

Atazanavir Sulfate Capsules
ATAVIR

COMPOSITION
ATAVIR

Each capsule contains:
Atazanavir sulfate 300 mg

DOSAGE FORM
Oral capsule

PHARMACOLOGY
Pharmacodynamics

Mechanism of Action

Atazanavir (ATV) 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 the formation of mature virions.

Effects on Electrocardiogram

Concentration- and dose-dependent prolongation of the PR interval in the electrocardiogram (ECG) has been observed in healthy volunteers receiving atazanavir. In a placebo-controlled study (AI424-076), the mean (\pm SD) maximum change in the PR interval from the pre-dose value was 24 (\pm 15) msec following oral dosing with 400 mg of atazanavir (n = 65) compared to 13 (\pm 11) msec following dosing with placebo (n = 67). The PR interval prolongations in this study were asymptomatic. There is limited information on the potential for a pharmacodynamic interaction in humans between atazanavir and other drugs that prolong the PR interval of the ECG (see **WARNINGS AND PRECAUTIONS, Cardiac Conduction Abnormalities**).

The ECG effects of atazanavir were determined in a clinical pharmacology study of 72 healthy subjects. Oral doses of 400 mg and 800 mg were compared with placebo; there was no concentration-dependent effect of atazanavir on the QTc interval (using Fridericia's correction). In 1793 HIV-infected patients receiving antiretroviral regimens, QTc prolongation was comparable in the atazanavir and comparator regimens. No atazanavir-treated healthy subject or HIV-infected patient had a QTc interval >500 msec (see **WARNINGS AND PRECAUTIONS, Cardiac Conduction Abnormalities**).

In a pharmacokinetic study between atazanavir 400 mg once daily and diltiazem 180 mg once daily, a cytochrome (CY) P3A substrate, there was a 2-fold increase in the diltiazem plasma concentration and an additive effect on the PR interval. In a pharmacokinetic study between atazanavir 400 mg once daily and atenolol 50 mg once daily, there was no substantial additive effect of atazanavir and atenolol on the PR interval (see **WARNINGS AND PRECAUTIONS, Cardiac Conduction Abnormalities**).

Pharmacokinetics

The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected patients after administration of atazanavir 400 mg once daily, and after administration of atazanavir 300 mg with ritonavir 100 mg once daily (see Table 1).

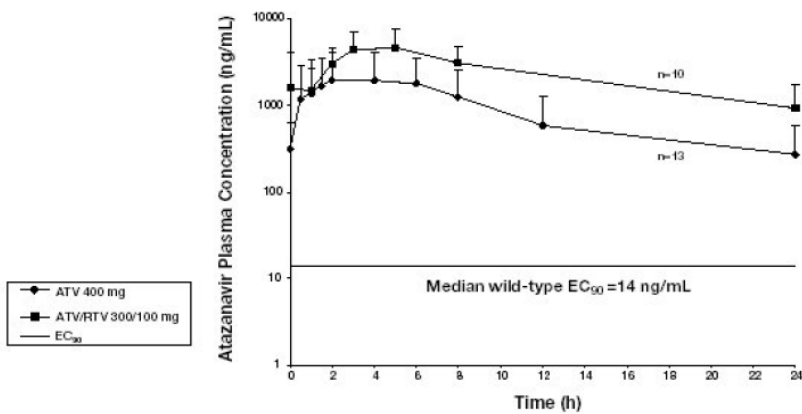
Table 1: Steady-state pharmacokinetics of atazanavir in healthy subjects or HIV-infected patients in the fed state

Parameter	400 mg once daily		300 mg with ritonavir 100 mg once daily	
	Healthy Subjects (n=14)	HIV-Infected Patients (n=13)	Healthy Subjects (n=28)	HIV-Infected Patients (n=10)
C_{max} (ng/mL)				
Geometric mean (CV%)	5199 (26)	2298 (71)	6129 (31)	4422 (58)
Mean (SD)	5358 (1371)	3152 (2231)	6450 (2031)	5233 (3033)
T_{max} (h)				
Median	2.5	2.0	2.7	3.0
AUC (ng•h/mL)				
Geometric mean (CV%)	28132 (28)	14874 (91)	57039 (37)	46073 (66)
Mean (SD)	29303 (8263)	22262 (20159)	61435 (22911)	53761 (35294)
T-half (h)				
Mean (SD)	7.9 (2.9)	6.5 (2.6)	18.1 (6.2) ^a	8.6 (2.3)
C_{min} (ng/mL)				
Geometric mean (CV%)	159 (88)	120 (109)	1227 (53)	636 (97)
Mean (SD)	218 (191)	273 (298) ^b	1441 (757)	862 (838)

^a n=26.
^b n=12.

Figure 1 displays the mean plasma concentrations of atazanavir at steady state after atazanavir 400 mg once daily (as two 200-mg capsules) with a light meal and after atazanavir 300 mg (as two 150-mg capsules) with ritonavir 100 mg once daily with a light meal in HIV-infected adult patients.

Figure 1: Mean (SD) Steady-State Plasma Concentrations of Atazanavir 400 mg (n=13) and 300 mg with Ritonavir (n=10) for HIV-Infected Adult Patients



Absorption

Atazanavir is rapidly absorbed with a T_{max} of approximately 2.5 hours. Atazanavir demonstrates non-linear pharmacokinetics with greater than dose-proportional increases in the AUC and C_{max} values over the dose range of 200 mg to 800 mg once daily. Steady-state is achieved between days 4 and 8, with an accumulation of approximately 2.3-fold.

Food Effect

Co-administration of a single 300 mg dose of atazanavir and a 100 mg dose of ritonavir with a light meal (336 kcal, 5.1 g fat, 9.3 g protein) resulted in a 33% increase in the AUC and a 40% increase in both the C_{max} and the 24-hour concentration of atazanavir relative to the fasting state.

Co-administration with a high-fat meal (951 kcal, 54.7 g fat, 35.9 g protein) did not affect the AUC of atazanavir relative to fasting conditions and the C_{max} was within 11% of fasting values. The 24-hour concentration following a high-fat meal was increased by approximately 33% due to delayed absorption; the median T_{max} increased from 2.0 hours to 5.0 hours. Co-administration of atazanavir with ritonavir with either a light or a high-fat meal decreased the coefficient of variation of the AUC and C_{max} by approximately 25% compared to the fasting state.

Distribution

Atazanavir is 86% bound to human serum proteins and 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). In a multiple-dose study in HIV-infected patients dosed with atazanavir 400 mg once daily along with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid and semen. The cerebrospinal fluid/plasma ratio for atazanavir (n = 4) ranged between 0.0021 and 0.0226 and seminal fluid/plasma ratio (n = 5) ranged between 0.11 and 4.42.

Metabolism

Atazanavir is extensively metabolized in humans. The major biotransformation pathways of atazanavir in humans consisted of mono-oxygenation and di-oxygenation. Other minor biotransformation pathways for atazanavir or its metabolites consisted of glucuronidation, N-dealkylation, hydrolysis, and oxygenation with dehydrogenation. Two minor metabolites of atazanavir in plasma have been characterized. Neither metabolite demonstrated *in vitro* antiviral activity. *In vitro* studies using human liver microsomes suggested that atazanavir is metabolized by CYP3A.

Elimination

Following a single 400 mg dose of ^{14}C -atazanavir, 79% and 13% of the total radioactivity was recovered in the feces and the urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the feces and the urine, respectively. The mean elimination half-life of atazanavir in healthy volunteers (n = 214) and HIV-infected adult patients (n = 13) was approximately 7 hours at steady state following a dose of 400 mg daily with a light meal.

INDICATIONS

ATAVIR Capsules are indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection.

The following points should be considered when initiating therapy with **ATAVIR**

Capsules:

- In Study AI424-045, atazanavir/ritonavir and lopinavir/ritonavir were similar for the primary efficacy outcome measure of time-averaged difference in change from baseline in the HIV RNA level. This study was not large enough to reach a definitive conclusion that atazanavir/ritonavir and lopinavir/ritonavir are equivalent on the secondary efficacy outcome measure of proportions below the HIV RNA lower limit of detection.
- The number of baseline primary protease inhibitor mutations affects the virologic response to atazanavir/ritonavir.

DOSAGE AND ADMINISTRATION

General Dosing Recommendations

- **ATAVIR Capsules** must be taken with food.
- The recommended oral dosage of **ATAVIR Capsules** depends on the treatment history of the patient and the use of other co-administered drugs. When co-administered with H₂-receptor antagonists, or proton-pump inhibitors, dose separation may be required (see dose recommendations below).
- When co-administered with didanosine buffered or enteric-coated formulations, **ATAVIR Capsules** should be given (with food) 2 hours before or 1 hour after didanosine.
- **ATAVIR Capsules** without ritonavir are not recommended for treatment-experienced patients with prior virologic failure.
- Efficacy and safety of atazanavir with ritonavir in doses greater than 100 mg once daily have not been established. The use of higher ritonavir doses might alter the safety profile of atazanavir (cardiac effects, hyperbilirubinemia) and, therefore, is not recommended. Prescribers should consult the complete prescribing information for ritonavir when using this agent.

Dose Recommendations for Therapy-Naive Adult Patients

For treatment-naive patients, the recommended dosage is **ATAVIR Capsules** 300 mg with ritonavir 100 mg once daily (all as a single dose with food).

OR

For treatment-naive patients who are unable to tolerate ritonavir, the recommended dosage is atazanavir 400 mg (without ritonavir) once daily taken with food.

Concomitant Therapy

ATAVIR Capsules 300 mg should be administered with ritonavir 100 mg once daily (all as a single dose with food) if combined with any of the following:

- Tenofovir
- H₂-Receptor Antagonist: The H₂-receptor antagonist dose should not exceed a dose comparable to famotidine 40 mg twice daily. **ATAVIR Capsules** 300 mg and ritonavir 100 mg should be administered simultaneously with, and/or at least 10 hours after, the dose of the H₂-receptor antagonist. For patients unable to tolerate ritonavir, atazanavir 400 mg once daily with food should be administered at least 2

hours before and at least 10 hours after the H₂ receptor antagonist. For these patients, no single dose of the H₂-receptor antagonist should exceed a dose comparable to famotidine 20 mg, and the total daily dose should not exceed a dose comparable to famotidine 40 mg.

- Proton-Pump Inhibitors: The proton-pump inhibitor dose should not exceed a dose comparable to omeprazole 20 mg and must be taken approximately 12 hours prior to the **ATAVIR Capsules** 300 mg and ritonavir 100 mg dose.
- If atazanavir is combined with efavirenz, atazanavir 400 mg (two 200 mg capsules) with ritonavir 100 mg should be administered once daily (all as a single dose with food), and efavirenz should be administered on an empty stomach, preferably at bedtime.

Dose Recommendations for Therapy-Experienced Adult Patients

ATAVIR Capsules 300 mg with ritonavir 100 mg once daily (all as a single dose with food).

Concomitant Therapy

- Whenever an H₂-receptor antagonist is given to a patient receiving atazanavir with ritonavir, the H₂-receptor antagonist dose should not exceed a dose comparable to famotidine 20 mg twice daily, and the atazanavir and ritonavir doses should be administered simultaneously with, and/or at least 10 hours after, the dose of the H₂-receptor antagonist.
 - **ATAVIR Capsules** 300 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with an H₂-receptor antagonist.
 - Atazanavir 400 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with both tenofovir and an H₂-receptor antagonist.
- Proton-pump inhibitors should not be used in treatment-experienced patients receiving atazanavir.
- Efavirenz: Do not co-administer **ATAVIR Capsules** with efavirenz in treatment-experienced patients due to decreased atazanavir exposure.

[For these drugs and other antiretroviral agents for which dosing modification may be appropriate, see **Drug Interactions**].

Patients with Renal Impairment

For patients with renal impairment, including those with severe renal impairment who are not managed with hemodialysis, no dose adjustment is required for **ATAVIR Capsules**. Treatment-naïve patients with end-stage renal disease managed with hemodialysis should receive **ATAVIR Capsules** 300 mg with ritonavir 100 mg. **ATAVIR Capsules should not be administered to HIV-treatment-experienced patients with end-stage renal disease managed with hemodialysis** (see *Use in Specific Populations, Renal Impairment*).

Patients with Hepatic Impairment

ATAVIR Capsules should be used with caution in patients with mild to moderate hepatic impairment. For patients with moderate hepatic impairment (Child-Pugh Class B) who have not experienced prior virologic failure, a dose reduction to 300 mg once daily should be considered. **ATAVIR Capsules** should not be used in patients with severe hepatic impairment (Child-Pugh Class C). Atazanavir/ritonavir have not been

studied in subjects with hepatic impairment and are not recommended (see **WARNINGS AND PRECAUTIONS**).

CONTRAINDICATIONS

ATAVIR Capsules are contraindicated in the following cases:

- in patients with previously demonstrated clinically significant hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of its ingredients, including atazanavir.
- When co-administered with drugs that are highly dependent on CYP3A or UGT1A1 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 2.

Table 2: Drugs that are contraindicated with ATAVIR Capsules

Drug Class	Drugs Within Class That Are Contraindicated with Atazanavir	Clinical Comment
Alpha 1 adrenoreceptor antagonist	Alfuzosin	Potential for increased alfuzosin concentrations, which can result in hypotension.
Antimycobacterials	Rifampin	Rifampin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect and development of resistance.
Antineoplastics	Irinotecan	Atazanavir inhibits UGT1A1 and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.

Benzodiazepines	Triazolam, orally administered midazolam ^a	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Co-administration of triazolam or orally administered midazolam with ATAVIR Capsules may cause large increases in the concentration of these benzodiazepines. Potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
Ergot Derivatives	Dihydroergotamine, ergotamine, ergonovine, methylergonovine	Potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Gastrointestinal Motility Agent	Cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products	St. John's wort (<i>Hypericum perforatum</i>)	Patients taking ATAVIR Capsules should not use products containing St. John's wort because co-administration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for serious reactions such as myopathy, including

		rhabdomyolysis.
Neuroleptic	Pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
PDE5 inhibitor	Sildenafil ^b when dosed for the treatment of pulmonary arterial hypertension	A safe and effective dose in combination with atazanavir has not been established for sildenafil when used for the treatment of pulmonary hypertension. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, priapism, and syncope)
Protease Inhibitors	Indinavir	Both atazanavir and indinavir are associated with indirect (unconjugated) hyperbilirubinemia.

^a See Drug Interactions, Table 3, for parenterally administered midazolam.

^b See Drug Interactions, Table 3 for sildenafil when dosed for erectile dysfunction.

WARNINGS AND PRECAUTIONS

Cardiac Conduction Abnormalities

Atazanavir has been shown to prolong the PR interval of the ECG in some patients. In healthy volunteers and in patients, abnormalities in atrioventricular (AV) conduction were asymptomatic and generally limited to first-degree AV block. There have been rare reports of second-degree AV block and other conduction abnormalities (see **OVERDOSAGE** and **UNDESIRABLE EFFECTS**). In clinical trials that included ECGs, asymptomatic first-degree AV block was observed in 5.9% of atazanavir-treated patients (n = 920), 5.2% of lopinavir/ritonavir-treated patients (n = 252), 10.4% of nelfinavir-treated patients (n = 48), and 3.0% of efavirenz-treated patients (n = 329). In Study AI424-045, asymptomatic first-degree AV block was observed in 5% (6/118) of atazanavir/ritonavir-treated patients and 5% (6/116) of lopinavir/ritonavir-treated patients who had on-study ECG measurements. Because of limited clinical experience in patients with pre-existing conduction system disease (eg, marked first-degree AV block or second- or third-degree AV block), **ATAVIR Capsules** should be used with caution in these patients (see **PHARMACOLOGY, Pharmacodynamics, Effects on Electrocardiogram**).

Atazanavir in combination with diltiazem increased diltiazem plasma concentration by 2-fold, with an additive effect on the PR interval. When used in combination with atazanavir, a dose reduction of diltiazem by one half should be considered and ECG monitoring is recommended. In a pharmacokinetic study between atazanavir 400 mg once daily and atenolol 50 mg once daily, no clinically significant additive effect of atazanavir and atenolol on the PR interval was observed. Dose adjustment of atenolol is not required when used in combination with atazanavir (see **WARNINGS AND PRECAUTIONS, Drug Interactions**). Pharmacokinetic studies between atazanavir and other drugs that prolong the PR interval, including beta-blockers (other than atenolol; see **WARNINGS AND PRECAUTIONS, Drug Interactions**), verapamil and digoxin, have not been performed. An additive effect of atazanavir and these drugs cannot be excluded; therefore, caution should be exercised when atazanavir is given concurrently with these drugs, especially those that are metabolized by CYP3A (eg, verapamil).

Rash

In controlled clinical trials, rash (all grades, regardless of causality) occurred in approximately 20% of patients treated with atazanavir. The median time to onset of rash was 7.1 weeks after initiation of atazanavir and the median duration of rash was 1.3 weeks. Rashes were generally mild to moderate maculopapular skin eruptions. Treatment-emergent adverse reactions of moderate or severe rash (occurring at a rate of $\geq 2\%$) are presented for the individual clinical studies (see **UNDESIRABLE EFFECTS**). Dosing with atazanavir was often continued without interruption in patients who developed rash. The discontinuation rate for rash in clinical trials was $< 1\%$. Atazanavir should be discontinued if severe rash develops. Cases of Stevens-Johnson syndrome and erythema multiforme have been reported in patients receiving atazanavir (see **CONTRAINDICATIONS**).

Hyperbilirubinemia

Most patients taking atazanavir experience asymptomatic elevations in indirect (unconjugated) bilirubin related to the inhibition of UDP-glucuronosyl transferase (UGT). This hyperbilirubinemia is reversible upon the discontinuation of atazanavir. Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies. No long-term safety data are available for patients experiencing persistent elevations in total bilirubin > 5 times the upper limit of normal (ULN). Alternative antiretroviral therapy to atazanavir may be considered if jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for patients. Dose reduction of atazanavir is not recommended since long-term efficacy of reduced doses has not been established (see **UNDESIRABLE EFFECTS, Laboratory Abnormalities**).

Hepatotoxicity

Caution should be exercised when administering **ATAVIR Capsules** to patients with hepatic impairment because atazanavir concentrations may be increased (see **DOSAGE AND ADMINISTRATION**). Patients with underlying hepatitis B or C viral infections or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation.

In these patients, appropriate laboratory testing should be conducted prior to initiating therapy with **ATAVIR Capsules** and these patients should be monitored during treatment (see **UNDESIRABLE EFFECTS**).

Nephrolithiasis

Cases of nephrolithiasis were reported during postmarketing surveillance in HIV-infected patients receiving atazanavir therapy. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made. If signs or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of therapy may be considered (see **UNDESIRABLE EFFECTS**).

Diabetes Mellitus/Hyperglycemia

New-onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established (see **UNDESIRABLE EFFECTS**).

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including atazanavir. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

Fat Redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

Resistance/Cross-Resistance

Various degrees of cross-resistance among protease inhibitors have been observed. Resistance to atazanavir may not preclude the subsequent use of other protease inhibitors.

Drug Interactions

Potential for atazanavir to affect Other Drugs

Atazanavir is an inhibitor of CYP3A and UGT1A1. Coadministration of **ATAVIR capsules** and drugs primarily metabolized by CYP3A or UGT1A1 may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects.

Atazanavir is a weak inhibitor of CYP2C8. Caution should be used when atazanavir capsules without ritonavir is coadministered with drugs highly dependent on CYP2C8 with narrow therapeutic indices (eg, paclitaxel, repaglinide). When atazanavir with ritonavir is coadministered with substrates of CYP2C8, clinically significant interactions are not expected. The magnitude of CYP3A-mediated drug interactions on coadministered drug may change when atazanavir is co-administered with ritonavir. See the complete prescribing information for ritonavir for information on drug interactions with ritonavir.

Potential for Other Drugs to Affect Atazanavir

Atazanavir is a CYP3A4 substrate; therefore, drugs that induce CYP3A4 may decrease atazanavir plasma concentrations and reduce atazanavir's therapeutic effect.

Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir are expected if proton-pump inhibitors, antacids, buffered medications, or H₂-receptor antagonists are administered with atazanavir.

Established and Other Potentially Significant Drug Interactions

Table 3 provides dosing recommendations as a result of drug interactions with atazanavir. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 3: Established and other potentially significant drug interactions: Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interactions (information in the table applies to atazanavir with or without ritonavir, unless otherwise indicated)

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir or Concomitant Drug	Clinical Comment
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HIV Antiviral Agents		
<p>Nucleoside Reverse Transcriptase Inhibitors (NRTIs) Didanosine buffered formulations Enteric-coated (EC) capsules</p>	<p>↓ atazanavir ↓ didanosine</p>	<p>Co-administration of atazanavir with didanosine buffered tablets resulted in a marked decrease in atazanavir exposure. It is recommended that atazanavir be given (with food) 2 hours before or 1 hour after didanosine buffered formulations.</p> <p>Simultaneous administration of didanosine EC and atazanavir with food results in a decrease in didanosine exposure. Thus, ATAVIR Capsules and didanosine EC should be administered at different times.</p>
<p>Nucleotide Reverse Transcriptase Inhibitors Tenofovir disoproxil fumarate</p>	<p>↓ atazanavir ↑ tenofovir</p>	<p>Tenofovir may decrease the AUC and C_{min} of atazanavir. When co-administered with tenofovir, it is recommended that ATAVIR Capsules 300 mg be given with ritonavir 100 mg and tenofovir 300 mg (all as a single daily dose with food).</p> <p>ATAVIR Capsules without ritonavir should not be co-administered with tenofovir. Atazanavir increases tenofovir concentrations. The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving atazanavir and tenofovir should be monitored for tenofovir-associated adverse events.</p>

<p>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) Efavirenz</p>	<p>↓ atazanavir</p>	<p>Efavirenz decreases atazanavir exposure.</p> <p>In treatment-naive patients If ATAVIR Capsules are combined with efavirenz, atazanavir 400 mg with ritonavir 100 mg should be administered once daily all as a single dose with food, and efavirenz 600 mg should be administered once daily on an empty stomach, preferably at bedtime.</p> <p>In treatment-experienced patients Do not co-administer ATAVIR Capsules with efavirenz in treatment-experienced patients due to decreased atazanavir exposure.</p>
<p>NNRTIs Nevirapine</p>	<p>↓ atazanavir ↑ nevirapine</p>	<p>Do not co-administer ATAVIR Capsules with nevirapine because of the following:</p> <ul style="list-style-type: none"> • Nevirapine substantially decreases atazanavir exposure. • Potential risk for nevirapine-associated toxicity due to increased nevirapine exposures.
<p>Protease Inhibitors Saquinavir (soft gelatin capsules)</p>	<p>↑ saquinavir</p>	<p>Appropriate dosing recommendations for this combination, with or without ritonavir, with respect to efficacy and safety have not been established. In a clinical study, saquinavir 1200 mg co-administered with atazanavir 400 mg and tenofovir 300 mg (all given once daily) plus nucleoside analog reverse transcriptase inhibitors did not provide adequate efficacy.</p>
<p>Protease Inhibitors Ritonavir</p>	<p>↑ atazanavir</p>	<p>If ATAVIR Capsules are co-administered with ritonavir, it is recommended that ATAVIR Capsules 300 mg once daily be given with ritonavir 100 mg once daily with food. See the complete prescribing information for ritonavir for information on drug interactions with ritonavir.</p>

Protease Inhibitors Others	↑ other protease inhibitor	Atazanavir/ritonavir: Although not studied, the co-administration of atazanavir/ritonavir and other protease inhibitors would be expected to increase exposure to the other protease inhibitor. Such co-administration is not recommended.
Other Agents		
Antacids and Buffered Medications	↓ atazanavir	Reduced plasma concentrations of atazanavir are expected if antacids, including buffered medications, are administered with atazanavir. Atazanavir should be administered 2 hours before or 1 hour after these medications.
Anti-Arrhythmics Amiodarone, bepridil, lidocaine (systemic), quinidine	↑ amiodarone, bepridil, lidocaine (systemic), quinidine	Co-administration with atazanavir has the potential to produce serious and/or life-threatening adverse events and has not been studied. Caution is warranted and therapeutic concentration monitoring of these drugs is recommended if they are used concomitantly with ATAVIR Capsules .
Anticoagulants Warfarin	↑ warfarin	Co-administration with atazanavir has the potential to produce serious and/or life-threatening bleeding and has not been studied. It is recommended that the International Normalized Ratio (INR) be monitored.
Antidepressants Tricyclic antidepressants	↑ tricyclic antidepressants	Co-administration with atazanavir has the potential to produce serious and/or life-threatening adverse events and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with ATAVIR Capsules .
Trazodone	↑ trazodone	Concomitant use of trazodone and ATAVIR Capsules with or without ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as atazanavir, the combination should be used with caution and a lower dose of trazodone should be considered.

<p>Antifungals Ketoconazole, itraconazole</p>	<p>Atazanavir/ritonavir ↑ ketoconazole ↑ itraconazole</p>	<p>Co-administration of ketoconazole has only been studied with atazanavir without ritonavir (negligible increase in atazanavir AUC and C_{max}). Due to the effect of ritonavir on ketoconazole, high doses of ketoconazole and itraconazole (>200 mg/day) should be used cautiously with atazanavir/ritonavir.</p>
<p>Antifungals Voriconazole</p>	<p>Effect is unknown</p>	<p>Co-administration of voriconazole with atazanavir, with or without ritonavir, has not been studied. Administration of voriconazole with ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%. Voriconazole should not be administered to patients receiving ATAVIR Capsules/ritonavir, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Co-administration of voriconazole with ATAVIR Capsules (without ritonavir) may increase atazanavir concentrations; however, no data are available.</p>
<p>Antigout: colchicine</p>	<p>↑ colchicine</p>	<p>ATAVIR Capsules should not be coadministered with colchicine to patients with renal or hepatic impairment.</p> <p>Recommended dosage of colchicine when administered with ATAVIR Capsules:</p> <p>Treatment of gout flares: 0.6 mg (1 tablet) for 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Not to be repeated before 3 days.</p> <p>Prophylaxis of gout flares: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day.</p> <p>If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day.</p>

		<p>Treatment of familial Mediterranean fever (FMF): Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).</p>
<p>Antimycobacterials Rifabutin</p>	<p>↑ rifabutin</p>	<p>A rifabutin dose reduction of up to 75% (eg, 150 mg every other day or three times per week) is recommended.</p>
<p>Benzodiazepines Parenterally administered midazolam^b</p>	<p>↑ midazolam</p>	<p>Concomitant use of parenteral midazolam with ATAVIR Capsules may increase plasma concentrations of midazolam. Co-administration should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Co-administration of oral midazolam with ATAVIR Capsule is CONTRAINDICATED.</p>
<p>Calcium Channel Blockers Diltiazem</p> <p>Eg, felodipine, nifedipine, nicardipine, and verapamil</p>	<p>↑ diltiazem and desacetyl-diltiazem</p>	<p>Caution is warranted. A dose reduction of diltiazem by 50% should be considered. ECG monitoring is recommended. Co-administration of atazanavir/ritonavir with diltiazem has not been studied.</p>
	<p>↑ calcium channel blockers</p>	<p>Caution is warranted. Dose titration of the calcium channel blocker should be considered. ECG monitoring is recommended.</p>
<p>Endothelin receptor antagonists: bosentan</p>	<p>↓ atazanavir ↑ bosentan</p>	<p>Plasma concentrations of atazanavir may be decreased when bosentan is administered with ATAVIR Capsules without ritonavir. Co-administration of bosentan and ATAVIR without ritonavir is not recommended.</p> <p>Coadministration of bosentan in patients on Atazanavir/ritonavir: For patients who have been receiving Atazanavir /ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based on individual tolerability.</p>

		<p>Coadministration of Atazanavir/ritonavir in patients on bosentan:</p> <p>Discontinue bosentan at least 36 hours before starting Atazanavir/ritonavir. At least 10 days after starting Atazanavir/ritonavir, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.</p>
<p>HMG-CoA Reductase Inhibitors Atorvastatin, rosuvastatin</p>	<p>↑ atorvastatin ↑ rosuvastatin</p>	<p>Use the lowest possible dose of atorvastatin and rosuvastatin with careful monitoring, or other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with ATAVIR Capsules (with or without ritonavir)</p> <p>The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including ATAVIR Capsules, are used in combination with these drugs.</p>
<p>H₂-Receptor Antagonists</p>	<p>↓ atazanavir</p>	<p>Plasma concentrations of atazanavir were substantially decreased when atazanavir 400 mg once daily was administered simultaneously with famotidine 40 mg twice daily, which may result in loss of therapeutic effect and development of resistance.</p>

In treatment-naive patients

ATAVIR Capsules 300 mg with ritonavir 100 mg once daily with food should be administered simultaneously with, or at least 2 hours before and at least 10 hours after the dose of the H₂-receptor antagonist. An H₂-receptor antagonist dose comparable to famotidine 20 mg once daily and up to a dose comparable to famotidine 40 mg twice daily can be used with **ATAVIR Capsules** 300 mg along with ritonavir 100 mg in treatment-naive patients.

OR

For patients unable to tolerate ritonavir, atazanavir 400 mg once daily with food should be administered at least 2 hours before and at least 10 hours after a dose of the H₂-receptor antagonist. No single dose of the H₂-receptor antagonist should exceed a dose comparable to famotidine 20 mg, and the total daily dose should not exceed a dose comparable to famotidine 40 mg.

In treatment-experienced patients

Whenever an H₂-receptor antagonist is given to a patient receiving **ATAVIR Capsules** with ritonavir, the H₂-receptor antagonist dose should not exceed a dose comparable to famotidine 20 mg twice daily, and the **ATAVIR Capsules** and ritonavir doses should be administered simultaneously with, and/or at least 10 hours after, the dose of the H₂-receptor antagonist.

- **ATAVIR Capsules** 300 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with an H₂-receptor antagonist.
- Atazanavir 400 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with both tenofovir and an H₂-receptor antagonist.

<p>Immunosuppressants Cyclosporine, sirolimus, tacrolimus</p>	<p>↑ immunosuppressants</p>	<p>Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with atazanavir.</p>
<p>Inhaled beta agonist: salmeterol</p>	<p>↑ salmeterol</p>	<p>Coadministration of salmeterol with atazanavir is not recommended. Concomitant use of salmeterol and atazanavir may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.</p>
<p>Inhaled/Nasal Steroid Fluticasone</p>	<p>Atazanavir ↑ fluticasone</p>	<p>Concomitant use of fluticasone propionate and atazanavir (without ritonavir) may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use.</p>
	<p>Atazanavir/ritonavir ↑ fluticasone</p>	<p>Concomitant use of fluticasone propionate and atazanavir/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression, have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Co-administration of fluticasone propionate and ATAVIR Capsule/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see WARNINGS AND PRECAUTIONS).</p>

<p>Macrolide Antibiotics Clarithromycin</p>	<p>↑ clarithromycin ↓ 14-OH clarithromycin ↑ atazanavir</p>	<p>Increased concentrations of clarithromycin may cause QTc prolongations; therefore, a dose reduction of clarithromycin by 50% should be considered when it is co-administered with atazanavir. In addition, concentrations of the active metabolite 14-OH clarithromycin are significantly reduced; consider alternative therapy for indications other than infections due to Mycobacterium avium complex. Co-administration of atazanavir/ritonavir with clarithromycin has not been studied.</p>
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<p>Opioids: Buprenorphine</p>	<p>↑ buprenorphine ↑ norbuprenorphine</p>	<p>Coadministration of buprenorphine and atazanavir with or without ritonavir increases the plasma concentration of buprenorphine and norbuprenorphine. Coadministration of atazanavir plus ritonavir with buprenorphine warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered. Coadministration of buprenorphine and atazanavir with ritonavir is not expected to decrease atazanavir plasma concentrations. Coadministration of buprenorphine and atazanavir without ritonavir may decrease atazanavir plasma concentrations. ATAVIR Capsules without ritonavir should not be coadministered with buprenorphine.</p>
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<p>PDE5 Inhibitors Sildenafil, tadalafil, vardenafil</p>	<p>↑ sildenafil ↑ tadalafil ↑ vardenafil</p>	<p>Coadministration with Atazanavir has not been studied but may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances, and priapism.</p> <p>Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH): Use of sildenafil for the treatment of pulmonary Hypertension (PAH) is contraindicated with ATAVIR Capsules [see CONTRAINDICATIONS].</p> <p>The following dose adjustments are recommended for the use of Tadalafil with ATAVIR Capsules: Coadministration of in patients on atazanavir (with or without ritonavir):</p> <ul style="list-style-type: none"> • For patients receiving atazanavir (with or without ritonavir) for at least one week, start at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability. <p>Coadministration of atazanavir (with or without ritonavir) in patients on: Avoid the use of when starting atazanavir (with or without ritonavir). Stop at least 24 hours before starting atazanavir (with or without ritonavir). At least one week after starting atazanavir (with or without ritonavir), resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability.</p> <p>Use of PDE5 inhibitors for erectile dysfunction: Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Use tadalafil with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events.</p>
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		<p>Atazanavir/ritonavir: Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events.</p> <p>Atazanavir: Use vardenafil with caution at reduced doses of no more than 2.5 mg every 24 hours with increased monitoring for adverse events.</p>
<p>Proton-Pump Inhibitors Omeprazole</p>	<p>↓ atazanavir</p>	<p>Plasma concentrations of atazanavir were substantially decreased when atazanavir 150 mg/300 mg/200 mg once daily was administered with omeprazole 40 mg once daily, which may result in loss of therapeutic effect and development of resistance.</p> <p>In treatment-naive patients The proton-pump inhibitor dose should not exceed at 20 mg dose equivalent to omeprazole and must be taken approximately 12 hours prior to the ATAVIR Capsules 300 mg with ritonavir 100 mg dose.</p> <p>In treatment-experienced patients In treatment-experienced patients proton-pump inhibitors should not be used in treatment-experienced patients receiving ATAVIR Capsules.</p>

^a See **CONTRAINDICATIONS, Table 2**, for orally administered midazolam

^b In combination with atazanavir 300 mg and ritonavir 100 mg once daily

^c In combination with atazanavir 400 mg once daily

Drugs with No Observed or Predicted Interactions with Atazanavir Clinically significant interactions are not expected between atazanavir and substrates of CYP2C19, CYP2C9, CYP2D6, CYP2B6, CYP2A6, CYP1A2, or CYP2E1. Clinically significant interactions are not expected between atazanavir when administered with ritonavir and substrates of CYP2C8. See the complete prescribing information for ritonavir for information on other potential drug interactions with ritonavir. Based on known metabolic profiles, clinically significant drug interactions are not expected between atazanavir and fluvastatin, pravastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, or erythromycin. Atazanavir does not interact with substrates of CYP2D6 (eg, nortriptyline, desipramine, metoprolol).

Additionally, no clinically significant drug interaction was observed when atazanavir was co-administered with methadone, fluconazole, acetaminophen, or atenolol.

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Cases of lactic acidosis syndrome, sometimes fatal, and symptomatic hyperlactatemia have occurred in pregnant women using atazanavir in combination with nucleoside analogs. In animal reproduction and prenatal and postnatal development studies, there was no evidence of adverse fetal effects or teratogenicity. Because animal reproduction studies are not always predictive of human response, **ATAVIR Capsules** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Cases of lactic acidosis syndrome, sometimes fatal, and symptomatic hyperlactatemia have been reported in patients (including pregnant women) receiving atazanavir in combination with nucleoside analogs. Nucleoside analogs are associated with an increased risk of lactic acidosis syndrome. In addition, hyperbilirubinemia occurred frequently with atazanavir. It is not known whether atazanavir administered during pregnancy will exacerbate physiological hyperbilirubinemia or increase the risk of kernicterus in neonates and young infants. In the prepartum period, additional monitoring and alternative therapy should be considered.

Lactation

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. It is not known whether atazanavir is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving ATAVIR Capsules.**

UNDESIRABLE EFFECTS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- cardiac conduction abnormalities [see **WARNINGS AND PRECAUTIONS**]
- rash [see **WARNINGS AND PRECAUTIONS**]
- hyperbilirubinemia [see **WARNINGS AND PRECAUTIONS**]
- nephrolithiasis [see **WARNINGS AND PRECAUTIONS**]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Treatment-Emergent Adverse Events in Treatment-Naive Adult Patients

The safety profile of atazanavir in treatment-naive adults is based on 1625 HIV-1-infected patients in clinical trials, wherein 536 patients received atazanavir 300 mg with ritonavir 100 mg and 1089 patients received atazanavir 400 mg or higher (without ritonavir). The most common adverse reactions were nausea, jaundice/scleral icterus, and rash.

Selected drug-related clinical adverse events of moderate or severe intensity reported in $\geq 2\%$ of treatment-naive patients receiving combination therapy, including atazanavir 300 mg and ritonavir 100 mg are presented in Table 4.

Table 4: Selected treatment-emergent adverse events^a of moderate or severe intensity reported in $\geq 2\%$ of adult treatment-naive patients^b

	96 Weeks^c Atazanavir 300 mg with Ritonavir 100 mg (Once Daily) and Tenofovir with Emtricitabine^d (n = 441)	96 Weeks^c Lopinavir 400 mg with Ritonavir 100 mg (Twice Daily) and Tenofovir with Emtricitabine^d (n = 437)
Digestive System		
Nausea	4%	8%
Jaundice/scleral icterus	5%	*
Diarrhea	2%	12 %
Skin and Appendages		
Rash	3%	2%

* None reported in this treatment arm.

^a Includes events of possible, probable, certain, or unknown relationship to treatment regimen.

^b Based on regimens containing atazanavir.

^c Median time on therapy.

^d As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

Table 5: Selected Treatment-Emergent Adverse Reactions^a of Moderate or Severe intensity Reported in $\geq 2\%$ of Adult Treatment-Naive Patients, Studies AI424-034, AI424-007, and AI424-008^b

	Study AI424-034		Studies AI424-007, -008	
	64 weeks^c Atazanavir 400 mg once daily	64 weeks^c efavirenz 600 mg once daily +	120 weeks^{c,d} Atazanavir 400 mg once daily +	73 weeks^{c,d} nelfinavir 750 mg TID or 1250

	+lamivudine + zidovudine^e (n=404)	lamivudine + zidovudine^e (n=401)	stavudine + lamivudine or didanosine (n=279)	mg BID + stavudine + lamivudine or (n=191)
Body as a Whole				
Headache	6%	6%	1%	2%
Digestive System				
Nausea	14%	12%	6%	4%
Jaundice/scleral icterus	7%	*	7%	*
Vomiting	4%	7%	3%	
Abdominal pain	4%	4%	4%	2%
Diarrhea	1%	2%	3%	16%
Nervous System				
Insomnia	3%	3%	<1%	*
Dizziness	2%	7%	<1%	*
Peripheral neurologic symptoms	<1%	1%	4%	3%
Skin and Appendages				
Rash	7%	10%	5%	1%

* None reported in this treatment arm.

^a Includes events of possible, probable, certain, or unknown relationship to treatment regimen.

^b Based on regimens containing atazanavir.

^c Median time on therapy.

^d Includes long-term follow-up.

^e As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

Treatment-Emergent Adverse Events in Treatment-Experienced Adult Patients

The safety profile of atazanavir in treatment-experienced adults is based on 119 HIV-1-infected patients in clinical trials.

The most common adverse reactions are jaundice/scleral icterus and myalgia.

Selected drug-related clinical adverse events of moderate-severe intensity in $\geq 2\%$ of treatment-experienced patients receiving atazanavir/ritonavir are presented in Table 6.

Table 6: Selected treatment-emergent adverse events^a of moderate or severe intensity reported in ≥2% of adult treatment-experienced patients^b (Study AI424-045)

	48 Weeks^c Atazanavir/Ritonavir 300/100 mg Once Daily + Tenofovir + NRTI (n = 119)	48 Weeks^c Lopinavir/Ritonavir 400/100 mg Twice Daily^d + Tenofovir + NRTI (n = 118)
Body as a Whole		
Fever	2%	*
Digestive System		
Jaundice/scleral icterus	9%	*
Diarrhea	3%	11%
Nausea	3%	2%
Nervous System		
Depression	2%	<1%
Musculoskeletal System		
Myalgia	4%	*

* None reported in this treatment arm.

^a Includes events of possible, probable, certain, or unknown relationship to treatment regimen.

^b Based on the regimen containing atazanavir.

^c Median time on therapy.

^d As a fixed-dose combination.

Laboratory Abnormalities in Treatment-Naive Adult Patients

The percentages of adult treatment-naive patients treated with combination therapy, including atazanavir sulfate 300 mg with ritonavir 100 mg with Grade 3–4 laboratory abnormalities are presented in Table 7.

Table 7: Grade 3–4 laboratory abnormalities reported in ≥2% of adult treatment-naive patients^a (Study AI424-138)

Variable	Limit^c	96 Weeks^b Atazanavir 300 mg with Ritonavir 100 mg (Once Daily) and Tenofovir with Emtricitabine^d (n = 441)	96 Weeks^b Lopinavir 400 mg with Ritonavir 100 mg (Twice Daily) and Tenofovir with Emtricitabine^d (n = 437)
Chemistry	<u>High</u>		
SGOT/AST	≥5.1 x ULN	3%	1%

SGPT/ALT	≥5.1 x ULN	3%	2%
Total Bilirubin	≥2.6 x ULN	44%	<1%
Lipase	≥2.1 x ULN	2%	2%
Creatine Kinase	≥5.1 x ULN	8%	7%
Total Cholesterol	≥240 mg/dL	11%	25%
Hematology	<u>Low</u>		
Neutrophils	<750 cells/mm ³	5%	2%

^a Based on the regimen containing atazanavir.

^b Median time on therapy.

^c ULN = Upper limit of normal.

^d As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily

Table 8: Grade 3–4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Naive Patients,^a Studies AI424-034, AI424-007, and AI424-008

Variable	Limit ^d	Study AI424-034		Studies AI424-007-008	
		64 weeks ^b atazanavir 400 mg once daily+ lamivudine +zidovudine ^e (n= 404)	64 weeks ^b Efavirenz 600 mg once daily +lamivudine +zidovudine ^e (n=401)	120 weeks ^{b,c} atazanavir 400mg once daily+stavudin e +lamivuidne or +stavudine+ didanosine (n=279)	73 weeks ^{b,c} nelfinavir 750 mg TID or 1250 mg BID + stavudine +lamivudin e or +stavudine +didanosin e (n=191)
Chemistry	High				
SGOT/AST	≥5.1 x ULN	2%	2%	7%	5%
SGPT/ALT	≥5.1 x ULN	4%	3%	9%	7%
Total Bilirubin	≥2.6 x ULN	35%	<1%	47%	3%

Amylase	≥2.1 x ULN	*	*	14%	10%
Lipase	≥2.1 x ULN	<1%	1%	4%	5%
Creatine Kinase	≥5.1 x ULN	6%	6%	11%	9%
Total Cholesterol	≥240 mg/dL	6%	24%	19%	48%
Triglycerides	≥751 mg/dL	<1%	3%	4%	2%
Hematology	<u>Low</u>				
Hemoglobin	<8.0 g/dL	5%	3%	<1%	4%
Neutrophils	<750 cells/mm ³	7%	9%	3%	7%

* None reported in this treatment arm.

^a Based on regimen(s) containing atazanavir.

^b Median time on therapy.

^c Includes long-term follow-up.

^d ULN = upper limit of normal.

^e As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

Laboratory Abnormalities in Treatment-Experienced Adult Patients The percentages of adult treatment-experienced patients treated with combination therapy, including atazanavir/ritonavir with Grade 3–4 laboratory abnormalities are presented in Table 9.

Table 9: Grade 3–4 laboratory abnormalities reported in ≥2% of adult treatment-experienced patients (Study AI424-045) ^a

Variable	Limit ^c	48 weeks ^b Atazanavir/Ritonavir 300/100 mg Once Daily + Tenofovir + NRTI (n = 119)	48 weeks ^b Lopinavir/Ritonavir 400/100 mg Twice Daily ^d + Tenofovir + NRTI (n = 118)
Chemistry	<u>High</u>		
SGOT/AST	≥5.1 x ULN	3%	3%
SGPT/ALT	≥5.1 x ULN	4%	3%
Total Bilirubin	≥2.6 x ULN	49%	<1%
Lipase	≥2.1 x ULN	5%	6%
Creatine Kinase	≥5.1 x ULN	8%	8%
Total Cholesterol	≥240 mg/dL	25%	26%
Triglycerides	≥751 mg/dL	8%	12%
Glucose	≥251 mg/dL	5%	<1%
Hematology	<u>Low</u>		
Platelets	<50,000 cells/mm ³	2%	3%
Neutrophils	<750 cells/mm ³	7%	8%

^a Based on regimen(s) containing atazanavir.

^b Median time on therapy.

^c ULN = Upper limit of normal.

^d As a fixed-dose combination.

Lipids, Change from Baseline in Treatment-Naive Patients For Study AI424-138 and Study AI424-034, changes from baseline in fasting LDL-cholesterol, HDL-cholesterol, total cholesterol, and fasting triglycerides are shown in Table 8 and 9 respectively.

Table 10: Lipid values, mean change from baseline (Study AI424-138)

	Atazanavir ^{a,b}					Lopinavir/Ritonavir ^{b,c}				
	Basel ine	Week 48		Week 96		Basel ine	Week 48		Week 96	
	mg/d L n = 428 ^e	mg/ dL n = 372 ^e	Chan ge ^d n = 372 ^e	mg/d L (n=34 2e)	Chan ge ^d (n=3 35)	mg/d L n = 424 ^e	mg/ dL n = 335 ^e	Chan ge ^d n = 335 ^e	mg/ dL n=2 91	Chan ge ^d (n=2 91)
LDL- Choleste	92	105	+14%	105	+14 %	93	111	+19%	110	+17 %

rol ^f										
HDL-Choleste rol ^f	37	46	+29%	44	+21 %	36	48	+37%	46	+29 %
Total Choleste rol ^f	149	169	+13%	169	+13 %	150	187	+25%	186	+25 %
Triglyceri des ^f	126	145	+15%	140	+13 %	129	194	+52%	184	+50 %

^a Atazanavir 300 mg with ritonavir 100 mg once daily with the fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily

^b Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 1% in the lopinavir/ritonavir treatment arm and 1% in the atazanavir/ritonavir arm. Through week 48, serum lipid-reducing agents were used in 8% in the lopinavir/ritonavir treatment arm and 2% in atazanavir/ritonavir arm

^c Lopinavir 400 mg with ritonavir 100 mg twice daily with the fixed-dose combination 300 mg tenofovir, 200 mg emtricitabine once daily

^d The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and week 48 values and is not a simple difference of the baseline and week 48 mean values

^e Number of patients with LDL-cholesterol measured

^f Fasting

Table 11: Lipid values, mean change from baseline (Study AI424-034)

	Atazanavir ^{a,b}			Efavirenz ^c		
	Baseline mg/dL n = 383 ^e	Week 48 mg/dL n = 283 ^e	Week 48 Change ^d n = 272 ^e	Baselin e mg/dL n = 378 ^e	Week 48 mg/dL n = 264 ^e	Week 48 Change ^d n = 253 ^e
LDL- Cholesterol ^f	98	98	+1%	98	114	+18%
HDL- Cholesterol	39	43	+13%	38	46	+24%
Total Cholesterol	164	168	+2%	162	195	+21%
Triglyceride s ^f	138	124	-9%	129	168	+23%

^a Atazanavir 400 mg once daily with the fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily

^b Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 0% in the efavirenz treatment arm and <1% in the atazanavir arm. Through Week 48 serum

lipid-reducing agents were used in 3% in the efavirenz treatment arm and 1% in the atazanavir arm

^c Efavirenz 600 mg once daily with the fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily

^d The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and week 48 values and is not a simple difference of the baseline and week 48 mean values

^e Number of patients with LDL-cholesterol measured

^f Fasting

Lipids, Change from Baseline in Treatment-Experienced Adult Patients For Study AI424-045, changes from baseline in fasting LDL-cholesterol, HDL-cholesterol, total cholesterol, and fasting triglycerides are shown in Table 10. The observed magnitude of dyslipidemia was less with atazanavir/ritonavir than with lopinavir/ritonavir. However, the clinical impact of such findings has not been demonstrated.

Table 12: Lipid values, mean change from baseline (Study AI424-045)

	Atazanavir/Ritonavir ^{a,b}			Lopinavir/Ritonavir ^{b,c}		
	Baseline mg/dL n = 111 ^e	Week 48 mg/dL n = 75 ^e	Week 48 Change ^d n = 74 ^e	Baseline mg/dL n = 108 ^e	Week 48 mg/dL n = 76 ^e	Week 48 Change ^d n = 73 ^e
LDL- Cholesterol ^f	108	98	-10%	104	103	+1%
HDL- Cholesterol	40	39	-7%	39	41	+2%
Total Cholesterol	188	170	-8%	181	187	+6%
Triglycerides ^f	215	161	-4%	196	224	+30%

^a Atazanavir 300 mg once daily + ritonavir + tenofovir + 1 NRTI.

^b Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. Use of serum lipid-reducing agents was more common in the lopinavir/ritonavir treatment arm (19%) than in the atazanavir/ritonavir arm (8%).

^c Lopinavir/ritonavir (400/100 mg) b.i.d. + tenofovir + 1 NRTI.

^d The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and week 48 values and is not a simple difference of the baseline and week 48 mean values.

^e Number of patients with LDL-cholesterol measured.

^f Fasting.

Patients Co-Infected with Hepatitis B and/or Hepatitis C Virus

Liver function tests should be monitored in patients with a history of hepatitis B or C. In Study AI424-138, 60 patients treated with atazanavir/ritonavir 300 mg/100 mg once daily, and 51 patients treated with lopinavir/ritonavir 400 mg/100 mg twice daily, each with fixed-dose tenofovir-emtricitabine, were seropositive for hepatitis B and/or C at

study entry. ALT levels >5 times the ULN developed in 10% (6/60) of the atazanavir/ritonavir-treated patients and 8% (4/50) of the lopinavir/ritonavir-treated patients. AST levels >5 times the ULN developed in 10% (5/60) of the atazanavir/ritonavir-treated patients and none (0/50) of the lopinavir/ritonavir-treated patients.

In Study AI424-045, 20 patients treated with atazanavir/ritonavir 300 mg/100 mg once daily, and 18 patients treated with lopinavir/ritonavir 400 mg/100 mg twice daily, were seropositive for hepatitis B and/or C at study entry. ALT levels >5 times the ULN developed in 25% (5/20) of the atazanavir/ritonavir-treated patients and 6% (1/18) of the lopinavir/ritonavir-treated patients. AST levels >5 times the ULN developed in 10% (2/20) of the atazanavir/ritonavir-treated patients and 6% (1/18) of the lopinavir/ritonavir-treated patients.

Postmarketing Experience

The following events given below have been identified during the postmarketing use of atazanavir. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Edema

Cardiovascular System: Second-degree AV block, third-degree AV block, left bundle branch block, QTc prolongation (see **WARNINGS AND PRECAUTIONS**)

Hepatobiliary Disorders: Cholelithiasis, cholecystitis, cholestasis

Gastrointestinal System: Pancreatitis

Hepatic System: Hepatic function abnormalities

Metabolic System and Nutrition Disorders: Hyperglycemia, diabetes mellitus (see **WARNINGS AND PRECAUTIONS, Diabetes Mellitus/Hyperglycemia**)

Musculoskeletal System: Arthralgia

Renal System: Nephrolithiasis (see **WARNINGS AND PRECAUTIONS, Nephrolithiasis**)

Skin and Appendages: Alopecia, maculopapular rash (see **WARNINGS AND PRECAUTIONS, Rash**), pruritus

OVERDOSAGE

Human experience of acute overdose with atazanavir is limited. Single doses up to 1200 mg have been taken by healthy volunteers without symptomatic untoward effects. A single self-administered overdose of 29.2 g of atazanavir in an HIV-infected patient (73 times the 400 mg recommended dose) was associated with asymptomatic bifascicular block and PR interval prolongation. These events resolved spontaneously. At high doses that lead to high drug exposures, jaundice due to indirect (unconjugated) hyperbilirubinemia (without associated liver function test changes) or PR interval

prolongation may be observed (see **WARNINGS AND PRECAUTIONS; PHARMACOLOGY, Pharmacodynamics, *Effects on Electrocardiogram***).

Treatment of overdosage with atazanavir should consist of general supportive measures, including monitoring of vital signs and ECG, and observations of the patient's clinical status. If indicated, elimination of unabsorbed atazanavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of the unabsorbed drug.

There is no specific antidote for overdose with atazanavir. Since atazanavir is extensively metabolized by the liver and is highly protein-bound, dialysis is unlikely to be beneficial in significant removal of this drug.

PACKAGING INFORMATION

ATAVIR Capsules.....Container of 30 capsules

Last updated: October 2010