP2C9, moderate inducer of CYP1A2, and potent inhibitor of CYP2D6. When co-administered with ritonavir, net effect is CYP3A inhibition.
Excretion	4.4% dose excreted in urine.
Dosing – Adult	500 mg po BID + ritonavir 200 mg po BID with food
Dosing – Pediatric	For patients ages 2-18 years: 14 mg/kg with 6 mg/kg ritonavir (or 375 mg/m^2 co-administered with ritonavir 150 mg/m^2) BID (maximum tipranavir 500/ritonavir 200 mg BID). For children who develop intolerance or toxicity, dose reduction to tipranavir 12 mg/kg plus ritonavir 5 mg/kg (or tipranavir 290 mg/m^2 co-administered with 115 mg/m^2 ritonavir) BID may be considered, providing the virus is not resistant to multiple protease inhibitors.
Special instructions for pediatric patients	Patients taking tipranavir oral solution should be advised not to take supplemental vitamin E greater than a standard multivitamin, the oral solution contains 116 IU/mL of vitamin E which is higher than the Reference Daily Intake (adults 30 IU, pediatrics approximately 10 IU).
Adjust in Liver Dysfunction	No dosage recommendation; use with caution in patients with hepatic impairment; TPV/RTV is contraindicated in pts with moderate to severe (Child -Pugh Class B & C) hepatic insufficiency. Plasma tipranavir concentrations are increased in patients with significant liver fibrosis (Metavir score $\geq$ 2) (Morello et al. 2007).
Adjust in Renal Failure/Dialysis	Dosage adjustment not required since tipranavir is extensively metabolized.
Toxicity	**GI:** diarrhea, nausea, vomiting. Diarrhea occurs 4-5 days after starting; most cases improve over time. No trend of dose-dependence observed. **Rash:** Mild to moderate rashes including urticarial rash, maculopapular rash, and possible photosensitivity have been reported (8-14% in phase 2 and 3 trials). Female gender associated with increased frequency of skin rash. Additionally, in one drug interaction trial in healthy female volunteers given a single dose of ethinyl estradiol followed by tipranavir/ritonavir, 33% of subjects developed a rash. Rash accompanied by joint pain or stiffness, throat tightness, or generalized pruritus (itching)

has been reported in both men and women receiving tipranavir/ritonavir.

Hepatotoxicity (Black Box warning): Tipranavir co-administered with low dose ritonavir has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. All patients should be followed closely with clinical and laboratory monitoring, especially those with chronic hepatitis B or C co-infection, as these patients have an increased risk of hepatotoxicity. Liver function tests should be performed at baseline and frequently through treatment. In addition, tipranavir is contraindicated in patients with moderate and severe (Child-Pugh Class B and C, respectively) hepatic insufficiency.

Intracranial Hemorrhage (ICH) - Black Box Warning:

- In clinical trials, TPV/r was associated with 14 ICH events including 8 fatalities, in 13 out of 6840 HIV-1 patients.
- Many of these events occurred in patients who had other risk factors for ICH. These risk factors may have caused or contributed to ICH events
    - Medical conditions: CNS lesions, head trauma, recent neurosurgery, coagulopathy, hypertension or alcohol abuse
    - Concomitant medications: anticoagulants, antiplatelet agents
- Median time to onset of an ICH event: 525 days after TPV/r initiation
- In *in vitro* experiments, TPV was observed to inhibit human platelet aggregation at levels consistent with exposures observed in patients receiving TPV/r. In general no pattern of abnormal coagulation parameters has been observed in patients receiving TPV.
- Therefore, routine measurement of coagulation parameters is not currently indicated in the management of patients on TPV.
- TPV/r should be used with caution in patients who are at increased risk for ICH.
- Aside – Risk Factors for ICH include: increased age, hypertension, high alcohol intake, smoking, CNS lesions, head trauma, recent neurosurgery, coagulopathy, male sex, non-white ethnicity, use of anticoagulants and/or antiplatelet agents.
- It is important to note that an increased risk of ICH has previously been observed in patients with advanced HIV-1 disease / AIDS.

Further investigations are ongoing to assess the role of TPV in ICH.

Sulfa Allergy: Tipranavir should be used with caution in patients with a known sulfonamide allergy. Tipranavir contains a sulfonamide component. The potential for cross-sensitivity between drugs in the sulfonamide class and tipranavir is unknown.

TPV/r did not prolong the QTc interval, exhibit QT prolongation

	or clinically important ECG effects with therapeutic dosing (TPV/r 500/200mg BID) or supra-therapeutic dosing (TPV/r 750/200mg BID) in 80 healthy subjects [Huettner et al. ICAAC 2007] Protease class effects include: hyperlipidemia, hypertriglyceridemia, hyperglycemia, fat maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis.
Pregnancy & Lactation	Pregnancy category C. No studies or experience in human pregnancy. Safety and pharmacokinetic in pregnancy data are insufficient to recommend use in pregnancy.
Drug Interactions	Tipranavir induces CYP3A, glucuronosyl transferase in vivo. Tipranavir is a slight inducer of CYP2C9, moderate inducer of CYP1A2, and potent inhibitor of CYP2D6.[2] Tipranavir also induces p-glycoprotein activity. Tipranavir has been shown to significantly ↓ concentrations of several co-administered protease inhibitors. See separate Drug Interaction table for more information. Tipranavir capsules contain alcohol; use with caution with metronidazole (may produce disulfiram-like reaction).
Baseline Assessment	Assess risk factors for diabetes, coronary artery disease, osteonecrosis (i.e. steroids, ETOH, diabetes, hyperlipidemia), and hepatic dysfunction (i.e. HBV/HCV, ETOH use). CBC/diff, LFTs, glucose, fasting cholesterol profile.
Routine Labs	CBC/diff, LFTs, glucose q 3 mos. Fasting lipids (8-12 hr level) q 3-6 months post-therapy, then annually. If TG > 2.3 mmol/L at baseline, repeat after 1-2 months.
Dosage Forms	250 mg soft gel capsules, DIN 02273322; 100 mg/mL oral solution. Capsules contain alcohol.
Storage	Capsules stable under refrigeration for at least 18 months; when stored unopened at room temperature, capsules are stable for up to 90 days. When stored at room temperature and opened twice daily, capsules are stable for up to 60 days. Tightly cap bottles after each use. Tipranavir oral solution is stable for 12 months at room temperature. Do not refrigerate or freeze; tightly cap bottle after each use.

References:

Intracranial Hemorrhage:

1. Dear Health Care Professional Letter, Boehringer Ingelheim Pharmaceuticals, Inc, June 30, 2006. Accessed online on August 20, 2007 http://www.fda.gov/medwaTCH/safety/2006/Aptivus-tipranavir_DHCP.pdf
2. Aptivus Drug Monograph. Accessed online through eCPS on August 20, 2007. https://www.e-therapeutics.ca/wps/myportal/!ut/p/_s.7_0_A/7_0_2UM/.cmd/acd/.ar/sa.DisplayContent/.c/6_0_2KM/.ce/7_0_2US/.p/5_0_281/.d/2?PC_7_0_2US_searchTerm=tipranavir&PC_7_0_2US_value=m700075&PC_7_0_2US_title=Aptivus#m700075n00044
3. Personal Communication with Ranka Rakcevic, Boehringer Ingelheim, Aug 22, 2007. The company has no new information on TPV and ICH since publication of Dear Health Care

Professional Letter.
4. Ariesen MJ. Claus SP. Rinkel GJ. Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. Stroke. 34(8):2060-5, 2003 Aug

Boehringer Ingelheim (Canada) Ltd. Aptivus® Product Monograph. Burlington, ON. May 14th, 2009.

Huettner S, Ring A, Sabo JP, Hoesl C, Ballow C, Roszko P, et al. No significant ECG effects are observed with therapeutic and supra-therapeutic doses of tipranavir co-administered with ritonavir [abstract A-1422]. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicaco, IL, September 17-20, 2007.

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort: CPE score predicts CSF suppression [abstract 430]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

McCallister S, Valdez H, Curry K, MacGregor T, Borin M, Freimuth W, Wang Y, Mayers DL. A 14-Day Dose-Response Study of the Efficacy, Safety, and Pharmacokinetics of the Nonpeptidic Protease Inhibitor Tipranavir in Treatment-Naive HIV-1-Infected Patients. J Acquir Immune Defic Syndr. 2004;35(4):376-382.

Morello J, et al. Higher plasma levels of tipranavir in patients with more significant liver fibrosis and risk of liver toxicity [abstract 35]. 8th International Workshop on Clinical Pharmacology of HIV Therapy, Budapest, Hungary. April 16-18, 2007.

Solas et al. Higher plasma trough concentrations of tipranavir in HIV-1 infected women compared with men treated with tipranavir/ritonavir 500/200 mg twice daily in clinical practice [abstract 42]. 8th International Workshop on Clinical Pharmacology of HIV Therapy, Budapest, Hungary. April 16-18, 2007.

Valdez H, Sabo J, Wruck J, et al. Tipranavir excretion mass balance and metabolite profile when coadministered with ritonavir [abstract A-455]. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, October 30-November 2, 2004, Washington, DC.

1. La Porte CJL, Cameron DW, Sabo J, Murray GE, Fagan N, Bosisio M, et al. The effect of omeprazole, food and formulation on the pharmacokinetics of tipranavir administered with ritonavir [abstract 59]. 8th International Workshop on Clinical Pharmacology of HIV Therapy, Budapest, Hungary. April 16-18, 2007.
2. Vourvahis M, Dumond J, Patterson K, Rezk N, Tien H, Li J, et al. Effects of tipranavir/ritonavir on the activity of cytochrome p450 enzymes 1A2, 2C9 and 2D6 in healthy volunteers [abstract 52]. 8th International Workshop on Clinical Pharmacology of HIV Therapy, Budapest, Hungary. April 16-18, 2007.

