

# Atazanavir

**Brand Name: Reyataz**



## Drug Description

Atazanavir, formerly known as BMS-232632, is an azapeptide protease inhibitor (PI) of HIV-1 protease that differs structurally from other approved peptidomimetic PIs by its C-2 symmetric chemical structure. [1] [2]

## HIV/AIDS-Related Uses

Atazanavir sulfate was approved by the FDA on June 20, 2003, for the treatment of HIV-1 infection in combination with other antiretroviral agents.

The FDA based its approval of atazanavir on data from two Phase 2 48-week trials and from 24 to 48 week data from Phase 3 studies. Results from these trials showed a decrease in viral load and an increase in CD4 cell counts in patients taking atazanavir in combination with other antiretroviral agents.[3] Atazanavir became commercially available in the United States under the principles of the accelerated review process of the FDA that allow approval based on analysis of surrogate markers of response (e.g., plasma HIV-1 RNA levels), rather than clinical end points such as disease progression or survival. There are no results to date from controlled studies evaluating the effects of atazanavir on clinical progression of HIV infection.[4]

Atazanavir is a PI with a unique HIV resistance profile that suggests it may be an appropriate component of antiviral regimens in treatment-naïve patients. Patients taking atazanavir on their first antiretroviral regimen develop a characteristic I50L mutation that increases viral susceptibility to other PIs. Unlike other PIs, atazanavir appears to have a minimal effect on lipid levels.[5]

The use of atazanavir sulfate may be considered in antiretroviral-experienced adults with HIV strains that are expected to be susceptible to atazanavir sulfate by genotypic and phenotypic testing.[6]

## Pharmacology

Atazanavir is an azapeptide PI that selectively inhibits the virus-specific processing of viral Gag

and Gag-Pol polyproteins in HIV-1 infected cells, preventing formation of mature virions.[7] Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC<sub>50</sub>) in the absence of human serum of 2 to 5 nM against a variety of laboratory and clinical HIV-1 isolates grown in peripheral blood mononuclear cells, macrophages, CEM-SS cells, and MT-2 cells. Two-drug combination studies with atazanavir showed additive to antagonistic antiviral activity in vitro with abacavir and the nonnucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine, efavirenz, and nevirapine and additive antiviral activity in vitro with the PIs amprenavir, indinavir, lopinavir, ritonavir, and saquinavir.[8]

Atazanavir is rapidly absorbed, with a median time to maximum plasma concentration of approximately 2.5 hours in healthy people and 2 hours in HIV infected patients.[9] Atazanavir demonstrates nonlinear pharmacokinetics, with greater than dose-proportional increases in area under the plasma concentration-time curve (AUC) and mean maximum plasma concentration (C<sub>max</sub>) values over the dose range of 200 to 800 mg once daily. Steady-state is achieved between Days 4 and 8, with an accumulation of approximately 2.3-fold. The pharmacokinetics of atazanavir in pediatric patients are under investigation. Administration of atazanavir with a light meal resulted in a 70% increase in AUC and a 57% increase in C<sub>max</sub> relative to the fasting state. Administration of a single 400 mg dose of atazanavir with a high-fat meal resulted in a mean increase in AUC of 35% and no change in C<sub>max</sub> relative to the fasting state.[10]

In a multiple-dose study in HIV infected patients taking 400 mg atazanavir once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid (CSF) and semen. The CSF/plasma ratio for atazanavir ranged between 0.0021 and 0.0226; the seminal fluid/plasma ratio ranged between 0.11 and 4.42.[11]

Atazanavir is in FDA Pregnancy Category B. There have been no adequate and well-controlled studies of atazanavir in pregnant women. Atazanavir should be used in pregnancy only if the potential

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## Pharmacology (cont.)

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benefit to the mother justifies the potential risk to the fetus. No significant effects on mating, fertility, or early embryonic development were observed in rats given daily doses up to two times the human clinical dose of 400 mg once daily. In studies with rabbits and rats given doses producing drug exposure levels up to two times the human clinical dose, atazanavir did not produce teratogenic effects. However, in pre- and postnatal studies of rats given atazanavir at maternally toxic exposure levels, two times the human clinical dose caused weight loss or weight gain suppression in the offspring. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to antiretroviral agents. Physicians may register their patients by calling 1-800-258-4263 or at <http://www.APREgistry.com>. [12]

It is not known whether atazanavir is secreted in human breast milk; however, it is distributed into the milk of rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in the nursing infant, mothers should be instructed not to breast-feed if they are receiving atazanavir. [13]

Atazanavir is 86% bound to human serum proteins; protein binding is independent of concentration. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively). Atazanavir is extensively metabolized in the liver by CYP3A [14] and inhibits CYP3A and UGT1A1. [15] The major biotransformation pathways of atazanavir consist of monooxygenation and dioxygenation. Other minor biotransformation pathways for atazanavir and its metabolites include glucuronidation, N-dealkylation, hydrolysis, and oxygenation with dehydrogenation. Two minor metabolites in plasma have been characterized, neither of which demonstrated in vitro antiviral activity. Elimination half-life of healthy or HIV infected adults is approximately 7 hours following a 400 mg daily dose with a light meal. [16] Atazanavir is primarily eliminated in the feces (79%) and the urine (13%). Unchanged drug accounted for approximately 20% and 7% of the administered dose in the feces and urine, respectively. [17]

Atazanavir is highly selective for HIV-1 protease and exhibits cytotoxicity at concentrations 6,500- to 23,000-fold higher than concentrations required for therapeutic antiviral activity. [18] This selectivity index is comparable to or better than that of other PIs. [19]

Data to date indicate that atazanavir has a resistance profile distinct from that of other PIs. [20] Treatment-naive patients developed a characteristic I50L mutation and increased susceptibility to other PIs. In contrast, treatment-experienced patients did not develop the I50L mutation; rather, these patients developed mutations (I84V, L90M, A71V/T, N88S/D, and M46I) that reduced response to atazanavir and conferred high cross resistance to other protease inhibitors. [21]

## Adverse Events/Toxicity

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Adverse effects observed with clinical use of atazanavir include allergic reaction; new onset or exacerbation of existing diabetes mellitus or hyperglycemia; asymptomatic hyperbilirubinemia, including yellow eyes or skin; lactic acidosis; PR interval prolongation; abdominal pain; back pain; increased cough; depression; diarrhea; headache; jaundice; lipodystrophy; nausea; scleral icterus; or vomiting. Incidences of these adverse effects cannot be determined because of insufficient data. [22] However, headache, nausea, and skin rash were reported in clinical trials as the most common treatment-emergent adverse effects of moderate or severe intensity. [23]

Cases of lactic acidosis syndrome (LAS), sometimes fatal, and symptomatic hyperlactatemia have been reported in patients receiving atazanavir in combination with nucleoside analogues. Nucleoside analogues, female gender, and obesity are all known risk factors for LAS. The contribution of atazanavir to the development of LAS has not been established. [24]

Microscopic hematuria, defined as greater than five red blood cells per high-powered field, has also been observed in patients taking atazanavir. Uric acid crystals were observed in some urine samples. The relationship between these observations and atazanavir therapy is not known. [25]

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## Adverse Events/Toxicity (cont.)

In contrast to other PIs, neither cholesterol nor triglycerides increased significantly in patients whose study regimen contained atazanavir.[26]

## Drug and Food Interactions

Atazanavir should be administered with food.[27]

Coadministration of atazanavir with efavirenz decreases atazanavir AUC and minimum concentration (C<sub>min</sub>) approximately 70%. This decreased exposure is due to the CYP3A4 induction effects of efavirenz. Similar effects would presumably occur when atazanavir is administered concomitantly with nevirapine.[28] It is recommended that atazanavir be administered with ritonavir when atazanavir is to be coadministered with efavirenz as part of an HIV treatment regimen.[29] In an attempt to overcome the effects of CYP3A4 induction when coadministered with efavirenz, atazanavir has been paired with various doses of ritonavir. When ritonavir (100 mg once daily) was added to a 300 mg once daily dose of atazanavir, atazanavir C<sub>min</sub> was increased approximately 10-fold above that observed in the absence of ritonavir, while the AUC and C<sub>max</sub> were increased 3.3- and 1.8-fold, respectively. This ritonavir-augmented exposure appears likely to permit atazanavir and efavirenz coadministration.[30]

Coadministration of atazanavir and saquinavir (soft-gelatin capsules) with a high-fat meal resulted in a fourfold to sevenfold increase in saquinavir AUC.[31] Dosing for coadministration with respect to efficacy and safety has not been established.[32]

Coadministration of atazanavir and rifabutin resulted in a twofold increase in rifabutin AUC; a dosage reduction of rifabutin is recommended.[33] [34]

Coadministration of atazanavir and diltiazem resulted in a twofold increase in diltiazem AUC; a dosage reduction of diltiazem is recommended, along with electrocardiogram monitoring.[35] [36]

Coadministration of atazanavir and clarithromycin

resulted in a 1.9-fold increase in clarithromycin AUC and a 30% increase in atazanavir AUC.[37] Increased concentrations of clarithromycin may cause QTc prolongations. When atazanavir is concurrently administered with clarithromycin, concentrations of the active metabolite 14-OH clarithromycin are significantly reduced while concentrations of atazanavir are increased. Dose reduction of clarithromycin should be considered. Alternative therapy for indications other than *Mycobacterium avium* infections should be considered.[38]

Concurrent administration of atazanavir with amiodarone, lidocaine, or quinidine may increase antiarrhythmic drug concentrations, resulting in potentially serious or life-threatening adverse events. Caution and concentration monitoring is suggested.[39]

Tenofovir may decrease the AUC and C<sub>min</sub> of atazanavir if the two medications are taken concurrently.[40] Atazanavir AUC and C<sub>min</sub> were decreased by approximately 25% and 40%, respectively, when unboosted atazanavir was coadministered with tenofovir. When atazanavir boosted with ritonavir was coadministered with tenofovir, atazanavir AUC and C<sub>min</sub> were decreased by approximately 25% and 23%, respectively, as compared to boosted atazanavir without tenofovir.[41] When coadministered with tenofovir, it is recommended that 300 mg atazanavir be given with 100 mg ritonavir and 300 mg tenofovir, all as a single dose with food. Atazanavir should not be coadministered with tenofovir unless it is administered along with ritonavir. Atazanavir increases tenofovir concentrations by approximately 24%; the increase in tenofovir AUC did not appear to be associated with increased toxicity during a 24-week study.[42]

There were no clinically significant effects on the AUC of zidovudine, lamivudine, or stavudine when administered concomitantly with atazanavir, and no dosage adjustment was necessary.[43]

A pharmacokinetic study of nucleoside analogue interactions in healthy individuals showed that coadministration of atazanavir and didanosine reduces atazanavir exposure by fourfold as assessed by AUC. However, this reduction was believed to

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## **Drug and Food Interactions (cont.)**

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be mediated by the antacid in the buffered formulation of didanosine and was avoided by administering atazanavir one hour after buffered didanosine. This interaction is not expected to occur with the enteric-coated formulation of didanosine, which does not include an antacid buffering agent.[44] Numerous drug interaction studies have been undertaken as part of the clinical development plan for atazanavir. Further studies of interactions with nevirapine, oral contraceptives, and methadone have not yet been completed. The most substantial effects are observed with coadministered drugs that are substrates or inhibitors of CYP3A4. Further studies are needed of atazanavir coadministered with proton-pump inhibitors, H2 blockers, and statins.[45]

Caution should be used when prescribing PDE5 inhibitors for erectile dysfunction (e.g., sildenafil, tadalafil, or vardenafil) to patients receiving PIs, including atazanavir. Coadministration of a PI with a PDE5 inhibitor is expected to substantially increase the adverse events associated with PDE5 inhibitors, including hypotension, visual changes, and priapism.[46]

## **Contraindications**

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Atazanavir is contraindicated in patients with known hypersensitivity to atazanavir or any of its ingredients. Coadministration of atazanavir is contraindicated with drugs that are highly dependent on CYP3A for clearance, including benzodiazepines (midazolam, triazolam); ergot derivatives (dihydroergotamine, ergotamine, ergonovine, methylergonovine); gastrointestinal (GI) motility agents (cisapride); and neuroleptics (pimozide). Coadministration of atazanavir is also contraindicated with rifampin, irinotecan, bepridil, lovastatin, simvastatin, indinavir, proton-pump inhibitors, and St. John's wort.[47]

Because atazanavir has been shown to prolong the PR interval of the electrocardiogram, risk-benefit should be considered in patients with pre-existing atrioventricular (AV) conduction abnormalities. Risk-benefit should also be considered in patients with obesity, diabetes mellitus, or hyperglycemia; hepatic function impairment, elevated transaminase

levels, or hepatitis B or C infection; or type A or B hemophilia (atazanavir may induce increased bleeding, spontaneous skin hematomas, and hemarthrosis).[48]

## **Clinical Trials**

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For information on clinical trials that involve Atazanavir, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Atazanavir AND HIV Infections.

## **Dosing Information**

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Mode of Delivery: Oral.[49]

Dosage Form: Capsules containing 100, 150, or 200 mg of atazanavir.[50] [51]

For antiretroviral naive patients, the recommended dose of atazanavir is 400 mg (two 200-mg capsules) once daily. The recommended dose of atazanavir in antiretroviral-experienced patients is 300 mg (two 150-mg capsules) taken with ritonavir 100 mg once daily with food.[52] When coadministered with efavirenz, it is recommended that atazanavir 300 mg and ritonavir 100 mg be given with efavirenz 600 mg (all as a single daily dose). When coadministered with tenofovir, it is recommended that atazanavir 300 mg be given with ritonavir 100 mg and tenofovir 300 mg, all in a single daily dose with food. Dosing modification may be appropriate for coadministration of atazanavir and other antiretroviral agents; recommendations for dosing modification are included in the Reyataz prescribing information.[53]

A dose reduction to 300 mg once daily should be considered for patients with moderate hepatic insufficiency (Child-Pugh Class B). [54]

Storage: Store at 25 C (77 F); excursions permitted to 15 C to 30 C (59 F to 86 F).[55]

## **Chemistry**

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CAS Name: 2,5,6,10,13-Pentaazatetradecanedioic acid, 3,12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-((4-(2-

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## Chemistry (cont.)

pyridinyl)phenyl)methyl)-, dimethyl ester, (3S,8S,9S,12S)-, sulfate (1:1) (salt) (atazanavir sulfate)[56]

CAS Number: 229975-97-7 (atazanavir sulfate)[57]

Molecular formula: C38-H52-N6-O7.H2-O4-S (atazanavir sulfate)[58]

C56.8%, H6.8%, N10.5%, O21.9%, S4.0% (atazanavir sulfate)[59]

Molecular weight: 801.94 (atazanavir sulfate)[60]

Physical Description: White to pale yellow crystalline powder.[61]

Solubility: Slightly soluble in water (4 to 5 mg/ml, free base equivalent), with the pH of a saturated solution in water of about 1.9 at 24 +/- 3 C.[62]

## Other Names

CGP 73547[63]

BMS-232632-05 (atazanavir sulfate)[64]

BMS 232632 (atazanavir)[65]

ATZ[66]

ATV[67]

## Further Reading

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## Manufacturer Information

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## For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: [http://aidsinfo.nih.gov/live\\_help](http://aidsinfo.nih.gov/live_help) Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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