

Selected Properties of Atazanavir

Other names	BMS 232632, Reyataz®
Manufacturer	BristolMyersSquibb
Pharmacology/Mechanism of Action	Atazanavir is an azapeptide HIV-1 protease inhibitor. The compound selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.
Activity	Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC50) in the absence of human serum of 2-5 nM against a variety of laboratory and clinical HIV-1 isolates. Atazanavir has additive in vitro antiviral activity with the protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir) and NRTIs (didanosine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine) without enhanced cytotoxicity.
Resistance - genotypic	<p>Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations):</p> <p>Major: I50L, I84V#, N88S Minor: L10I/F/V#, G16E#, K20R/M/I, L24I, V32I, L33I/F/V#, M36I/L/V, M46I/L#, G48V, I54L/V/M/T, D60E#, I62V, A71V/I/T/L, G73C/S/T/A, V82A/T, I85V#, L90M, I93L</p> <p>*as major & minor mutations accumulate, susceptibility to PIs decreases</p> <p>#presence of 3 or more of these mutations predicts a reduced virologic response at 3 months, particularly when L90M is present</p>
Resistance - phenotypic	<p>Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/):</p> <p>I50L: 6-fold ↑ (intermediate-to-high level resistance) I84V + L90M: 10-fold ↑ (high level resistance)</p>

Cross-Resistance	<p>Baseline phenotypic and genotypic analyses of clinical isolates from atazanavir clinical trials of protease inhibitor-experienced subjects indicate:</p> <ul style="list-style-type: none"> • the I50L and I50V substitutions yield selective resistance to atazanavir and amprenavir, respectively, and do not appear to confer cross-resistance. • other atazanavir-resistant isolates are highly cross-resistant (51%-100%) to other protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). • a clear trend toward decreased atazanavir susceptibility as isolates exhibited resistance to multiple protease inhibitors.
Oral Bioavailability	<p>Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir if antacids, buffered medications, H₂-receptor antagonists, and proton-pump inhibitors are administered with atazanavir. Avoid concomitant use (kinetic study showed significantly reduced atazanavir exposure when coadministered with omeprazole; atazanavir absorption did not improve when given either boosted with ritonavir or with 8 oz cola).</p>
Effect of Food	<p>Administration of atazanavir and atazanavir/ritonavir with food enhances bioavailability (35-70% ↑ AUC) and reduces pharmacokinetic variability by 50%.</p>
Protein Binding	<p>86%, binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively).</p>
Vd	
Tmax	2-2.5 hours
serum T_{1/2}	Approximately 7 hours
Drug Concentrations	<p>Steady-state atazanavir concentrations in HIV-positive subjects after 400 mg QD administration with food: C_{max} 3152 ng/mL, C_{min} 273 ng/mL, AUC 22262 ng.h/mL</p> <p>Atazanavir plasma concentrations after 300/100 mg ritonavir QD: C_{max} 5233 ng/mL, C_{min} 862 ng/mL, AUC 53761 ng.h/mL</p>
Minimum target trough concentrations (for wildtype virus)	<p>Median wild-type EC₉₀ = 14 ng/mL Suggested minimum trough: 150 ng/mL.</p>

CSF (% of serum)	<p>In 4 HIV-positive subjects dosed with atazanavir 400 mg QD for 12 weeks, the cerebrospinal fluid/plasma ratio ranged between 0.0021 and 0.0226.</p> <p>In 26 participants receiving atazanavir 300/ritonavir 100 mg QD, ATV concentrations in the CSF were highly variable, and were 100-fold lower than plasma concentrations. 17 (65%) CSF samples were >11 ng/mL (ATV IC50 for WT) [Best et al. CROI 2006].</p>
Metabolism	<p>Extensively metabolized by CYP3A4. Atazanavir inhibits CYP3A and UGT1A1 at clinically relevant concentrations. Atazanavir also competitively inhibits CYP1A2 and CYP2C9. Atazanavir does not inhibit CYP2C19 or CYP2E1 at clinically relevant concentrations.</p>
Excretion	<p>Approximately 7% excreted unchanged in the urine.</p> <p>47 HIV-positive patients treated with ATV containing regimens were tested to determine if ABCB1 and CYP3A5 polymorphisms are associated with ATV concentrations and/or immunological responses.</p> <ul style="list-style-type: none"> • ABCB1 haplotype (3435CT-2677GT) was significantly associated with faster ATV oral clearance than 3435CC-2677GG (mean 12.79 VS 7.3L/hr, p=0.018). Trend for ↑ clearance observed in C3435T and G2677T variant carriers • Mean CD4 counts were 375 for ABCB1 2677GG and 547 for 2677GT (p=0.036) • No relationships were identified with CYP 3A5 <p>Authors state these pilot data provide rationale for the development of individualized ATV regimens [Ma et al. ICAAC 2007].</p>
Dosing – Adult	<p>400 mg once daily with food is approved dose.</p> <p>Atazanavir 300 mg /day + ritonavir 100 mg/day has a better PK profile which may yield better clinical results.</p> <p>If taken with efavirenz or tenofovir: atazanavir 300 mg /day + ritonavir 100 mg/day.</p>
Dosing – Pediatric	<p>Should not be administered to infants < 3 months due to risk of hyperbilirubinemia. Not approved in children; phase I/II trials underway.</p>
Special instructions for pediatric patients	<p>Investigational po powder used in trials. Powder may be mixed with small amount of water, applesauce, milk, or yogurt (consume within 3 hours of mixing). Do not mix with juices or foods with high pH.</p>

Adjust in Liver Dysfunction	<p>In adults with moderate to severe hepatic impairment (Child-Pugh B and C), mean atazanavir AUC after a single 400 mg dose was 42% greater than in healthy volunteers, while the mean half-life was 12.1 hours compared to 6.4 hours.</p> <p>The following dosage adjustments are recommended: Child-Pugh Score 7-9: 300 mg QD Child-Pugh score >9: not recommended</p>
Adjust in Renal Failure/Dialysis	<p>In an open-label study in HIV-negative participants, steady-state kinetics of atazanavir 400 mg QD were compared between renally impaired (Clcr<30 mL/min) and non-renally impaired (Clcr>80 mL/min) subjects. Compared to controls, atazanavir AUC ↑ 19% and Cmin ↑ 96% in the renally impaired group. No dosage adjustment of atazanavir is necessary in renal impairment not managed with hemodialysis.[Agarwala et al. 2007]</p> <p>In subjects on hemodialysis, atazanavir exposures were ↓ 25-40% compared to non-renally impaired controls; atazanavir exposures were decreased independent of time of administration in relation to dialysis. Atazanavir dialysis clearance was low, with 2.1% of the administered dose eliminated over a 4 hour dialysis period. May wish to consider boosted atazanavir (300 mg/ritonavir 100 mg QD) in hemodialysis patients.[Agarwala et al. 2007]</p>

<p>Toxicity</p>	<p>Skin rash (21%), < 1% severe rash; asymptomatic indirect hyperbilirubinemia (30%), jaundice (10%), headache, fever, arthralgias, depression, insomnia, dizziness, nausea/vomiting/diarrhea, paresthesias, prolongation of PR interval of EKG.</p> <p>Risk of hyperlipidemia appears to be negligible.</p> <p>Protease class effects include: hyperlipidemia & hypertriglyceridemia (except atazanavir), hyperglycemia, fat maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis.</p> <p>Kidney Stones (uncommon)</p> <ul style="list-style-type: none"> • American Reports: 30 cases ATV associated nephrolithiasis recorded between Dec 2002 to Jan 2007 in the US FDA Adverse Event Reporting System Database (Voluntary reporting) • French Case Series: 11/1134 patients developed ATV nephrolithiasis (Mar 2004 – Feb 2007). 4 pts had history of kidney stones before ATV exposure. Mean onset for ADR ~ 23 months. 1/6 patients that were kept on ATV developed recurrent kidney stones despite instructions to drink more fluids, including acidic beverages such as cola. • Reports suggest kidney stones composed of 60-100% ATV crystals • Exact mechanism for ADR is unknown. • 7% of the ATV dose is excreted unchanged in the urine. Like IDV, the solubility of ATV is increased in acid fluids <p>Risk Factors: not drinking enough fluid, having urine that is not acidic, having a history of kidney stones</p>
<p>Pregnancy & Lactation</p>	<p>Pregnancy risk category B. No experience in human pregnancy. Theoretical risk with indirect hyperbilirubinemia which may be additive with neonatal elevations in bilirubin. Placental passage unknown, however it has been low with other PIs.</p>

Drug Interactions	Avoid concomitant administration with antacids, proton-pump inhibitors, or H2-blockers, as atazanavir absorption is significantly compromised. Atazanavir is an inhibitor of CYP3A and UGT1A1. See separate Drug Interaction Table for more information.
Baseline Assessment	Assess risk factors for diabetes, coronary artery disease (less with ATV), 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	<i>100 mg capsules (blue/white) available in U.S.</i> 150 mg capsules (blue/powder blue); DIN 02248610 200 mg capsules (blue/blue); DIN 02248611 300 mg capsules (blue/red); DIN 02294176
Storage	Store at room temperature.

References:

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