PRODUCT MONOGRAPH

PrAPO-ATAZANAVIR

Atazanavir capsules

Apotex Standard

150 mg, 200 mg and 300 mg, Oral

(as atazanavir sulfate)

Azapeptide Inhibitor of HIV-1 Protease

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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non medicinal Ingredients
Oral	Capsules, 150, 200 and 300 mg atazanavir	colloidal silicon dioxide, lactose monohydrate, magnesium stearate, and sodium starch glycolate. The capsule shells contains, edible black ink, FD&C Blue #2 (for all strength), iron oxide black (300 mg only), iron oxide red (300 mg only), gelatin and titanium dioxide (for all strengths) and sodium lauryl sulfate (300 mg only). Imprinting ink contains black iron oxide, potassium hydroxide, propylene glycol, shellac and strong ammonia solution.

INDICATIONS AND CLINICAL USE

APO-ATAZANAVIR (atazanavir sulfate) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts from controlled studies of 96 weeks duration in antiretroviral-naive patients and 48 weeks duration in antiretroviral-treatment-experienced patients.

In antiretroviral-treatment experienced patients with prior virologic failure, coadministration of APO-ATAZANAVIR/ritonavir is recommended (see **CLINICAL TRIALS**).

The number of baseline primary protease inhibitor mutations affects the virologic response to APO-ATAZANAVIR/ritonavir (see **MICROBIOLOGY** - Resistance *in vivo*).

(See **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION**, **MICROBIOLOGY** - Resistance *in vivo*.)

Geriatrics (> 65 years of age)
Clinical studies of atazanavir sulfate did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose

selection for an elderly patient should reflect the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatrics (from 6 to 18 years of age)
Dosage is based on body weight not to exceed the adult dose (See **DOSAGE AND ADMINISTRATION**). There are no dosing recommendations for pediatric patients less than 6 years of age.

CONTRAINDICATIONS

Patients with previously demonstrated clinically significant hypersensitivity (eg. Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any component of the product or container, including atazanavir. For a complete listing see (**DOSAGE FORMS, COMPOSITION AND PACKAGING**).

Coadministration of APO-ATAZANAVIR is contraindicated with drugs that are highly dependent on CYP3A4 and/or UGT1A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in **Table 1**.

Table 1 Drugs that are Contraindicated with APO-ATAZANAVIR[a]

Drug Class	Drugs within class that are contraindicated with APO-ATAZANAVIR
Alpha 1-Adrenoreceptor Antagonists	alfuzosin
Antiarrhythmics	quinidine
Anticoagulants: Direct-acting oral anticoagulants (DOACs)	apixaban, rivaroxaban (when used with ritonavir)[b]
Antimycobacterials	rifampin
Antineoplastics	irinotecan
Antipsychotics	lurasidone (when used with ritonavir), pimozide
Benzodiazepines	triazolam
Ergot Derivatives	dihydroergotamine, ergotamine, ergonovine, methylergonovine
Hepatitis C Direct-Acting Antivirals	elbasvir/grazoprevir, glecaprevir/pibrentasvir
Herbal Products	St. John's wort (*Hypericum perforatum*)
Lipid-Modifying Agents: HMG-CoA Reductase Inhibitors Other Lipid-Modifying agents:	lovastatin, simvastatin Lomitapide
PDE5 Inhibitors	sildenafil[b] (when used for the treatment of pulmonary arterial hypertension [PAH])
Protease Inhibitors	indinavir
Non-nucleoside Reverse	nevirapine

Transcriptase Inhibitors	

[a] See **Table 13** for more detailed information.
[b] See Table 14 for apixaban and rivaroxaban when co-administered with APO-ATAZANAVIR without ritonavir
[c] See **Table 14** for sildenafil when dosed for erectile dysfunction.

WARNINGS AND PRECAUTIONS

General
Atazanavir should always be used in combination with other antiretroviral agents. Atazanavir should not be added as a single agent when antiretrovirals are changed due to loss of virologic response.

Coadministration of APO-ATAZANAVIR and drugs primarily metabolized by CYP3A4 may result in increased plasma concentrations of the other drug with the potential for increased toxicity (see **DRUG INTERACTIONS**).

Due to inhibition of CYP3A4 by atazanavir sulfate, co-administration of APO-ATAZANAVIR with quetiapine may result in increased quetiapine concentrations. Serious and/or life-threatening quetiapine-related adverse reactions, including severe sedation and coma, have been reported for concomitant use of HIV protease inhibitors and quetiapine. APO-ATAZANAVIR should not be used in combination with quetiapine. If co-administration is necessary, reduce the quetiapine dose and monitor for quetiapine-associated adverse reactions as recommended in the quetiapine product monograph (see **DRUG INTERACTIONS**).

Antiretroviral Treatment-Experienced Patients
Atazanavir 400 mg once daily has been shown to be inferior to lopinavir/ritonavir in antiretroviral experienced patients. There are limited safety data from controlled trials for atazanavir sulfate plus ritonavir regimens without tenofovir DF. (See **DRUG INTERACTIONS, DOSAGE AND ADMINISTRATION** and **CLINICAL TRIALS**.)

Carcinogenesis and Mutagenesis
The incidence of benign hepatocellular adenomas was increased in high-dose female mice at systemic exposures approximately 7-fold higher than those in humans at the recommended 400 mg clinical dose. There was no increase in the incidence of tumors in male mice or in male or female rats at any dose tested. The clinical significance of the carcinogenic findings in female mice is unknown as the benign hepatic tumors occurred only at doses that induced liver toxicity. (see **TOXICOLOGY - Carcinogenicity and Mutagenicity**).

Cardiovascular
Cardiac Conduction Abnormalities: Atazanavir has been shown to prolong the PR interval of the electrocardiogram in some patients. In healthy volunteers and in patients, abnormalities in atrioventricular (AV) conduction were asymptomatic and limited to first degree AV block with some exceptions (see **OVERDOSAGE**). There have been post-marketing reports of second-degree AV block, third-degree AV block, QTc prolongation, Torsades de Pointes and other conduction abnormalities in patients treated with atazanavir sulfate (see **ADVERSE**

REACTIONS – **Post-Market Adverse Drug Reactions**). In clinical trials, asymptomatic first-degree AV block was observed in 5.9% of atazanavir-treated patients (n = 920), 3.0% of efavirenz treated patients (n = 329), 5.2% of lopinavir/ritonavir treated patients (n = 252) and 10.4% of nelfinavir treated patients (n = 48). In study AI424-045 asymptomatic first degree AV block was observed in 5% (6/118) of atazanavir sulfate/ritonavir-treated patients and 5% (6/116) of lopinavir/ritonavir-treated patients who had on-study electrocardiogram measurements. Because of limited clinical experience, atazanavir should be used with caution in patients with preexisting conduction system disease (e.g., marked first-degree AV block or second or third-degree AV block).

Dose related asymptomatic prolongations in PR interval with atazanavir sulfate have been observed in clinical studies. Caution should be used with medicinal products known to induce PR prolongations. In patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), APO-ATAZANAVIR should be used with caution and only if the benefits exceed the risk. Particular caution should be used when prescribing APO-ATAZANAVIR in association with medicinal products which have the potential to increase the QT interval and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances). (See **ACTION AND CLINICAL PHARMACOLOGY**.)

In a pharmacokinetic study between atazanavir 400 mg once daily and diltiazem 180 mg once daily, a CYP3A substrate, there was a 2-fold increase in the diltiazem plasma concentration and 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, there was no substantial additive effect of atazanavir and atenolol on the PR interval. When used in combination with atazanavir, there is no need to adjust the dose of atenolol. (See **DRUG INTERACTIONS**.)

Pharmacokinetic studies between atazanavir and other drugs that prolong the PR interval including beta blockers (other than atenolol), 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 CYP3A4 (e.g., verapamil). (See **DRUG INTERACTIONS**.)

Endocrine and Metabolism

Diabetes mellitus/Hyperglycemia: New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing 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.

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.

Hematologic

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.

Hepatic/Biliary

Hepatic Impairment and Toxicity: Atazanavir sulfate is principally metabolized by the liver; caution should be exercised when administering this drug 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, test for liver enzymes before initiating therapy with APO-ATAZANAVIR and monitor liver enzymes during treatment. APO-ATAZANAVIR should not be administered to patients with severe hepatic impairment. APO-ATAZANAVIR/ritonavir is not recommended for use in patients with hepatic impairment.

Hyperbilirubinemia: Most patients taking atazanavir experience elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT). This hyperbilirubinemia is generally reversible upon discontinuation of atazanavir sulfate. If hepatic transaminase elevations occur with hyperbilirubinemia while a patient is receiving atazanavir, consideration should be given to also evaluating alternative etiologies. No long-term safety data are available for patients experiencing persistent elevations in total bilirubin > 5 x ULN. Alternative antiretroviral therapy to APO-ATAZANAVIR may be considered if jaundice or scleral icterus associated with bilirubin elevations present cosmetic concerns for patients. Dose reduction of atazanavir is not recommended since long-term efficacy of reduced doses has not been established. (See **ADVERSE REACTIONS**.)

Cholelithiasis, Cholecystitis, and Cholestasis: There have been post-marketing reports of cholelithiasis, cholecystitis, and cholestasis in patients treated with atazanavir with ritonavir as part of their ART regimen (see **ADVERSE REACTIONS – Post-Market Adverse Drug Reactions**).

Immune

Immune Reconstitution Inflammatory Syndrome: Immune reconstitution inflammatory syndrome has been reported in patients treated with combination antiretroviral therapy, including atazanavir sulfate. During the initial phase of treatment, a patient whose immune system responds to therapy may develop an inflammatory response to indolent or residual opportunistic

infections (such as MAC, CMV, PCP and TB), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Angioedema: Cases of angioedema have been reported in patients taking atazanavir (see **ADVERSE REACTIONS**, **Less Common Clinical Trial Adverse Drug Reactions (<2%)**, **Post-market Adverse Drug Reactions**).

Renal

Renal Impairment: In healthy subjects, approximately 7% of the dose of atazanavir is eliminated unchanged in the urine. Atazanavir has been studied in adult subjects with severe renal impairment (n=20), including those on hemodialysis, at multiple doses of 400 mg once daily. The impact of renal impairment on atazanavir elimination for patients without hemodialysis is anticipated to be low. Moderate increases in atazanvir clearance and decreased exposure levels were seen in patients managed with hemodialysis. APO-ATAZANAVIR should not be administered to HIV-treatment-experienced patients with end stage renal disease managed with hemodialysis. (See **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

Chronic kidney disease: Chronic kidney disease (CKD) has been reported in patients treated with atazanavir, with or without ritonavir, during postmarketing surveillance. Some resulted in fatal outcomes in patients with pre-existing CKD, and some resulted in the need for hemodialysis in patients with or without pre-existing CKD. APO-ATAZANAVIR should be used with caution, particularly in those patients with other risk factors for chronic kidney disease. Prescribers should consider the risk-benefit in continuing APO-ATAZANAVIR therapy if patients develop signs and symptoms of CKD.

Nephrolithiasis and Cholelithiasis: Cases of nephrolithiasis and/or cholelithiasis were reported during post-marketing surveillance in HIV-infected patients receiving atazanavir therapy. Some patients required hospitalization for additional management and some had complications. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made. If signs or symptoms of nephrolithiasis and/or cholelithiasis occur, temporary interruption or discontinuation of therapy may be considered.

Resistance / Cross-Resistance

Resistance

In vitro HIV-1 isolates with a decreased susceptibility to ATV have been selected *in vitro* and obtained from patients treated with ATV or atazanavir/ritonavir (ATV/RTV). HIV-1 isolates that were 93- to 183-fold resistant to ATV from three different viral strains were selected *in vitro* by 5 months. The mutations in these HIV-1 viruses that contributed to ATV resistance included I50L, N88S, I84V, A71V, and M46I. Changes were also observed at the protease cleavage sites following drug selection. Recombinant viruses containing the I50L mutation were growth

impaired and displayed increased *in vitro* susceptibility to other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). The I50L and I50V substitutions yielded selective resistance to ATV and amprenavir, respectively, and did not appear to be cross-resistant.

Both genotypic and phenotypic resistances have developed during clinical studies (see **MICROBIOLOGY**, **Resistance**).

Cross Resistance

Cross-resistance among PIs has been observed. Baseline phenotypic and genotypic analyses of clinical isolates from ATV clinical trials of PI-experienced subjects showed that isolates cross-resistant to multiple PIs were cross-resistant to ATV. Greater than 90% of the isolates with mutations that included I84V or G48V were resistant to ATV. Greater than 60% of isolates containing L90M, G73S/T/C, A71V/T, I54V, M46I/L, or a change at V82 were resistant to ATV, and 38% of isolates containing a D30N mutation in addition to other changes were resistant to ATV. Isolates resistant to ATV were also cross-resistant to other PIs with >90% of the isolates resistant to indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir, and 80% resistant to amprenavir. In treatment-experienced patients, PI-resistant viral isolates that developed the I50L mutation in addition to other PI resistance-associated mutations were also cross-resistant to other PIs.

Genotypic and/or phenotypic analysis of baseline virus may aid in determining ATV susceptibility before initiation of ATV/RTV therapy.

Overall, both the number and type of baseline PI mutations affected response rates in treatment-experienced patients (see **MICROBIOLOGY**, **Cross-Resistance**).

Sexual Function/Reproduction

In a fertility and early embryonic development study in rats, atazanavir altered estrus cycling with no effects on mating, fertility or early embryonic development. Systemic drug exposure levels were equal (in male rats) or two times (in female rats) those at the human clinical dose (400 mg/day).

Skin

Rash: In controlled clinical trials, rash (all grades, regardless of causality) occurred in approximately 20% of patients treated with atazanavir sulfate. The median time to onset of rash in clinical studies was 7.3 weeks and the median duration of rash was 1.4 weeks. Rashes were generally mild-to-moderate maculopapular skin eruptions. Treatment-emergent adverse reactions of moderate or severe rash (occurring at a rate of ≥2%) are presented for the individual clinical studies (see **ADVERSE REACTIONS**). Dosing with atazanavir sulfate was often continued without interruption in patients who developed rash. The discontinuation rate for rash in clinical trials was <1%. APO-ATAZANAVIR should be discontinued if severe rash develops. Cases of Stevens-Johnson syndrome, erythema multiforme and toxic skin eruptions including drug rash, eosinophilia, and systemic symptoms (DRESS) syndrome have been reported in patients receiving atazanavir sulfate. (See **CONTRAINDICATIONS**.)

Special Populations

Pregnant Women: APO-ATAZANAVIR should be used during pregnancy only if the potential benefit justifies the potential risk. (See **WARNINGS AND PRECAUTIONS: Endocrine and Metabolism**.) There are no adequate and well-controlled studies in pregnant women. Cases of lactic acidosis, sometimes fatal, and symptomatic hyperlactatemia have been reported in patients (including pregnant women) receiving atazanavir sulfate in combination with nucleoside analogues, which are known to be associated with increased risk of lactic acidosis. Female gender and obesity are also known risk factors for lactic acidosis syndrome. The contribution of atazanavir sulfate to the risk of development of lactic acidosis syndrome has not been established.

Hyperbilirubinemia occurred frequently during treatment with atazanavir sulfate. It is not known whether atazanavir sulfate administered to the mother during pregnancy will exacerbate physiologic hyperbilirubinemia and lead to kernicterus in neonates and young infants. In the prepartum period, additional monitoring and alternative therapy should be considered. Atazanavir sulfate has been shown to cross the placenta.

In the pre-and post-natal development assessment in rats, atazanavir produced a transient reduction in body weight in the offspring at maternally toxic drug exposure levels two times those at the human clinical dose.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to APO-ATAZANAVIR, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Antiretroviral Pregnancy Registry Data: As of January 2010 the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 635 exposures to atazanavir-containing regimens (425 exposed in the first trimester and 160 and 50 exposed in second and third trimester respectively. Birth defects occurred in 9 of 393 (2.3%) live births (first trimester exposure) and 5 of 212 (2.4%) live births (second/third trimester exposure). There was no association between atazanavir and specific birth defects observed in the APR.

Nursing Women: Atazanavir has been detected in human milk. No data are available regarding atazanavir effects on milk production.

A study in lactating rats demonstrated that atazanavir is secreted in 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 breast-feed if they are receiving APO-ATAZANAVIR.

Pediatrics (from 6 to 18 years of age): APO-ATAZANAVIR should not be administered in pediatric patients below the age of 3 months due to the risk of kernicterus. The safety, pharmacokinetic profile, and virologic response of atazanavir sulfate were evaluated in pediatric patients in an open-label, multicenter clinical trial PACTG 1020A (see **CLINICAL TRIALS**). The safety profile in pediatric patients was comparable to that observed in adults (see **ADVERSE REACTIONS**). The safety, activity, and pharmacokinetic profiles of atazanavir sulfate in pediatric patients ages 3 months to less than 6 years have not been established.

Geriatrics (> 65 years of age): Clinical studies of atazanavir sulfate did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, appropriate caution should be exercised in the administration and monitoring of APO-ATAZANAVIR in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Drug Interaction
Atazanavir is an inhibitor of CYP3A and UGT1A1. Coadministration of atazanavir sulfate and drugs primarily metabolized by CYP3A [eg, calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants, and phosphodiesterase (PDE5) inhibitors], or UGT1A1 (eg, irinotecan) 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 APO-ATAZANAVIR without ritonavir is coadministered with drugs highly dependent on CYP2C8 with narrow therapeutic indicies (eg, paclitaxel, repaglinide). When atazanavir sulfate with ritonavir is coadministered with substrates of CYP2C8, clinically significant interactions are not expected. See the complete prescribing information for NORVIR® for information on other potential drug interactions with ritonavir. Clinically significant interactions are not expected between atazanavir and substrates of CYP2C19, CYP2C9, CYP2D6, CYP2B6, CYP2A6, CYP1A2, or CYP2E1 (see **DRUG INTERACTIONS**).

ADVERSE REACTIONS

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximate rates.

Clinical Trial Experience in Adults

Atazanavir sulfate has been evaluated for safety and tolerability in combination therapy with other antiretroviral medications in controlled clinical trials in 1806 adult patients receiving atazanavir sulfate 400 mg once daily (1151 patients, 52 weeks median duration and 152 weeks maximum duration), or atazanavir sulfate 300 mg once daily plus ritonavir 100 mg once daily (655 patients, 96 weeks median duration and 108 weeks maximum duration).

The more frequent adverse events of any severity with at least a possible relationship to regimens containing atazanavir sulfate and one or more NRTIs were nausea (20%), diarrhea (10%) and jaundice (13%).

Jaundice was reported within a few days to a few months after the initiation of treatment and resulted in discontinuation of treatment in <1% of patients. Discontinuation of treatment due to adverse reactions was 5% in treatment-naive patients and 5% in treatment-experienced patients.

Lipodystrophy, of moderate intensity or greater, was reported in regimens containing atazanavir sulfate and one or more NRTIs as shown in **Table 3** and **Table 4** below (see **WARNINGS AND PRECAUTIONS**).

Treatment-Emergent Adverse Events in Antiretroviral Treatment-Naive Patients
Drug-related clinical adverse events of moderate or severe intensity in ≥ 2% of treatment-naive patients receiving combination therapy including atazanavir sulfate 300 mg with ritonavir 100 mg and atazanavir sulfate 400 mg (without ritonavir) are presented in **Table 2** and **Table 3**, respectively.

Table 2 Selected Treatment-Emergent Adverse Events[a] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-Naïve Patients[b], Study AI424-138

	Phase III Study AI424-138	
	96 weeks[c] atazanavir sulfate 300 mg plus ritonavir 100 mg (once daily) and tenofovir DF plus emtricitabine[d] N = 441	**96 weeks[c] lopinavir 400 mg plus ritonavir 100 mg (twice daily) and tenofovir DF plus 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 the regimen containing atazanavir sulfate .
[c] Median time on therapy.
[d] As a fixed-dose combination: 300 mg tenofovir DF, 200 mg emtricitabine once daily.

Table 3 Treatment-Emergent Adverse Events[a] of Moderate or Severe Intensity Reported in ≥ 2% of Adult Treatment-Naive Patients[b], Studies AI424-034, AI424-007 and AI424-008

	Phase III Study AI424-034		**Phase II Studies AI424-007, -008**	
	64 weeks[c] atazanavir sulfate 400 mg once daily + lamivudine + zidovudine[e] N = 404	**64 weeks[c] efavirenz 600 mg once daily + lamivudine + zidovudine[e] N = 401**	**120 weeks[c,d] atazanavir sulfate 400 mg once daily + stavudine / lamivudine or + stavudine / didanosine N = 279**	**73 weeks[c,d] nelfinavir 750 mg TID or 1250 mg BID + stavudine + lamivudine or + stavudine + didanosine N = 191**
Body as a Whole				

Table 3 Treatment-Emergent Adverse Events[a] of Moderate or Severe Intensity Reported in ≥ 2% of Adult Treatment-Naive Patients[b], Studies AI424-034, AI424-007 and AI424-008

	Phase III Study AI424-034		Phase II Studies AI424-007, -008	
	64 weeks[c] atazanavir sulfate 400 mg once daily + lamivudine + zidovudine[e] N = 404	64 weeks[c] efavirenz 600 mg once daily + lamivudine + zidovudine[e] N = 401	120 weeks[c,d] atazanavir sulfate 400 mg once daily + stavudine / lamivudine or + stavudine / didanosine N = 279	73 weeks[c,d] nelfinavir 750 mg TID or 1250 mg BID + stavudine + lamivudine or + stavudine + didanosine N = 191
Headache	6%	6%	1%	2%
Digestive System				
Diarrhea	1%	2%	3%	16%
Dyspepsia	2%	2%	< 1%	<1%
Scleral icterus	2%	*	2%	*
Jaundice	5%	*	5%	*
Nausea	14%	12%	6%	4%
Abdominal pain	4%	4%	4%	2%
Vomiting	4%	7%	3%	3%
Metabolic and Nutritional System				
Lipodystrophy	1%	1%	7%	3%
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%

* Not reported in this treatment arm.

[a] Includes adverse events of possible, probable, certain, or unknown relationship to treatment regimen. Assessments of relationship refer to regimens containing atazanavir sulfate or comparator.

[b] Based on regimen(s) containing atazanavir sulfate.

[c] Median time on therapy. In study AI424-034 efficacy analyses are based on 48 week data. Safety data are derived from a 64 week safety update report.

[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 Antiretroviral Treatment-Experienced Patients

Drug related clinical adverse events of moderate or severe intensity in ≥ 2% of treatment-experienced patients receiving combination therapy including atazanavir sulfate are presented in **Table 4.**

Table 4 Treatment-Emergent Adverse Events[a] of Moderate or Severe Intensity Reported in ≥ 2% of Adult Treatment-Experienced Patients[b], Studies AI424-043 and AI424-045

	Phase III Study AI424-043		Phase III Study AI424-045**	
	48 weeks[c] atazanavir sulfate 400 mg once daily + 2 NRTIs N = 144	48 Weeks[c] lopinavir + ritonavir (400/100 mg) BID[d] + 2 NRTIs N = 146	48 weeks[c] atazanavir sulfate 300 mg once daily + ritonavir 100 mg once daily + tenofovir DF + NRTI N = 119	48 weeks[c] lopinavir + ritonavir (400/100 mg) BID[d] + tenofovir DF + NRTI N = 118
Body as a Whole				
Headache	4%	3%	< 1%	<1%
Fever	-	-	2%	*
Digestive System				
Diarrhea	2%	4%	3%	11%
Scleral icterus	*	*	3%	*
Jaundice	3%	*	6%	*
Nausea	3%	4%	3%	2%
Vomiting	2%	2%	*	<1%
Pain abdomen	3%	2%	2%	2%
Metabolic and Nutritional System				
Lipodystrophy	6%	1%	5%	4%
Weight decreased	2%	<1%	*	2%
Musculoskeletal System				
Myalgia	*	*	4%	*
Nervous System				
Peripheral neurologic symptom	2%	5%	< 1%	3%
Depression	-	-	2*	*
Skin and Appendages				
Rash	2%	*	*	<1%

** NOTE: There are limited safety data from controlled trials for atazanavir sulfate plus ritonavir regimens without tenofovir DF. (See **DRUG INTERACTIONS**.)

* Not reported in this treatment arm.

[a] Includes adverse events of possible, probable, certain, or unknown relationship to treatment regimen. Assessments of relationship refer to regimens containing atazanavir sulfate or comparator.
[b] Based on regimen(s) containing atazanavir sulfate.
[c] Median time on therapy.
[d] As a fixed dose combination.

Less Common Clinical Trial Adverse Drug Reactions (< 2%)

Treatment-Emergent Adverse Events in all Atazanavir sulfate -Treated Patients

Treatment-emergent adverse events of at least moderate intensity occurring in less than 2% of adult patients receiving atazanavir sulfate in all phase II/III clinical trials with at least a possible relationship to treatment with atazanavir sulfate-containing regimens, and not listed in **Table 2, Table 3** or **Table 4** are listed below by body system.

Body as a Whole:	allergic reaction, asthenia, chest pain, fatigue, malaise
Cardiovascular System:	hypertension, palpitation, syncope, edema
Digestive System:	abdominal distension, aphthous stomatitis, dysgeusia, flatulence, gastritis, hepatitis, hepatosplenomegaly, pancreatitis, dry mouth
Immune System:	allergic reaction, angioedema
Metabolic and Nutritional Disorders:	weight gain, anorexia, appetite increased, weight decreased
Musculoskeletal System:	arthralgia, muscle atrophy, myopathy
Nervous System:	abnormal dream, abnormal gait, amnesia, anxiety, confusion, sleep disorder, somnolence
Respiratory System:	dyspnea
Skin and Appendages:	alopecia, eczema, pruritus, urticaria, vesiculobullous rash, vasodilatation
Urogenital System:	gynecomastia, hematuria, kidney pain, proteinuria, pollakiuria, nephrolithiasis

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory Abnormalities

The percentages of adult treatment-naive and treatment-experienced patients treated with combination therapy including atazanavir sulfate 300 mg with ritonavir 100 mg and atazanavir sulfate 400 mg (without ritonavir) with Grade 3-4 laboratory abnormalities are presented in **Table 5**, **Table 6** and **Table 7**. The most frequently reported laboratory abnormality in patients

receiving regimens containing atazanavir sulfate and one or more NRTIs was elevated bilirubin. Elevations in bilirubin were reported predominantly as elevated indirect [unconjugated] bilirubin.

In clinical studies, the observed magnitude of dyslipidemia was less with atazanavir sulfate than with comparators. However, the clinical impact of such findings has not been demonstrated.

Table 5 Grade 3-4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Naïve Patients[a], Studies AI424-138

Variable	Limit[c]	Treatment-Naive Patients	
		Phase III Studies AI424-138	
		96 weeks[b] Atazanavir sulfate 300 mg plus ritonavir 100 mg (once daily) and tenofovir DF plus emtricitabine[d] N = 441	96 weeks[b] lopinavir 400 mg plus ritonavir 100 mg (twice daily) and tenofovir DF plus emtricitabine[d] N = 437
Chemistry	**High**		
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	**Low**		
Neutrophils	<750 cells/mm^3	5%	2%
Prothrombin Time	≥ 1.51 x ULN	2%	6%

[a] Based on the regimen containing atazanavir sulfate .
[b] Median time on therapy.
[c] ULN = upper limit of normal.
[d] As a fixed-dose combination: 300 mg tenofovir DF, 200 mg emtricitabine once daily.

Table 6 Selected 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]	Treatment-Naive Patients			
		Phase III Study AI424-034		Phase II Studies AI424-007, -008	
		64 weeks[b] atazanavir sulfate 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 sulfate 400 mg once daily + stavudine + lamivudine or + stavudine + didanosine N = 279	73 weeks[b,c] nelfinavir 750 mg TID or 1250 mg BID + stavudine + lamivudine or + stavudine + didanosine N = 191
Chemistry	**High**				
AST	≥ 5.1 X ULN	2%	2%	7%	5%
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%
Hematology	**Low**				
Hemoglobin	<8.0 g/L	5%	3%	<1%	4%
Neutrophils	<750 cells/mm^3	7%	9%	3%	7%

** NOTE: There are limited safety data from controlled trials for atazanavir sulfate plus ritonavir regimens without tenofovir DF. (See **DRUG INTERACTIONS**.)

* Not reported in this treatment arm.

[a] Based on regimen(s) containing atazanavir sulfate .

[b] Median time on therapy. In Study AI424-034 efficacy analyses are based on 48 week data. Safety data are derived from a 64 week safety update report.

[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.

Table 7 Selected Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Treatment-Experienced Patients[a], Studies AI424-043 and AI424-045

Variable	Limit[c]	Treatment-Experienced Patients			
		Phase III Study AI424-043		Phase III Studies AI424-045**	
		48 weeks[b]		48 weeks[b]	48 weeks[b]
		atazanavir sulfate 400 mg once daily + 2NRTIs N = 144	lopinavir + ritonavir (400/100 mg) BID[d] + 2NRTIs N = 146	atazanavir sulfate 300 mg once daily + ritonavir 100 mg once daily + tenofovir DF + NRTI N = 119	lopinavir + ritonavir (400/100 mg) BID[d] + tenofovir DF + NRTI N = 118
Chemistry	**High**				
AST	≥ 5.1 X ULN	3%	3%	3%	3%
ALT	≥ 5.1 X ULN	7%	3%	4%	3%
Total Bilirubin	≥ 2.6 X ULN	25%	<1%	49%	<1%
Lipase	≥ 2.1 X ULN	4%	3%	5%	6%
Creatine Kinase	≥ 5.1 X ULN	8%	6%	8%	8%
Hematology	**Low**				
Platelets	<50,000/mm^3	*	*	2%	3%
Neutrophils	<750 cells/mm^3	6%	5%	7%	8%

** NOTE: There are limited safety data from controlled trials for atazanavir sulfate plus ritonavir regimens without tenofovir DF. (See **DRUG INTERACTIONS**.)

* Not reported in this treatment arm.

[a] Based on regimen(s) containing atazanavir sulfate.

[b] Median time on therapy. In Study AI424-034 efficacy analyses are based on 48 week data. Safety data are derived from a 64 week safety update report.

[c] ULN = upper limit of normal.

[d] As a fixed dose combination.

Lipids – Treatment-Naïve Patients

Table 8 and **Table 9** present the changes in lipids, insulin and glucose for the treatment-naive studies.

Table 8 Lipid, Glucose and Insulin Mean Values, Study AI424-138

	Atazanavir sulfate/ritonavir [a,b]					Lopinavir/ritonavir [b,c]				
	Baseline mmol/L [h] N=428[e]	Week 48 mmol/L [h] N=372[e]	Week 48 Change [d, g] N=372[e]	Week 96 mmol/L [h] N = 342[e]	Week 96 Change [d, g] N = 342[e]	Baseline mmol/L [h] N = 424[e]	Week 48 mmol/L [h] N = 335[e]	Week 48 Change[d], [g] N = 335[e]	Week 96 mmol/L [h] N = 291[e]	Week 96 Change[d], [g] N = 291[e]
Total-Cholesterol [f]	3.86	4.36	+13%	4.38	+13%	3.88	4.84	+25%	4.81	+25%
HDL-Cholesterol [f]	0.95	1.2	+29%	1.14	+21%	0.93	1.24	+37%	1.19	+29%
LDL-Cholesterol [f]	2.38	2.70	+14%	2.72	+14%	2.4	2.87	+19%	2.84	+17%
Triglycerides[f]	1.42	1.63	+15%	1.58	+13%	1.46	2.2	+52%	2.08	+50%
Insulin	57.7	76.6	+ 18.1	58.9	+1.1	59.9	61.1	+1.2	51.8	-5.5
Glucose	4.77	4.86	+0.12	4.97	+0.22	4.88	4.9	+0.01	4.96	+0.05

[a] Atazanavir sulfate 300 mg plus ritonavir 100 mg once daily with the fixed-dose combination: 300 mg tenofovir DF, 200 mg emtricitabine once daily.

[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 (8%) than in the atazanavir sulfate /ritonavir arm (2%). Through Week 96, serum lipid-reducing agents were used in 10% in the lopinavir/ritonavir treatment arm and 3% in the atazanavir sulfate /ritonavir arm.

[c] Lopinavir 400 mg plus ritonavir 100mg twice daily with the fixed-dose combination 300 mg tenofovir DF, 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 or Week 96 values and is not a simple difference of the baseline and Week 48 or Week 96 mean values, respectively.

[e] Number of patients with LDL-cholesterol measured.

[f] Fasting.

[g] Absolute changes are reported for insulin and glucose levels

[h] Units are pmol/L for insulin

Table 9 Lipid, Insulin, and Glucose Mean Values From Study AI424-034*

	Atazanavir sulfate [a]			Efavirenz[b]		
	Baseline	Week 48		Baseline	Week 48	
	mmol/L[c] (n = 383[e])	mmol/L[c] (n = 283[e])	% Change[c,f] (n = 272[e])	mmol/L[c] (n = 378[e])	mmol/L[c] (n = 264[e])	% Change[c,f] (n = 253[e])
Total Cholesterol	4.24	4.34	+ 2%	4.19	5.04	+ 21%
HDL-Cholesterol	1.01	1.11	+ 13%	0.98	1.19	+ 24%
LDL-Cholesterol [g]	2.53	2.53	+ 1%	2.53	2.95	+ 18%
Triglycerides [g]	1.56	1.4	- 9%	1.46	1.9	+ 23%
Total-to-HDL Cholesterol Ratio < 3	13%	17%		9%	14%	
Insulin[d, g]	81.1	88.3	+9.3	71	82.5	+10.1
Glucose[d, g]	5	5.2	+0.17	5	5.2	+0.33

* No multivariate analyses were performed on these data.
a Atazanavir sulfate 400 mg once daily with the fixed dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.
b Efavirenz 600 mg once daily with the fixed dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.
c Units are pmol/mL for insulin levels.
d Absolute changes are reported for insulin and glucose levels.
e Number of patients with LDL cholesterol measured.
f 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.
g Fasting

Lipids – Treatment-Experienced Patients

Table 10, **Table 11** and **Table 12** present the changes from baseline in lipids, insulin and glucose for the treatment-experienced studies.

Table 10 Lipid, Insulin, and Glucose Mean Values From Study AI424-043*

	Atazanavir sulfate [a]			Lopinavir + ritonavir[b]		
	Baseline	Week 48		Baseline	Week 48	
	mmol/L (n =143[e])	mmol/L[c] (n = 101[e])	% Change[d,g] (n = 101[e])	mmol/L[c] (n = 144[e])	mmol/L[c] (n = 99[e])	% Change[d,g] (n = 99[e])
Total Cholesterol	4.68	4.50	- 2%	4.53	5.02	+ 12%
HDL-Cholesterol	1.01	1.06	+ 9%	0.96	1.11	+ 10%
LDL-Cholesterol[f, h]	2.74	2.56	- 6%[f]	2.66	2.79	+ 3%
Triglycerides [h]	2.17	4.50	+ 1%	2.17	6.52	+ 53%
Total-to-HDL Cholesterol Ratio <3	7%	12%		7%	10%	
Insulin [h]	76.1	86.1	+14.4	71.0	78.9	+7.9
Glucose [h]	4.9	5.1	+0.17	5	5.0	-0.6

* No multivariate analyses were performed on these data.

[a] Atazanavir sulfate 400 mg once daily + 2 NRTIs.
[b] Lopinavir + ritonavir (400/100 mg) BID + 2 NRTIs.
[c] Units are pmol/mL for insulin levels.
[d] Absolute changes are reported for insulin and glucose levels.
[e] Number of patients with LDL cholesterol measured.
[f] Protocol-defined co-primary safety outcome measure.
[g] 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.
[h] Fasting

Table 11 Lipid and Glucose Mean Values from Study AI424-045*

	ATV 300/RTV[a]			LPV/RTV[b]		
	Baseline	Week 48		Baseline	Week 48	
	mmol/L (n = 112[c])	mmol/L (n = 75[c])	% Change (n = 74)	mmol/L (n = 108[c])	mmol/L (n = 76[c])	% Change (n = 73)
Total Cholesterol	4.86	4.40	-8%	4.68	4.83	6%
HDL-Cholesterol	1.03	1.00	-7%	1.01	1.06	2%
LDL-Cholesterol [e]	2.82	2.53	-10%	2.69	2.66	1%
Triglycerides	2.43	4.16	-4%	2.21	5.79	30%
Total-to-HDL Cholesterol Ratio <3	9%	13%		12%	13%	
Glucose [d, e]	5.27	5.49	+0.22	5.00	5.10	+0.06

* There are limited safety data from controlled trials for atazanavir sulfate plus ritonavir regimens without tenofovir DF. (See **DRUG INTERACTIONS**.)
No multivariate analyses were performed on these data.
[a] Atazanavir sulfate 300 mg + ritonavir 100 mg once daily + tenofovir DF + 1 NRTI
[b] Lopinavir + ritonavir (400/100 mg) BID + tenofovir DF + 1 NRTI.
[c] Number of patients with LDL cholesterol measured.
[d] Absolute changes are reported for glucose levels.
[e] Fasting

Table 12 Lipid, Insulin and Glucose Values from Study AI424-044 (Nelfinavir patients in study AI424-008 who switched to Atazanavir sulfate[a] in the long term AI424-044 study)*

	Baseline Study AI424-008	Entry Study AI424-044	Week 12 Study AI424-044	
	mmol/L[a] (n = 54[b])	mmol/L[a] (n = 33[b])	mmol/L[a] (n = 41[b])	% Change[c] (n = 29[b])
Total Cholesterol	4.34	5.53	4.53	-16%
HDL-Cholesterol	1.09	1.19	1.24	+5%
LDL-Cholesterol[d]	2.53	3.57	2.69	-21%
Triglycerides[d]	1.19	1.77	1.22	-28%
Insulin[d]	-	70.3	66.7	-
Glucose[d]	-	4.77	4.88	-

* No multivariate analyses were performed on these data.
[a] Units are pmol/mL for insulin levels.

[b] Number of patients with LDL cholesterol measured.
[c] The change from entry is the mean of within patient changes from entry for patients with both entry and Week 12 values and is not a simple difference of the entry and Week 12 mean values.
[d] Fasting

Clinical Trial Experience in Pediatric Patients

The safety and tolerability of atazanavir sulfate capsules with and without ritonavir have been established in pediatric patients at least 6 years of age from the open-label, multicenter clinical trial PACTG 1020A. Use of atazanavir sulfate in pediatric patients less than 6 years of age is under investigation.

The safety profile of atazanavir sulfate in pediatric patients (6 to less than 18 years of age) was comparable to that observed in clinical studies of atazanavir sulfate in adults. The most common Grade 2–4 adverse events (≥5%, regardless of causality) reported in pediatric patients were cough (21%), fever (19%), rash (14%), jaundice/scleral icterus (13%), diarrhea (8%), vomiting (8%), headache (7%), and rhinorrhea (6%). Asymptomatic second-degree atrioventricular block was reported in <2% of patients. The most common Grade 3–4 laboratory abnormality was elevation of total bilirubin (≥3.2 mg/dL) which occurred in 49% of pediatric patients. All other Grade 3–4 laboratory abnormalities occurred with a frequency of less than 3%. Both the frequency and severity of cardiac conduction abnormalities were greater in pediatric patients in this study than observed in clinical studies in adults.

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 sulfate /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 DF-emtricitabine were seropositive for hepatitis B and/or C at study entry. ALT levels >5 times ULN developed in 10% (6/60) of the atazanavir sulfate/ritonavir-treated patients, and 8% (4/50) of the lopinavir/ritonavir-treated patients. AST levels >5 times ULN developed in 10% (6/60) of the atazanavir sulfate/ritonavir-treated patients and none (0/50) of the lopinavir/ritonavir-treated patients.

In study AI424-045, 20 patients treated with atazanavir sulfate/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 ULN developed in 25% (5/20) of the atazanavir sulfate/ritonavir-treated patients and 6% (1/18) of the lopinavir/ritonavir-treated patients. AST levels > 5 times ULN developed in 10% (2/20) of the atazanavir sulfate/ritonavir-treated patients and 6% (1/18) of the lopinavir/ritonavir-treated patients (see **WARNINGS AND PRECAUTIONS: Hepatic/Biliary**).

In studies AI424-008 and AI424-034, 74 patients treated with 400 mg of atazanavir sulfate once daily, 58 who received efavirenz, and 12 who received nelfinavir were seropositive for hepatitis B and/or C at study entry. AST levels >5 times the upper limit of normal (ULN) developed in 9% of the atazanavir sulfate-treated patients, 5% of the efavirenz-treated patients, and 17% of the nelfinavir-treated patients. ALT levels >5 times ULN developed in 15% of the atazanavir sulfate-

treated patients, 14% of the efavirenz-treated patients, and 17% of the nelfinavir-treated patients. Within atazanavir and control regimens, no difference in frequency of bilirubin elevations was noted between seropositive and seronegative patients.

Post-market Adverse Drug Reactions

The following events have been identified during post approval use of atazanavir sulfate. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, or causal connection to atazanavir sulfate, or a combination of these factors.

Body as a Whole: edema

Cardiac disorders and vascular disorders: second-degree AV block, third-degree AV block, QTc prolongation, Torsades de Pointes, left bundle branch block

Gastrointestinal system: pancreatitis

Hepatic system: hepatic function abnormalities

Hepatobiliary disorders: cholelithiasis, cholecystitis, cholestasis

Immune system: angioedema

Metabolism and nutrition disorders: hyperglycemia, diabetes mellitus

Musculoskeletal system: arthralgia

Renal system: nephrolithiasis, interstitial nephritis, chronic kidney disease

Skin and appendages: pruritus, alopecia, maculopapular rash

DRUG INTERACTIONS

Serious Drug Interactions

Atazanavir is an inhibitor of CYP3A and UGT1A1. Coadministration of APO-ATAZANAVIR 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 APO-ATAZANAVIR without ritonavir is coadministered with drugs highly dependent on CYP2C8 with narrow therapeutic indices (eg, paclitaxel, repaglinide). When APO-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 APO-ATAZANAVIR is coadministered with ritonavir. See the complete prescribing information for NORVIR® (ritonavir) for information on drug interactions with ritonavir.

- Refer to CONTRAINDICATIONS
- Refer to **Table 13** for Drugs That Are Contraindicated or Not Recommended for Coadministration with APO-ATAZANAVIR.
- Refer to **Table 14** for Established and Other Potentially Significant Drug Interactions

Overview

Atazanavir is a metabolism-dependent CYP3A inhibitor, with a K_{inact} value of 0.05 to 0.06 min^{-1} and K_i value of 0.84 to 1.0 mcM. Atazanavir is also a direct inhibitor for UGT1A1 (K_i=1.9 mcM).

Coadministration of atazanavir and drugs primarily metabolized by CYP3A4 (e.g., calcium channel blockers, HMG CoA reductase inhibitors, immunosuppressants and phosphodiesterase (PDE5) inhibitors) or UGT1A1 (e.g., irinotecan) may result in increased plasma concentrations of the other drug that could increase or prolong both its therapeutic and adverse effects. Coadministration of atazanavir and drugs that induce CYP3A4, such as rifampin, may decrease atazanavir plasma concentrations and reduce its therapeutic effect. Coadministration of atazanavir and drugs that inhibit CYP3A4 may increase atazanavir plasma concentrations (see **Table 13** and **Table 14**, **DRUG INTERACTIONS**).

Clinically significant interactions are not expected between atazanavir and substrates of CYP2C19, CYP2C9, CYP2D6, CYP2B6, CYP2A6, CYP1A2, or CYP2E1. Atazanavir is a weak inhibitor of CYP2C8. Caution should be used when APO-ATAZANAVIR without ritonavir is coadministered with drugs highly dependent on CYP2C8 with narrow therapeutic indices (e.g. paclitaxel, repaglinide). When atazanavir sulfate with ritonavir is coadministered with substrates of CYP2C8, clinically significant interactions are not expected.

Atazanavir should not be administered concurrently with medications with narrow therapeutic windows that are substrates of CYP3A or UGT1A1 (see **CONTRAINDICATIONS**).

Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir are expected if antacids, buffered medications, H_2- receptor antagonists, and proton-pump inhibitors are administered with atazanavir.

Coadministration of atazanavir sulfate and PDE5 inhibitors has not been studied. Particular caution should be used when prescribing phosphodiesterase (PDE5) inhibitors for erectile dysfunction (i.e., sildenafil, tadalafil) in patients receiving protease inhibitors, including atazanavir sulfate. Coadministration of a protease inhibitor with a PDE5 inhibitor is expected to substantially increase PDE5 inhibitor concentrations and may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances, and priapism. Use with caution and monitor for adverse events (see **PRECAUTIONS**, Information for Patients, and the complete Product Monographs for sildenafil, and tadalafil).

Vardenafil should not be coadministered with APO-ATAZANAVIR (with and without ritonavir) (see **Table 13**).

For the treatment of pulmonary arterial hypertension, coadministration of sildenafil with APO-ATAZANAVIR is contraindicated, and coadministration of tadalafil and APO-ATAZANAVIR is not recommended (see **Table 13**).

Simvastatin and lovastatin are contraindicated with APO-ATAZANAVIR (see **Table 13**). Caution should be exercised if HIV protease inhibitors, including APO-ATAZANAVIR, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A pathway. Use the lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with APO-ATAZANAVIR (with and without ritonavir). The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including APO-ATAZANAVIR, are used in combination with these drugs.

Midazolam is extensively metabolised by CYP3A4. Although not studied, coadministration of midazolam with APO-ATAZANAVIR may cause a large increase in the concentration of this benzodiazepine. Increases in benzodiazepine concentration are expected to be significantly higher with oral administration of the benzodiazepine, relative to parenteral. Therefore, APO-ATAZANAVIR should not be coadministered with orally administered midazolam, whereas caution should be used with coadministration of APO-ATAZANAVIR and parenteral midazolam. If APO-ATAZANAVIR is coadministered with parenteral midazolam, a close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.

Concomitant use of APO-ATAZANAVIR and St. John's wort (*Hypericum perforatum*), or products containing St. John's wort, is contraindicated. Coadministration of protease inhibitors, including APO-ATAZANAVIR, with St. John's wort is expected to substantially decrease concentrations of the protease inhibitor and may result in suboptimal levels of atazanavir and lead to loss of virologic response and possible resistance to atazanavir or to the class of protease inhibitors.

The magnitude of CYP3A4-mediated drug interactions (effect on atazanavir or effect on coadministered drug) may change when APO-ATAZANAVIR is coadministered with ritonavir, a potent CYP3A4 inhibitor. The Product Monograph for ritonavir should be consulted for information on drug interactions with ritonavir.

Atazanavir has the potential to prolong the PR interval of the electrocardiogram in some patients. Caution should be used when coadministering APO-ATAZANAVIR with medicinal products known to induce PR interval prolongation (eg, atenolol, diltiazem).

The exposure to buprenorphine and the active metabolite, norbuprenorphine, were significantly increased when coadministered with atazanavir (with or without ritonavir), due to CYP3A4 and UGT1A1 inhibition. Coadministration of buprenorphine and APO-ATAZANAVIR/ritonavir

warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered. There was no significant effect on atazanavir plasma concentration when atazanavir sulfate plus ritonavir were coadministered with buprenorphine. Coadministration of buprenorphine and atazanavir sulfate without ritonavir may substantially decrease atazanavir plasma concentrations. APO-ATAZANAVIR without ritonavir should not be coadministered with buprenorphine.

A drug interaction study in healthy subjects has shown that ritonavir significantly increases plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Concomitant use of atazanavir sulfate with ritonavir and fluticasone propionate is expected to produce the same effects. Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression, have been reported during post-marketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Therefore, coadministration of fluticasone propionate and APO-ATAZANAVIR/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Exposure to rifabutin was significantly increased when coadministered with atazanavir (with or without ritonavir). Increased monitoring for neutropenia should be performed if these drugs are coadministered. Dosage reduction of rifabutin is recommended (see **Table 14**).

Drugs that are contraindicated or not recommended for coadministration with APO-ATAZANAVIR are included in **Table 13**. Drugs with established and other potentially significant drug interactions are included in **Table 14**. 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 13 Drugs That Are Contraindicated or Not Recommended for Coadministration with APO-ATAZANAVIR

Drug Class: Specific Drugs	Clinical Comment
Alpha 1-adrenoreceptor antagonist: alfuzosin	CONTRAINDICATED due to potential for increased alfuzosin concentrations which can result in hypotension.
Anticoagulants: • Direct-acting oral anticoagulants (DOACs) - rivaroxaban apixaban	 APO-ATAZANAVIR /ritonavir: CONTRAINDICATED if APO-ATAZANAVIR /ritonavir is coadministered with rivaroxaban due to potential for severe bleeding to occur. APO-ATAZANAVIR /ritonavir: CONTRAINDICATED if APO-ATAZANAVIR /ritonavir is coadministered with apixaban due to potential for severe bleeding to occur.

Table 13 Drugs That Are Contraindicated or Not Recommended for Coadministration with APO-ATAZANAVIR

Drug Class: Specific Drugs	Clinical Comment
Antiarrhythmics: quinidine	APO-ATAZANAVIR/ritonavir: CONTRAINDICATED if APO-ATAZANAVIR is coadministered with ritonavir due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antineoplastics: irinotecan	Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan resulting in increased irinotecan toxicities.
Antimycobacterials: rifampin	CONTRAINDICATED since rifampin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect and development of resistance.
Antipsychotics: quetiapine lurasidone pimozide	Coadministration of quetiapine and APO-ATAZANAVIR is not recommended. Due to CYP3A4 inhibition by APO-ATAZANAVIR, concentrations of quetiapine are expected to increase, which can result in serious and/or life-threatening adverse reactions. If coadministration is necessary, monitoring and quetiapine dose reduction may be required. CONTRAINDICATED due to potential for serious and/or life-threatening reactions if APO-ATAZANAVIR is coadministered with ritonavir. CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Benzodiazepines: triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
Endothelin receptor antagonist: bosentan	Coadministration of bosentan and APO-ATAZANAVIR without ritonavir is not recommended.
Ergot Derivatives: dihydroergotamine, ergotamine, ergonovine, methylergonovine	CONTRAINDICATED due to 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.
Proton Pump Inhibitors omeprazole	Coadministration of omeprazole (40 mg once daily) with atazanavir sulfate and ritonavir (300/100 mg once daily) resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C_{max}, and C_{min}). Coadministration of omeprazole (20 mg once daily) with an increased dose of atazanavir sulfate and ritonavir (400/100 mg once daily) in healthy volunteers

Table 13 Drugs That Are Contraindicated or Not Recommended for Coadministration with APO-ATAZANAVIR

Drug Class: Specific Drugs	Clinical Comment
	resulted in a decrease of approximately 30% in the AUC, C_{max} and C_{min} of atazanavir relative to atazanavir sulfate and ritonavir (300/100 mg once daily) without omeprazole. This decrease in AUC, C_{max} and C_{min} was not mitigated when an increased dose of atazanavir sulfate and ritonavir (400/100 mg once daily) was temporally separated from omeprazole by 12 hours. Although not studied, similar results are expected with other proton pump inhibitors. This decrease in atazanavir exposure might negatively impact the efficacy of atazanavir. Coadministration of APO-ATAZANAVIR with proton pump inhibitors is not recommended. If the combination of APO-ATAZANAVIR with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of APO-ATAZANAVIR to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded.
Hepatitis C Direct-Acting Antivirals elbasvir/grazoprevir	CONTRAINDICATED: Coadministration of atazanavir sulfate with grazoprevir-containing products, including elbasvir/grazoprevir fixed-dose combination, is contraindicated because of the increase in grazoprevir and elbasvir plasma concentrations and the potential for increase in risk of ALT elevations associated with the increase in grazoprevir concentrations.
glecaprevir/pibrentasvir sofosbuvir/velpatasvir/voxilaprevir	CONTRAINDICATED: Coadministration of APO-ATAZANAVIR with glecaprevir/pibrentasvir is contraindicated because of the increased risk of ALT elevations due to an increase in glecaprevir and pibrentasvir plasma concentrations. Coadministration of the fixed dose combination sofosbuvir/velpatasvir/voxilaprevir with APO-ATAZANAVIR resulted in increased voxilaprevir plasma concentrations. Coadministration of voxilaprevir with APO-ATAZANAVIR is not recommended.
Lipid-Modifying Agents: HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	CONTRAINDICATED due to potential for serious reactions such as myopathy including rhabdomyolysis.

Table 13 Drugs That Are Contraindicated or Not Recommended for Coadministration with APO-ATAZANAVIR

Drug Class: Specific Drugs	Clinical Comment
Other Lipid-Modifying Agents: lomitapide	CONTRAINDICATED: Coadministration of APO-ATAZANAVIR because of the potential for risk of markedly increased transaminase level and hepatotoxicity associated with increased plasma concentrations of lomitapide. The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir (see WARNINGS AND PRECAUTIONS - Drug Interaction).
Inhaled beta agonists: salmeterol	Concomitant use of salmeterol and atazanavir sulfate may result in increased cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. Salmeterol and APO-ATAZANAVIR should not be coadministered.
Protease Inhibitors: indinavir	CONTRAINDICATED Both atazanavir sulfate and indinavir are associated with indirect (unconjugated) hyperbilirubinemia. Combinations of these drugs have not been studied and coadministration of APO-ATAZANAVIR and indinavir is not recommended.
Herbal Products: St. John's wort (*Hypericum perforatum*)	CONTRAINDICATED Patients taking APO-ATAZANAVIR should not use products containing St. John's wort (*Hypericum perforatum*) because coadministration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance.
PDE5 inhibitors: *For* erectile dysfunction: vardenafil	Vardenafil should not be coadministered with APO-ATAZANAVIR (with or without ritonavir).
For pulmonary arterial hypertension: sildenafil tadalafil	Sildenafil is CONTRAINDICATED in combination with APO-ATAZANAVIR for the treatment of pulmonary arterial hypertension since a safe and effective dose has not been established. Coadministration of APO-ATAZANAVIR and tadalafil for the treatment of pulmonary hypertension is not recommended. There is an increased potential for PDE5 inhibitor-associated adverse effects when PDE5 inhibitors are administered with APO-ATAZANAVIR.

Table 14 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir sulfate or Concomitant Drug	Clinical Comment
Human Immunodeficiency Virus Antiviral Agents		
Nucleoside Reverse Transcriptase Inhibitors (NRTIs): • didanosine buffered formulations	↓ atazanavir	Coadministration with atazanavir sulfate did not alter exposure to didanosine; however, exposure to atazanavir was markedly decreased by coadministration of atazanavir sulfate with didanosine buffered tablets (presumably due to the increase in gastric pH caused by buffers in the didanosine tablets). Atazanavir should be given with food, 2 hours before or 1 hour after didanosine buffered formulations (which are given on an empty stomach).
• didanosine EC formulation	↓ atazanavir ↓ didanosine	Due to the different food restrictions (didanosine EC given without food and atazanavir given with food) they should be administered at different times. Administration of the enteric-coated formulation of didanosine with atazanavir or atazanavir/ritonavir and a light meal decreased exposure to didanosine.
Nucleotide Reverse Transcriptase Inhibitors (NRTIs): tenofovir DF	↓ atazanavir ↑ tenofovir	Atazanavir sulfate as a single PI, without ritonavir, may be less effective due to decreased atazanavir concentrations in patients taking atazanavir sulfate and tenofovir DF (see **Table 22**, **DETAILED PHARMACOLOGY**, **Drug-Drug Interactions**). If APO-ATAZANAVIR is to be coadministered with tenofovir **DF**, it is recommended that APO-ATAZANAVIR 300 mg with ritonavir 100 mg be coadministered with tenofovir DF 300 mg (see **DOSAGE AND ADMINISTRATION**). APO-ATAZANAVIR without ritonavir should not be coadministered with tenofovir DF. Atazanavir increases tenofovir concentrations. Higher tenofovir

Table 14 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir sulfate or Concomitant Drug	Clinical Comment
		concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving atazanavir and tenofovir DF should be monitored for tenofovir-associated adverse events. No dose adjustment for tenofovir DF is recommended.
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs): • efavirenz	↓ atazanavir	Efavirenz decreases atazanavir exposure (see **Table 22**, **DETAILED PHARMACOLOGY**, **Drug-Drug Interactions**). **For treatment-naive patients:** If APO-ATAZANAVIR is combined with efavirenz, APO-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. **For Treatment-experience patients:** Do not coadminister APO-ATAZANAVIR with efavirenz in treatment-experienced patients due to decreased atazanavir exposure.
• nevirapine	↓ atazanavir	Nevirapine, an inducer of CYP3A4, substantially decreases atazanavir exposure. There is a potential risk for nevirapine associated toxicity due to the increased nevirapine exposures. Do not coadminister APO-ATAZANAVIR with nevirapine.
Protease Inhibitor PIs: • boceprevir	↓ atazanavir	Exposure to atazanavir was decreased when boceprevir at 800 mg three times daily was coadministered with atazanavir sulfate 300 mg and ritonavir 100 mg once daily while exposure to boceprevir was not significantly altered.

Table 14 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir sulfate or Concomitant Drug	Clinical Comment
• saquinavir (soft gelatin capsules)	↑saquinavir	The safety and efficacy of this combination have not been established. In a clinical study, saquinavir 1200 mg coadministered with atazanavir sulfate 400 mg and tenofovir 300 mg (all given once daily) plus a nucleoside reverse transcriptase inhibitor did not provide adequate efficacy (see **CLINICAL TRIALS**).
• ritonavir	↑ atazanavir	If APO-ATAZANAVIR is coadministered with ritonavir, it is recommended that APO-ATAZANAVIR 300 mg once daily be given with ritonavir 100 mg once daily with food (see **DOSAGE AND ADMINISTRATION**). See the complete product monograph for NORVIR® (ritonavir) for information on drug interactions with ritonavir.
• Other protease inhibitors	↑ Other PIs	Although not studied, the coadministration of atazanavir sulfate plus ritonavir with other protease inhibitors would be expected to increase exposure to the other protease inhibitor and 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 sulfate. APO-ATAZANAVIR should be administered 2 hours before or 1 hour after these medications.
Antiarrhythmics:	↑ amiodarone, lidocaine (systemic), quinidine	Coadministration with atazanavir sulfate 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 APO-ATAZANAVIR. Quinidine is

Table 14 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir sulfate or Concomitant Drug	Clinical Comment
		contraindicated when APO-ATAZANAVIR is coadministered with ritonavir.
Anticoagulants: • Vitamin K Antagonists • Direct-acting oral anticoagulants (DOACs)	↑ warfarin ↑ dabigatran, edoxaban ↑ rivaroxaban ↑ apixaban	Coadministration with APO-ATAZANAVIR has the potential to produce serious and/or life-threatening bleeding and has not been studied. It is recommended that INR (International Normalized Ratio) be monitored. Concomitant use of APO-ATAZANAVIR and ritonavir, a strong CYP3A4/P-gp inhibitor, with either dabigatran or edoxaban, may result in an increased exposure of the respective DOAC, which could lead to an increased risk of bleeding. Refer to the respective DOAC prescribing information regarding dosing instructions for coadministration with P-gp inhibitors. Concomitant use of APO-ATAZANAVIR, a CYP3A4 inhibitor, and rivaroxaban, may result in increased exposure of rivaroxaban, which could lead to an increased risk of bleeding. Close monitoring is recommended when rivaroxaban is coadministered with APO-ATAZANAVIR. Concomitant use of APO-ATAZANAVIR, a CYP3A4 inhibitor, and apixaban may result in increased exposure of apixaban, which could lead to an increased risk of bleeding. Close monitoring is recommended when apixaban is coadministered with APO-ATAZANAVIR.

Table 14 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir sulfate or Concomitant Drug	Clinical Comment
Antidepressants:	↑ tricyclic antidepressants	Coadministration with APO-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 APO-ATAZANAVIR.
	↑ trazodone	Concomitant use of trazodone and atazanavir sulfate with or without ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as APO-ATAZANAVIR, the combination should be used with caution and a lower dose of trazodone should be considered.
Antiepileptics: • carbamazepine	↓ atazanavir ↑ carbamazepine	Plasma concentrations of atazanavir may be decreased when carbamazepine is administered with atazanavir sulfate without ritonavir. Coadministration of carbamazepine and APO-ATAZANAVIR without ritonavir is not recommended. Ritonavir may increase plasma levels of carbamazepine. If patients beginning treatment with APO-ATAZANAVIR /ritonavir have been titrated to a stable dose of carbamazepine, a dose reduction for carbamazepine may be necessary.
• phenytoin, phenobarbital	↓ atazanavir ↓ phenytoin ↓ phenobarbital	Plasma concentrations of atazanavir may be decreased when phenytoin or phenobarbital is administered with atazanavir sulfate without ritonavir. Coadministration of phenytoin or phenobarbital and APO-ATAZANAVIR without ritonavir is not recommended. Ritonavir may decrease plasma levels of phenytoin and phenobarbital. When APO-

Table 14 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir sulfate or Concomitant Drug	Clinical Comment
		ATAZANAVIR with ritonavir is coadministered with either phenytoin or phenobarbital, a dose adjustment of phenytoin or phenobarbital may be required.
• lamotrigine	↓ lamotrigine	Coadministration of lamotrigine and APO-ATAZANAVIR ***with*** ritonavir may decrease lamotrigine plasma concentrations. Dose adjustment of lamotrigine may be required when coadministered with APO-ATAZANAVIR and ritonavir. Coadministration of lamotrigine and atazanavir sulfate ***without*** ritonavir is not expected to decrease lamotrigine plasma concentrations. No dose adjustment of lamotrigine is required when coadministered with APO-ATAZANAVIR without ritonavir.
Antifungals: • ketoconazole, itraconazole	↑ atazanavir ↑ ritonavir ↑ ketoconazole ↑ itraconazole	Coadministration of ketoconazole has only been studied with atazanavir sulfate 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 with caution with APO-ATAZANAVIR/ritonavir.
• voriconazole	***Atazanavir sulfate / ritonavir in subjects with a functional CYP2C19 allele:*** ↓ atazanavir ↓ voriconazole	Voriconazole should not be administered to patients receiving APO-ATAZANAVIR and ritonavir (100 mg once daily) unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Patients should be carefully monitored for voriconazole-associated adverse events and loss of either voriconazole or atazanavir efficacy during the co-administration of voriconazole and APO-ATAZANAVIR/ritonavir.

Table 14 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir sulfate or Concomitant Drug	Clinical Comment
	Atazanavir sulfate / ritonavir in subjects without a functional CYP2C19 allele: ↓ atazanavir ↑ voriconazole	Coadministration of voriconazole with atazanavir sulfate (without ritonavir) may increase atazanavir concentrations; however, no data are available. Coadministration of voriconazole with high-dose ritonavir (400 mg every 12 hours) is contraindicated due to a significant reduction in voriconazole plasma concentrations and possible loss of effect. Please see the NORVIR® and VFEND* Product Monograph for additional information.
Antigout: • colchicine	↑ colchicine	APO-ATAZANAVIR should not be coadministered with colchicine to patients with renal or hepatic impairment. Exposure to colchicine may be increased when coadministered with APO-ATAZANAVIR. Colchicine is a CYP3A4 substrate. *Recommended dosage of colchicine when administered with* APO-ATAZANAVIR: *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. *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. If the original regimen was 0.6 mg *once* a day, the regimen should be adjusted to 0.3 mg once every other day.

Table 14 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir sulfate or Concomitant Drug	Clinical Comment
		Treatment of familial Mediterranean fever (FMF): Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimycobacterials:	↑ rifabutin	A rifabutin dose reduction of up to 75% (eg, 150 mg every other day or 3 times per week) is recommended. Concomitant use of atazanavir sulfate with or without ritonavir and rifabutin may result in decreased neutrophil count or neutropenia. Increased monitoring for neutropenia should be performed if these drugs are coadministered. Further dosage reduction of rifabutin may be necessary.
Antipsychotics: quetiapine	↑ quetiapine	APO-ATAZANAVIR should not be used in combination with quetiapine. Due to CYP3A4 inhibition by APO-ATAZANAVIR, concentrations of quetiapine are expected to increase, which can result in serious and/or life-threatening adverse reactions. If coadministration is necessary, monitoring and quetiapine dose reduction may be required (see **WARNINGS AND PRECAUTIONS**, **General**).
• lurasidone	*Atazanavir sulfate* ↑ lurasidone	***APO-ATAZANAVIR without ritonavir*** If coadministration is necessary, reduce the lurasidone dose. Refer to the lurasidone prescribing information for concomitant use with moderate CYP3A4 inhibitors.
	Atazanavir sulfate /ritonavir ↑ lurasidone	***APO-ATAZANAVIR /ritonavir*** Use of lurasidone is contraindicated.
Benzodiazepines: Parenterally administered midazolam	↑ midazolam	If atazanavir sulfate is coadministered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.

Table 14 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir sulfate or Concomitant Drug	Clinical Comment
Endothelin receptor antagonists: • bosentan	↓ atazanavir ↑ bosentan	Bosentan is metabolized by CYP3A4 and is an inducer of CYP3A4. Plasma concentrations of atazanavir may be decreased when bosentan is administered with APO-ATAZANAVIR without ritonavir. Coadministration of bosentan and APO-ATAZANAVIR without ritonavir is not recommended. *Coadministration of bosentan in patients on APO-ATAZANAVIR/ ritonavir:* For patients who have been receiving APO-ATAZANAVIR/ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based on individual tolerability. *Coadministration of APO-ATAZANAVIR/ ritonavir in patients on bosentan:* Discontinue bosentan at least 36 hours before starting APO-ATAZANAVIR/ritonavir. At least 10 days after starting APO-ATAZANAVIR/ritonavir, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.
Calcium channel blockers:	↑ diltiazem and desacetyl-diltiazem ↑ felodipine, nifedipine, nicardipine, and verapamil	A dose reduction of diltiazem by 50% should be considered. Caution is warranted. Coadministration of 400 mg atazanavir once daily and diltiazem 180 mg once daily had an added effect on the PR interval. ECG monitoring is recommended. Coadministration of atazanavir sulfate/ritonavir with diltiazem has not been studied. Caution is warranted. Dose titration of the calcium channel blocker should be

Table 14 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir sulfate or Concomitant Drug	Clinical Comment
		considered. ECG monitoring is recommended.
PDE5 inhibitors:	↑ sildenafil ↑ tadalafil ↑vardenafil	Coadministration of atazanavir sulfate and PDE5 inhibitors has not been studied. Coadministration of a protease inhibitor with a PDE5 inhibitor is expected to substantially increase the PDE5 inhibitor concentration and may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances and priapism. 1. *For the treatment of erectile dysfunction* • Vardenafil should not be coadministered with APO-ATAZANAVIR (with or without ritonavir). • Sildenafil: reduced doses (25 mg every 48 hours) are recommended when coadministered with APO-ATAZANAVIR with or without ritonavir. • Tadalafil: reduced doses (10 mg every 72 hours) are recommended when coadministered with APO-ATAZANAVIR with or without ritonavir. Use with caution and monitor adverse events. 2. *For the treatment of pulmonary arterial hypertension* • Use of sildenafil for the treatment of pulmonary arterial hypertension is contraindicated with APO-ATAZANAVIR (see **CONTRAINDICATIONS**, **Table 1**).

Table 14 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir sulfate or Concomitant Drug	Clinical Comment
		Coadministration of APO-ATAZANAVIR and tadalafil for the treatment of pulmonary hypertension is not recommended (**Table 13**)
H_2-Receptor Antagonists	↓ atazanavir	Plasma concentrations of atazanavir were substantially decreased when atazanavir sulfate 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. Although not studied, similar results are expected with other H_2-receptor antagonists. **In treatment-naive patients:** The H_2-receptor antagonist dose should not exceed a 40 mg dose equivalent of famotidine twice daily. APO-ATAZANAVIR 300 mg with ritonavir 100 mg once daily (all as a single dose with food) should be administered simultaneously with, and/or at least 10 hours after, the dose of the H2-receptor antagonist. **In treatment-experienced patients:** The H_2-receptor antagonist dose should not exceed a dose equivalent to famotidine 20 mg twice daily, and the APO-ATAZANAVIR and ritonavir doses should be administered simultaneously with, and/or at least 10 hours after, the dose of the H_2-receptor antagonist. • APO-ATAZANAVIR 300 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with an H_2-receptor • APO-ATAZANAVIR 400 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with both tenofovir DF and an H_2-receptor antagonist.

Table 14 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir sulfate or Concomitant Drug	Clinical Comment
HMG-CoA Reductase Inhibitors:	↑ atorvastatin ↑ rosuvastatin	The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including APO-ATAZANAVIR, are used in combination with these drugs. Caution should be exercised. Use the lowest possible dose with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with APO-ATAZANAVIR (with and without ritonavir).
Immunosuppressants:	↑ cyclosporin, sirolimus, tacrolimus	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with APO-ATAZANAVIR.
Inhaled/nasal corticosteroids (interaction with ritonavir)	↑ fluticasone propionate	In healthy volunteers, ritonavir significantly increased plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Concomitant use of atazanavir sulfate/ritonavir with fluticasone propionate is expected to produce the same effects. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported when ritonavir was coadministered with inhaled or intranasally administered fluticasone propionate. These effects could also occur with other corticosteroids metabolized via the cytochrome P450 3A pathway, eg, budesonide. Therefore, concomitant use of APO-ATAZANAVIR/ritonavir and fluticasone propionate or other glucocorticoids that are metabolized by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. Concomitant use of fluticasone propionate and atazanavir sulfate (without ritonavir) may increase plasma concentrations of fluticasone

Table 14 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir sulfate or Concomitant Drug	Clinical Comment
		propionate. Use with Caution. Consider alternatives to fluticasone propionate, particularly for long-term use.
Macrolide Antibiotics:	↑ clarithromycin ↓ 14-OH clarithromycin ↑ atazanavir	Increased concentrations of clarithromycin may cause QTc prolongations; therefore, a dose reduction of clarithromycin by 50% should be considered when it is coadministered with APO-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. Caution is advised during coadministration as a high incidence of rash (20%) was observed in the pharmacokinetic trial in healthy volunteers. Coadministration of atazanavir sulfate/ritonavir with clarithromycin has not been studied.
Oral Contraceptives: ethinyl estradiol and norgestimate or norethindrone	↑ ethinyl estradiol ↑ norethindrone[b] ↓ ethinyl estradiol ↑ norgestimate[c]	Mean concentrations of ethinyl estradiol and norethindrone, when coadministered with atazanavir sulfate, are increased. Administration of atazanavir sulfate /ritonavir with ethinyl estradiol and norgestimate decreases the mean concentration of ethinyl estradiol, and increases the mean concentration of 17- deacetyl norgestimate, the active metabolite of norgestimate. If an oral contraceptive is administered with APO-ATAZANAVIR plus ritonavir, it is recommended that the oral contraceptive contain at least 30 mcg of ethinyl estradiol. If APO-ATAZANAVIR is administered without ritonavir, the oral contraceptive

Table 14 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir sulfate or Concomitant Drug	Clinical Comment
		should contain no more than 30 mcg of ethinyl estradiol. Use with caution as the effect of increases in concentration of the progestational agent are unknown and could increase the risk of acne, dyslipidemia, and insulin resistance. Coadministration of atazanavir sulfate or atazanavir sulfate/ritonavir with other hormonal contraceptives (eg, contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestagens other than norethindrone or norgestimate, or less than 25 mcg of ethinyl estradiol have not been studied; therefore alternative methods of contraception are recommended.

[a] For magnitude of interactions see **DETAILED PHARMACOLOGY**: **Drug-Drug Interactions**
[b] In combination with atazanavir 400 mg once daily.
[c] In combination with atazanavir 300 mg and ritonavir 100 mg once daily.

Based on known metabolic profiles, clinically significant drug interactions are not expected between atazanavir sulfate and fluvastatin, pravastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin or erythromycin. Coadministration of methadone and atazanavir sulfate in subjects chronically treated with methadone did not result in clinically relevant interactions. Atazanavir sulfate does not interact with substrates of CYP2D6 (eg, nortriptyline, desipramine, metoprolol). Additionally, no clinically significant drug interaction was observed when atazanavir sulfate was coadministered with fluconazole or acetaminophen.

Refer to Norvir® Product Monograph for drug interaction of ritonavir with these drugs before prescribing APO-ATAZANAVIR 300 mg with ritonavir 100 mg.

DOSAGE AND ADMINISTRATION

Recommended Adult Dose

Therapy-Naïve Patients

- APO-ATAZANAVIR 300 mg once daily taken with ritonavir 100 mg once daily taken with food.

OR

- APO-ATAZANAVIR 400 mg (two 200-mg capsules) once daily (without ritonavir) taken with food, for patients who are unable to tolerate ritonavir.

Therapy-Experienced Patients

- APO-ATAZANAVIR 300 mg once daily taken with ritonavir 100 mg once daily taken with food.

Capsules should not be opened, they should be swallowed whole with water.

Recommended Pediatric Dose (from 6 to 18 years of age)

The recommended dosage of APO-ATAZANAVIR for pediatric patients (6 to less than 18 years of age) is based on body weight as shown below in **Table 15** and should not exceed the recommended adult dosage. APO-ATAZANAVIR Capsules must be taken with food. The data are insufficient to recommend dosing of APO-ATAZANAVIR for any of the following: (1) patients less than 6 years of age, (2) without ritonavir in patients less than 13 years of age, and (3) patients less than 40 kg receiving concomitant tenofovir DF, H_2-receptor antagonists, or proton-pump inhibitors.

Table 15 Dosage for Pediatric Patients (6 to less than 18 years of age)[a] for Atazanavir sulfate Capsules with ritonavir

Body Weight		Atazanavir sulfate dose (mg)	ritonavir dose [b] (mg)
(kg)	(lbs)		
15 to less than 20	33 to less than 44	150	100[c]
20 to less than 40	44 to less than 88	200	100
at least 40	at least 88	300	100

[a] The atazanavir sulfate and ritonavir dose should be taken once daily with food.

[b] Ritonavir capsules, tablets or oral solution.

[c] Ritonavir oral solution no lower than 80 mg and not more than 100 mg may be used for pediatric patients from 15 kg to less than 20 kg who cannot swallow ritonavir capsules/tablets.

For treatment-naive patients at least 13 years of age and at least 40 kg, who are unable to tolerate ritonavir, the recommended dose is APO-ATAZANAVIR 400 mg (without ritonavir) once daily with food. For patients at least 13 years of age and at least 40 kg receiving concomitant tenofovir DF, H_2-receptor antagonists, or proton-pump inhibitors, APO-ATAZANAVIR should not be administered without ritonavir.

Dosing Considerations

Concomitant Therapy: (See **ACTION AND CLINICAL PHARMACOLOGY**: **Drug-Drug Interactions**, **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**.)

Ritonavir: Efficacy and safety of atazanavir sulfate 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. There are limited safety data from controlled trials for atazanavir sulfate plus ritonavir regimens without tenofovir DF. (See **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**.)

Efavirenz - Therapy-Naïve Patients:
If APO-ATAZANAVIR is combined with efavirenz, APO-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.

Efavirenz - Therapy-Experienced Patients:
Do not coadminister APO-ATAZANAVIR with efavirenz in treatment-experienced patients due to decreased atazanavir exposure.

Didanosine: When coadministered with didanosine buffered formulations, APO-ATAZANAVIR should be given (with food) two hours before or one hour after didanosine.

Tenofovir disoproxil fumarate (DF): If coadministered with tenofovir DF, it is recommended that 300 mg of APO-ATAZANAVIR and ritonavir 100 mg be given with tenofovir DF 300 mg (together as single daily doses with food). There are limited safety data from controlled trials for atazanavir sulfate plus ritonavir regimens without tenofovir DF. APO-ATAZANAVIR without ritonavir should not be coadministered with tenofovir DF. (See **DRUG INTERACTIONS**.)

Dose Adjustments:

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 APO-ATAZANAVIR. Treatment-naive patients with end stage renal disease managed with hemodialysis should receive APO-ATAZANAVIR 300 mg with ritonavir 100 mg. APO-ATAZANAVIR, with or without ritonavir, should not be used in antiretroviral-treatment experienced patients with end stage renal disease managed with hemodialysis. APO-ATAZANAVIR without ritonavir should not be administered to treatment-naive patients managed with hemodialysis. (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions**).

Patients with Hepatic Impairment
APO-ATAZANAVIR 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. APO-ATAZANAVIR should not be used in patients with severe hepatic impairment (Child-Pugh

Class C). Atazanavir sulfate/ritonavir has not been studied in subjects with hepatic impairment and is not recommended. (See **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary**.)

Pregnant Women
APO-ATAZANAVIR should not be administered without ritonavir.

During pregnancy:
For pregnant patients, no dose adjustment is required based on a PK study: Atazanavir sulfate 300 mg with ritonavir 100 mg (see Pregnancy under **ACTION AND CLINICAL PHARMACOLOGY** and **CLINICAL TRIALS** sections) with the following exception:

For treatment-experienced pregnant women during the second or third trimester, when APO-ATAZANAVIR is coadministered with either an H_2-receptor antagonist ***or*** tenofovir DF, APO-ATAZANAVIR 400 mg with ritonavir 100 mg once daily is recommended. There are insufficient data to recommend a atazanavir sulfate dose for use with ***both*** an H_2-receptor antagonist ***and*** tenofovir DF in treatment-experienced women.

During postpartum:
No dose adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir exposures could be higher during the first 2 months after delivery.

Missed Dose
If a dose of APO-ATAZANAVIR is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped, the patient should not double the next dose.

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

Administration of activated charcoal may be used to aid in removal of unabsorbed drug. 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. 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 medicine.

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 58.4 g of atazanavir in an HIV-infected patient (146 times the 400 mg recommended dose) was associated with asymptomatic bilateral bundle branch 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 cardiac conduction abnormalities, including PR and/or QT interval prolongations, may be observed. (See **WARNINGS AND PRECAUTIONS**: **Cardiovascular**, and **DETAILED PHARMACOLOGY**: **Electrocardiogram**.)

ACTION AND CLINICAL 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.

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.

Table 16 Steady-State Pharmacokinetics of Atazanavir in Healthy Adult 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)

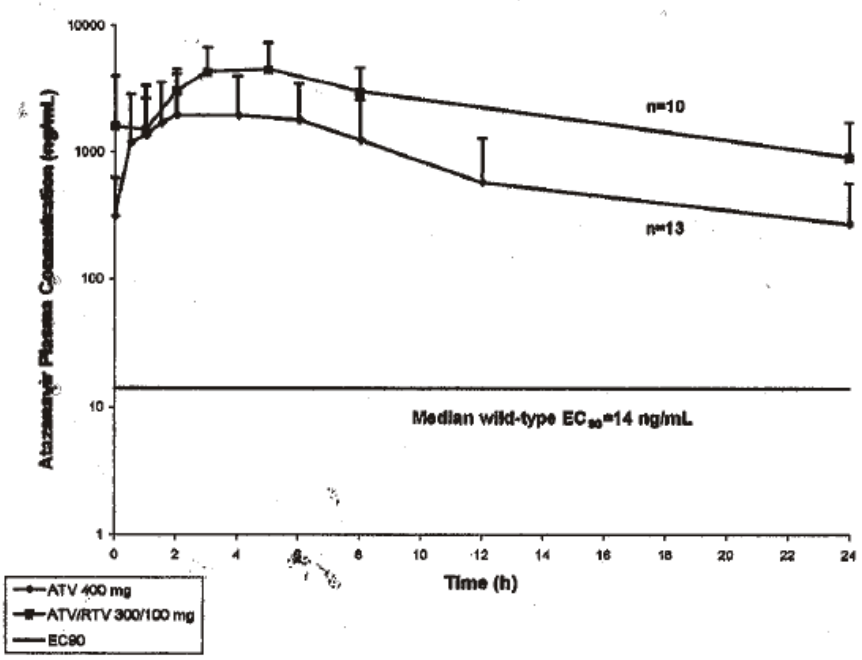
[a] n = 26
[b] n = 12

Absorption

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

Figure 1 displays the mean plasma concentrations of atazanavir on Day 29 (steady state) following 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



Food Effect

Administration of a single 400-mg dose of atazanavir with a light meal (357 kcal, 8.2 g fat, 10.6 g protein) resulted in a 70% increase in AUC and 57% increase in C_{max} relative to the fasting state. Administration of a single 400-mg dose of atazanavir with a high fat meal (721 kcal, 37.3 g fat, 29.4 g protein) resulted in a mean increase in AUC of 35% with no change in C_{max} relative to the fasting state. Administration of atazanavir with either a light meal or high-fat meal decreased the coefficient of variation of AUC and C_{max} by approximately one half compared to the fasting state. Thus, atazanavir is taken with food in order to enhance its bioavailability and reduce the pharmacokinetic variability.

Coadministration of atazanavir and ritonavir with food optimizes the bioavailability of atazanavir. Coadministration of a single 300-mg dose of atazanavir and a 100-mg dose of ritonavir with a light meal (336 total kcal, 5.1 g fat, 9.3 g protein and 63.3 g carbohydrates) 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. Coadministration with a high-fat meal (951 total kcal, 54.7 g fat, 35.9 g protein and 77.9 g carbohydrates) 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 to 5.0 hours. Coadministration of

atazanavir with ritonavir with either a light or a high-fat meal decreased the coefficient of variation of 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 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
Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that atazanavir is principally metabolized by CYP3A4 isozyme to oxygenated metabolites, which are then excreted in the bile as either free or glucuronidated metabolites. Additional minor metabolic pathways consist of N-dealkylation, hydrolysis and oxygenation with dehydrogenation.
Two minor metabolites of atazanavir in plasma have been characterized. Neither metabolite demonstrated *in vitro* antiviral activity.

Elimination
Following a single 400-mg dose of ^{14}C-atazanavir, 79% and 13% of the total radioactivity was recovered in the feces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the feces and 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.

Electrocardiogram: Effect on PR and QT intervals
Concentration - and dose - dependent prolongation of the PR interval in the electrocardiogram has been observed in healthy volunteers receiving atazanavir. In a placebo-controlled study (AI424-076), the mean (+ / -SD) maximum change in PR interval from the pre-dose value was 24 (+ / -15 msec) following oral dosing with 400 mg of atazanavir (n = 65) compared to 13 (+ 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 pharmacodynamic interaction in humans between atazanavir and other drugs that prolong the PR interval of the electrocardiogram (see **WARNINGS AND PRECAUTIONS**).

Electrocardiographic 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.

Special Populations and Conditions

Age/Gender/Race
A study of the pharmacokinetics of atazanavir was performed in young (n=29; 18-40 years) and elderly (n=30; ≥65 years) healthy subjects. There were no clinically important pharmacokinetic differences observed due to age or gender. There are insufficient data to determine whether there are any effects of race on the pharmacokinetics of atazanavir.

Pediatrics (from 6 to 18 years of age)
The pharmacokinetic data from pediatric patients receiving atazanavir capsules with ritonavir based on body surface area are presented in **Table 17**.

Table 17 Steady-State Pharmacokinetics of Atazanavir with ritonavir in HIV Infected Pediatric Patients (6 to 18 years of age) in the Fed State

	205 mg/m^2 atazanavir with 100 mg/m^2 ritonavir once daily	
	Age range (years)	
	At least 6 to 13 (n=17)	**At least 13 to 18 (n=10)**
Dose mg Median [min-max]	200 [150-400]	400 [250-500]
C_{max} ng/mL Geometric Mean (CV%)	4451 (33)	3711 (46)
AUC ng●h/mL Geometric Mean (CV%)	42503 (36)	44970 (34)
C_{min} ng/mL Geometric Mean (CV%)	535 (62)	1090 (60)

Pregnancy
The pharmacokinetic data from HIV-infected pregnant women receiving atazanavir capsules with ritonavir are presented in **Table 18.**

Table 18 Steady-State Pharmacokinetics of Atazanavir with ritonavir in HIV-Infected Pregnant Women in the Fed State

Atazanavir 300 mg with ritonavir 100 mg			
Pharmacokinetic Parameter	**2nd Trimester (n=9)**	**3rd Trimester (n=20)**	**Postpartum [a] (n=36)**
C_{max} ng/mL Geometric mean (CV%)	3729.09 (39)	3291.46 (48)	5649.10 (31)
AUC ng•h/mL Geometric mean (CV%)	34399.1 (37)	34251.5 (43)	60532.7 (33)
C_{min} ng/mL [b] Geometric mean (CV%)	663.78 (36)	668.48 (50)	1420.64 (47)

[a] Atazanavir peak concentrations and AUCs were found to be approximately 26–40% higher during the postpartum period (4-12 weeks) than those observed historically in HIV-infected, non-pregnant patients. Atazanavir plasma trough concentrations were approximately 2-fold higher during the postpartum period when compared to those observed historically in HIV-infected, non-pregnant patients.

[b] C_{min} is concentration 24 hours post-dose.

Renal impairment

In healthy subjects, approximately 7% of the dose of atazanavir is eliminated unchanged in the urine. Atazanavir has been studied in adult subjects with severe renal impairment (n=20), including those on hemodialysis, at multiple doses of 400 mg once daily. The mean atazanavir C_{max} was 9% lower, AUC was 19% higher, and C_{min} was 96% higher in subjects with severe renal impairment not undergoing hemodialysis (n=10), than in age, weight, and gender matched subjects with normal renal function. Atazanavir was not appreciably cleared during hemodialysis. In a 4-hour dialysis session, 2.1% of the administered dose was removed. Subjects on hemodialysis appeared to display lower exposures as compared to healthy subjects and renally-impaired subjects without hemodialysis. The geometric means for ATV AUC, C_{max} and C_{min}, for atazanavir administered immediately following dialysis in subjects on hemodialysis (n=10) were 42%, 37% and 54% lower, respectively, relative to subjects with normal renal function. When atazanavir was administered 2 hours before a 4-hour hemodialysis session, the geometric means for ATV AUC, C_{max} and C_{min} in hemodialysis subjects were 28%, 25% and 43% lower, respectively, than subjects with normal renal function. The mechanism of this decrease is unknown. (See **DOSAGE AND ADMINISTRATION**)

Impaired hepatic function

Atazanavir is metabolized and eliminated primarily by the liver. Atazanavir has been studied in adult patients with moderate to severe hepatic impairment (14 Child-Pugh B and 2 Child-Pugh C) after a single 400-mg dose. The mean AUC(0-∞) was 42% greater in patients with impaired hepatic function than in healthy volunteers. The mean half-life of atazanavir in hepatically impaired patients was 12.1 hours compared to 6.4 hours in healthy volunteers. Increased concentrations of atazanavir are expected in patients with moderately or severely impaired hepatic function. The pharmacokinetics of atazanavir in combination with ritonavir have not been studied in subjects with hepatic impairment. APO-ATAZANAVIR should not be administered to patients with severe hepatic impairment. APO-ATAZANAVIR/ritonavir is not recommended for use in patients with hepatic impairment (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

STORAGE AND STABILITY

APO-ATAZANAVIR capsules should be stored at 15°C to 30°C. Protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-ATAZANAVIR (atazanavir sulfate) capsules are available for oral administration in strengths containing atazanavir sulfate equivalent to 150 mg, 200 mg or 300 mg of atazanavir and the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, and sodium starch glycolate. The capsule shells are imprinted with black edible ink and contain the following inactive ingredients: FD&C Blue #2 (for all strength), iron oxide black (300 mg only), iron oxide red (300 mg only), gelatin and titanium dioxide (for all strength), and sodium lauryl sulfate (300 mg only).
The complete composition for Blank edible ink (Imprinting ink) is as follows:

Ingredients	**Percentage by weight**
Black Iron Oxide - NF	24-28 %
Potassium Hydroxide - NF	0.05-0.1 %
Propylene Glycol - USP	3-7 %
Shellac - NF	24-27 %
Strong Ammonia Solution - NF	1-2 %

APO-ATAZANAVIR capsules are supplied in HDPE bottles containing 30 capsules, 60 capsules [150 mg and 200 mg], 500 capsules and blister packages of 60 (6x10) capsules [150 mg and 200 mg] and 30 (3x10) capsules [300 mg only].

150 mg capsule
Hard gelatin capsules with blue opaque cap and powdered-blue opaque body, imprinted "APO" on cap and "A150" on body in black ink, filled with white to off-white colored granules.

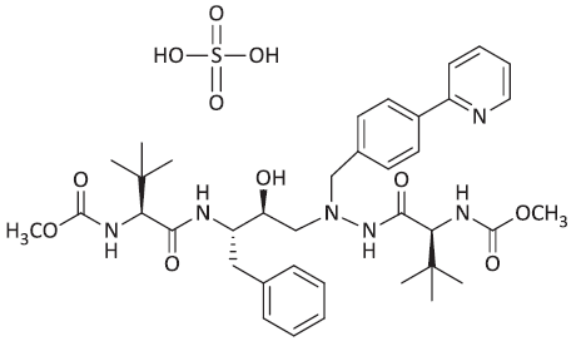
200 mg capsule
Hard gelatin Capsules with blue opaque cap and blue opaque body, imprinted “APO” on cap and “A200” on body in black ink, filled with white to off-white colored granules.

300 mg capsule
Hard gelatin capsules with red opaque cap and blue opaque body, imprinted "APO" on cap and "A300" on body in black ink, filled with white to off-white colored granules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Atazanavir sulfate
Chemical Name:	(3S,8S,9S,12S)-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9- (phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13- pentaazatetradecanedioic acid dimethyl ester, sulfate (1:1)
Empirical Formula:	$C_{38}H_{52}N_6O_7 \bullet H_2SO_4$
Structural Formula:	
Molecular Weight:	802.9 g/mol (sulfuric acid salt) 704.9 g/mol (free base)

Physicochemical Properties

Description:	APO-ATAZANAVIR (atazanavir sulfate) is an azapeptide inhibitor of HIV-1 protease. Atazanavir sulfate is a light yellow to white powder.
Solubility:	It is very slightly soluble in water (0.1 mg/mL)
pH:	The pH of a saturated solution in water being about 1.9 at 24 ± 3°C.

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, single dose, blinded, two-treatment, three-period, reference replicated, crossover comparative bioavailability study was conducted under fasting conditions, on healthy Asian male volunteers from 20 to 44 years of age (N=51). The rate and extent of absorption of atazanavir was measured and compared following a single oral dose (1 x 300 mg capsule) of APO-ATAZANAVIR (atazanavir) 300 mg capsule (Apotex Inc.) and REYATAZ* (atazanavir) 300 mg capsule (Bristol-Myers Squibb Canada). The results from measured data in 46 subjects are summarized in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA: ATAZANAVIR DATA

Atazanavir (1 x 300 mg) From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	Ratio of Geometric Means (%)	90% Confidence Interval (%)[#]
AUC_T (ng•h/mL)	5998.42 8776.79 (77.6)	6461.76 8901.15 (74.8)	92.8	77.0- 111.9
AUC_I (ng•h/mL)	6117.18 8936.50 (78.4)	6566.38 9059.27 (75.4)	93.2	77.4 – 112.1
Cmax (ng/mL)	1166.28 1754.96 (69.5)	1291.82 1835.25 (70.6)	90.3	72.4- 112.5
T_{max}[§] (h)	1.59 (49.7)	1.55 (48.7)		
$T_{1/2}$[§] (h)`	6.20 (23.2)	6.11 (22.5)		

* APO-ATAZANAVIR (atazanavir) 300 mg capsules (Apotex Inc.).
† REYATAZ* (atazanavir) 300 mg capsules (Bristol-Myers Squibb Canada) was purchased in Canada.
[§] Expressed as arithmetic means (CV%) only.
[#] Bioequivalence acceptance limits were scaled to the within-subject Reference variability for AUC_t

Antiretroviral Treatment-Naive Adult Patients

Study AI424-138: a 96 Week study comparing the antiviral efficacy and safety of atazanavir/ritonavir with lopinavir/ritonavir, each in combination with fixed-dose tenofoviremtricitabine in HIV-1 infected treatment naive subjects

Study AI424-138 is a 96 Week open label, randomized, multicenter study, comparing atazanavir sulfate (300 mg once daily) with ritonavir (100 mg once daily) to lopinavir plus ritonavir (400/100 mg twice daily), each in combination with fixed-dose tenofovir DF plus emtricitabine (300/200 mg once daily), in 883 antiretroviral treatment-naive patients. Patients had a mean age of 36 years (range 19–72), 48% were Caucasian, 18% Black, 9% Asian, 24% Hispanic/Mestizo/mixed race and 69% were male. The median baseline plasma CD4+ cell count was 205 cells/mm^3 (range 2 to 810 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.94 log10 copies/mL (range: 2.60 to 5.88 log_{10} copies/mL). Treatment response and outcomes through Week 48 and Week 96 are presented in **Table 19**.

Table 19 Outcomes of Randomized Treatment Through Week 48 and Week 96 (Study AI424-138)

Outcome	Atazanavir sulfate 300 mg + ritonavir 100 mg (once daily) with tenofovir DF/emtricitabine (once daily)[a] (n = 440)		Lopinavir 400 mg + ritonavir 100 mg (twice daily) with tenofovir DF/emtricitabine (once daily)[a] (n = 443)	
	48 Weeks	96 Weeks	48 Weeks	96 Weeks
Responder[b]	78%[c]	75%[d]	76%[c]	69%[d]
Virologic failure[e]	13%	9%	10%	11%
Rebound	4%	7%	4%	9%
Never suppressed through Week 48 or Week 96	9%	2%	6%	1%
Death	1%	1%	<1%	<1%
Discontinued due to adverse event	2%	3%	3%	5%
Discontinued for other reasons[f]	6%	12%	9%	15%

[a] As a fixed-dose combination: 300 mg tenofovir DF, 200 mg emtricitabine once daily.
[b] Patients achieved confirmed HIV RNA <50 copies/mL at Week 48. Roche Amplicor®, v1.5 ultra-sensitive assay.
[c] Pre-specified ITT analysis using as-randomized cohort: ATV/RTV 78% and LPV/RTV 76% [difference estimate: 1.7 (95% confidence interval: -3.8, 7.1)].
[d] Pre-specified ITT analysis using as-randomized cohort: ATV/RTV 74% and LPV/RTV 68% [difference estimate: 6.1 (95% confidence interval: 0.3, 12.0)].
[e] Includes viral rebound and failure to achieve confirmed HIV RNA <50 copies/mL through Week 48 and Week 96, respectively.
[f] Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons.

The proportion of responders among patients with high viral loads (ie, baseline HIV RNA ≥100,000 copies/mL) were comparable for the atazanavir sulfate /ritonavir (164 of 223 patients, 74% at 48 weeks and 165 of 223 patients, 74% at 96 weeks) and lopinavir/ritonavir 161 of 222 patients, 73% at 48 weeks and 149 of 222 patients, 67% at 96 weeks) arms. The median increase from baseline in CD4+ cell count was 191 (48 weeks) and 261 (96 weeks) cells/mm^3 for the atazanavir sulfate /ritonavir arm and 200 (48 weeks) and 273 (96 weeks) cells/mm^3 for the lopinavir/ritonavir arm.

Study AI424-034: Atazanavir sulfate once daily compared to efavirenz once daily, each in combination with fixed dose lamivudine + zidovudine twice daily

Study AI424-034 was a randomized, double-blind, multicenter trial comparing atazanavir sulfate (400 mg once daily) (n=405) to efavirenz (600 mg once daily) (n=405), each in combination with a fixed dose combination of lamivudine (3TC) (150 mg) and zidovudine (ZDV) (300 mg) given twice daily, in 810 antiretroviral treatment-naive patients. Patients had a mean age of 34 years (range: 18 to 73), 36% were Hispanic, 33% were Caucasian, and 65% were male. The mean baseline CD4 cell count was 321 cells/mm^3 (range: 64 to 1424 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.8 log_{10} copies/mL (range: 2.2 to 5.9 log_{10} copies/mL).

The primary endpoint for this study was the proportion of treated patients who achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.

Through 48 weeks of therapy, there was a similar proportion of patients with HIV RNA <400 copies/mL in the atazanavir sulfate arm compared to the efavirenz arm (67% vs. 63%, respectively). Virologic failure was the most frequent reason for treatment failure on both regimens (20% vs. 19% respectively). Few subjects on either regimen did not achieve viral suppression through Week 48 (7% on both regimens) and virologic failure was mainly due to viral rebound (13% and 11%, respectively). Discontinuation due to adverse events (AEs) and due to other reasons was slightly higher on EFV than on atazanavir (9% vs. 6% for discontinuation due to AEs, and 9% vs. 7% for discontinuation due to other reasons). Results for the proportion of patients in the atazanavir sulfate arm compared to the efavirenz arm with HIV RNA <50 copies/mL were 31% vs. 36%, respectively. The mean increase from baseline in CD4 cell count was 176 cells/mm^3 for the atazanavir sulfate arm and 160 cells/mm^3 for the efavirenz arm.

Table 20 Outcomes of Randomized Treatment Through Week 48 (Study AI424-034)

Outcome	Atazanavir sulfate 400 mg once daily + lamivudine + zidovudine[d] (n = 405)	efavirenz 600 mg once daily + lamivudine + zidovudine[d] (n = 405)
Responder by TRWPF analysis[a] LOQ<400 copies/mL (< 50 copies/mL)	67% (31%)	63% (36%)
Virologic failure[b] Rebound Never suppressed through Week 48	20% 13% 7%	19% 11% 7%
Death or Disease Progression	<1%	<1%
Discontinued due to adverse event	6%	9%
Discontinued for other reasons[c]	6%	9%

[a] The TRWPF defined as responders patients who achieved and maintained confirmed HIV RNA <400 copies/mL (< 50 copies/mL) through week 48 without intervening replicated rebound, CDC Class C AIDS events, or treatment discontinuation. ATV-EFV (95% CI): 3.8 (-2.8, 10.3); ATV is similar to EFV as the lower 95% confidence interval is > -12%, the pre-defined criteria for similarity. Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.0 or 1.5 as geographically appropriate.

[b] Includes confirmed viral rebound and failure to achieve confirmed HIV RNA <400 copies/mL through Week 48.
[c] Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation and other reasons.
[d] As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

Study AI424-008: Atazanavir sulfate 400 mg once daily compared to atazanavir sulfate 600 mg once daily, and compared to nelfinavir 1250 mg twice daily, each in combination with stavudine and lamivudine twice daily

Study AI424-008 was a 48-week, randomized, open-label, multicenter trial, blinded to dose of atazanavir sulfate, comparing atazanavir sulfate at two dose levels (400 mg and 600 mg once daily) (n=181 and n=195, respectively), to nelfinavir (1250 mg twice daily) (n=91), each in combination with stavudine (40 mg) and lamivudine (150 mg) given twice daily, in antiretroviral treatment-naive patients. Patients had a mean age of 35 years (range: 18 to 69), 55% were Caucasian, and 63% were male. The mean baseline CD4 cell count was 295 cells/mm^3 (range: 4 to 1003 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.7 log_{10} copies/mL (range: 1.8 to 5.9 log_{10} copies/mL).

Table 21 Outcomes of Randomized Treatment Through Week 48 (Study AI424-008)

Outcome	Atazanavir sulfate 400 mg once daily + lamivudine + stavudine (n = 181)	nelfinavir 1250 mg twice daily + lamivudine + stavudine (n = 91)
Responder by TRWPF[a]	65% (31%)	59% (38%)
Virologic failure[b]	23%	35%
Rebound	11%	14%
Never suppressed through Week 48	12%	21%
Death or disease progression	2%	-
Discontinued due to adverse event	4%	3%
Discontinued for other reasons[c]	4%	2%

[a] TRWPF defined responders as patients who achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48 without intervening replicated rebound, CDC Class C AIDS events, or treatment discontinuation. Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.0 or 1.5 as geographically appropriate.
[b] Includes confirmed viral rebound and failure to achieve confirmed HIV RNA <400 copies/mL through Week 48.
[c] Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation and other reasons.

Through 48 weeks of treatment, the proportion of patients with HIV RNA <400 (<50) copies/mL was 65% (31%) for the atazanavir sulfate 400-mg arm and 59% (38%) for the nelfinavir arm. The mean increase from baseline in CD4 cell count was 234 cells/mm^3 for the atazanavir sulfate 400-mg arm and 211 cells/mm^3 for the nelfinavir arm. Virologic failure was comparable across all study regimens and was due to approximately equal numbers of subjects who never achieved virologic suppression (12% on ATV 400, 13% on ATV 600 and 21% on NFV).

Antiretroviral Treatment-Experienced Adult Patients

Study AI424-043: Atazanavir sulfate once daily compared to lopinavir + ritonavir twice daily, each in combination with two nucleosides
Study AI424-043 is a, randomized, open-label, multicenter trial comparing atazanavir sulfate (400 mg once daily) to lopinavir + ritonavir (400/100 mg twice daily), each in combination with two NRTIs, in 300 randomized subjects who experienced virologic failure to only one prior PI containing regimen. The mean time of prior exposure to antiretrovirals was 141 weeks for PIs, 181 weeks for NRTIs, and 93 weeks for NNRTIs (14% of patients had prior exposure to NNRTIs). The mean age was 38 years (range: 20 to 65); 51% were Hispanic, 42% were Caucasian, and 79% were male. The mean baseline CD4 cell count was 323 cells/mm^3 (range: 54 to 1210 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.14 log_{10} copies/mL (range: 2.60 to 5.87 log_{10} copies/mL). Based on results of the Week 24 analysis, patients in the atazanavir sulfate treatment arm were offered alternative treatment after 24 weeks of study therapy.

The co-primary endpoints for this study were the time-averaged difference in change from baseline in HIV RNA levels through Week 48 (efficacy) and the Week 48 percentage change from baseline in fasting LDL cholesterol (safety). Through 48 weeks of therapy, 57% of patients treated with atazanavir sulfate has > 1 log10 virologic suppression (or < 400 copies/mL) compared to 75% of patients treated with lopinavir/ritonavir. There was a greater proportion of patients with HIV RNA <400 copies/mL and HIV RNA <50 copies/mL in the lopinavir/ritonavir arm compared to the atazanavir sulfate arm (67% vs. 45% and 51% vs. 32%).

Based on the results of this study, atazanavir sulfate without ritonavir is inferior to lopinavir/ritonavir in PI-experienced patients with prior virologic failure and is not recommended for such patients.

Study AI424-043 also compared changes from baseline in LDL-cholesterol. Through 48 weeks, atazanavir sulfate resulted in significantly lower fasting LDL-cholesterol (co-primary endpoint), total cholesterol, and fasting triglyceride concentrations than lopinavir + ritonavir, as assessed by change from baseline. HDL cholesterol rose modestly and comparably between baseline to week 48 on both regimens. (For more details, see **ADVERSE REACTIONS**, **Table 10**)

Antiretroviral Treatment- Experienced Adult Patients (Salvage)

Study AI424-045: Atazanavir sulfate once daily + ritonavir once daily compared to atazanavir sulfate once daily + saquinavir (soft gelatin capsules) once daily, and compared to lopinavir + ritonavir twice daily, each in combination with tenofovir DF + one NRTI
Study AI424-045 is an ongoing, randomized, open-label, multicenter trial comparing atazanavir sulfate (300 mg once daily) taken with ritonavir (100 mg once daily) and atazanavir sulfate (400 mg once daily) in combination with saquinavir soft gelatin capsules (1200 mg once daily), to lopinavir + ritonavir (400/100 mg fixed dose combination twice daily), each in combination with tenofovir DF and one NRTI, in 358 randomized subjects with virologic failure on HAART

regimens containing PIs, NRTIs, and NNRTIs. The mean time of prior antiretroviral exposure was 138 weeks for PIs, 281 weeks for NRTIs, and 85 weeks for NNRTIs. The mean age was 41 years (range: 24 to 74); 60% were Caucasian and 78% were male. The mean baseline CD4 cell count was 337 cells/mm^3 (range: 14 to 1543 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.40 log_{10} copies/mL (range: 2.6 to 5.9 log_{10} copies/mL). The primary endpoint for this study was the time-averaged difference in change from baseline in HIV RNA through 48 weeks.

There are limited safety data from controlled clinical trials for atazanavir sulfate plus ritonavir regimens without tenofovir DF.

The similarity (non-inferiority) of the antiviral efficacy of the ATV 300/RTV and LPV/RTV regimens was demonstrated for the primary efficacy endpoint through Week 48 (TAD [97.5% CI] for ATV 300/RTV - LPV/RTV was 0.13 [-0.12, 0.39]). In contrast, the antiviral efficacy of the ATV 400/SQV regimen was lower than that of the LPV/RTV regimen (TAD [97.5% CI] ATV 400/SQV - LPV/RTV was 0.31 [0.07, 0.55]0.33 [0.07, 0.60]). At Week 48, HIV RNA levels declined from baseline by a mean of 1.93 log_{10} c/mL for ATV 300/RTV, and 1.87 log_{10} c/mL for LPV/RTV.

The comparability of the ATV 300/RTV regimen relative to the LPV/RTV regimen was supported by the analyses which included the proportion of subjects with HIV RNA levels < 400 c/mL. Response rates at Week 48 were comparable between the ATV 300/RTV and LPV/RTV treatment groups. Using the TRWPF definition, response rates were 53% for ATV 300/RTV and 54% for LPV/RTV.

Study AI424-045, however was not large enough to reach a definite conclusion that atazanavir sulfate/ritonavir and lopinavir/ritonavir are equivalent on the secondary endpoint of proportions below the HIV RNA lower limit of detection.

Table 22 Outcomes of Treatment Through 48 Weeks in Study AI424-045 (Patients with Prior Antiretroviral Experience)*[a]

Outcome	Atazanavir sulfate 300 mg once daily + ritonavir 100 mg once daily + tenofovir DF + NRTI N = 120	lopinavir + ritonavir (400/100 mg) BID + tenofovir DF + NRTI N = 123
HIV RNA Mean Change from Baseline (log_{10} copies/mL)a,b,c	-1.93	-1.87
CD4 Mean Change from Baseline (cell/mm^3)[d]	110	121
Percent of Randomized Patients Responding[e]		
HIV RNA <400 copies/mL[a]	53%	54%
HIV RNA <50 copies/mL[a]	36%	42%

* There are limited safety data from controlled trials for atazanavir sulfate plus ritonavir regimens without tenofovir DF. (See **DRUG INTERACTIONS**.)

[a] Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.5.
[b] Based on patients with baseline and Week 48 HIV-1 RNA measurements (atazanavir sulfate + ritonavir, n=90; lopinavir + ritonavir, n=99).
[c] Protocol-defined primary efficacy outcome measure.
[d] Based on patients with baseline and Week 48 CD4 cell count measurements (atazanavir sulfate + ritonavir, n=83; lopinavir + ritonavir, n=94).
[e] TRWPF defined as responders patients who achieved and maintained confirmed HIV RNA <400 copies/mL (< 50 copies/mL) through week 48 without intervening replicated rebound, CDC Class C AIDS events, or treatment discontinuation.

Pediatric Patients
Assessment of the pharmacokinetics, safety, tolerability, and efficacy of atazanavir sulfate is based on data from the open-label, multicenter clinical trial PACTG 1020A conducted in patients from 3 months to 21 years of age. In this study, 182 patients (83 antiretroviral-naive and 99 antiretroviral-experienced) received once daily atazanavir sulfate, with or without ritonavir, in combination with two NRTIs.

Ninety-nine patients (6 to less than 18 years of age) treated with the atazanavir sulfate capsule formulation, with or without ritonavir, were evaluated. In this cohort, the overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <400 copies/mL at week 24 were 68% (28/41) and 33% (19/58), respectively. The overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <50 copies/mL at week 24 were 59% (24/41) and 24% (14/58), respectively. The median increase from baseline in absolute CD4 count at 20 weeks of therapy was 171 cells/mm^3 in antiretroviral-naive patients and 116 cells/mm^3 in antiretroviral-experienced patients. The efficacy of atazanavir sulfate in the pediatric population beyond 24 weeks has not yet been established.

Pregnant Women
In clinical trial AI424-182 atazanavir sulfate/ritonavir (300/100 mg or 400/100 mg) in combination with zidovudine/lamivudine was administered to 41 pregnant women during the second or third trimester. Among the 39 women who completed the study, 38 women achieved an HIV RNA <50 copies/mL at time of delivery. Six of 20 (30%) women on atazanavir sulfate/ritonavir 300/100 mg and 13 of 21 (62%) women on atazanavir sulfate/ritonavir 400/100 mg experienced grades 3 to 4 hyperbilirubinemia.

Forty infants had test results that were negative for HIV-1 DNA at the time of delivery and/or during the first 6 months postpartum. All 40 infants received antiretroviral prophylactic treatment containing zidovudine. Three of 20 infants (15%) born to women treated with atazanavir sulfate/ritonavir 300/100 mg and four of 20 infants (20%) born to women treated with atazanavir sulfate/ritonavir 400/100 mg experienced grade 3-4 bilirubin. There was no evidence of pathologic jaundice and six of 40 infants in this study received phototherapy for a maximum of 4 days.

See **DOSAGE AND ADMINISTRATION**: **Dosage Adjustments**, **Pregnant Women**.

DETAILED PHARMACOLOGY

Electrocardiogram: Effect on PR and QT intervals
Concentration - and dose - dependent prolongation of the PR interval in the electrocardiogram has been observed in healthy volunteers receiving atazanavir. In a placebo-controlled study (AI424-076), the mean (+ / -SD) maximum change in PR interval from the pre-dose value was 24 (+ / -15 msec) following oral dosing with 400 mg of atazanavir (n = 65) compared to 13 (+ 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 pharmacodynamic interaction in humans between atazanavir and other drugs that prolong the PR interval of the electrocardiogram (see **WARNINGS AND PRECAUTIONS**).

Electrocardiographic 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.

Drug-Drug Interactions
See also **CONTRAINDICATIONS** and **DRUG INTERACTIONS**.

Atazanavir is metabolized in the liver by the cytochrome P450 enzyme system and inhibits CYP3A4 and UGT1A1 at clinically relevant concentrations with Ki of 2.35 mcM (CYP3A4 isoform) and 1.9 mcM. Atazanavir should not be administered concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4 (see **CONTRAINDICATIONS**). Drugs that induce CYP3A4 activity would be expected to increase the clearance of atazanavir, resulting in lowered plasma concentrations. Coadministration of atazanavir and other drugs that inhibit CYP3A4 may increase atazanavir plasma concentrations.

Clinically significant interactions are not expected between atazanavir and substrates of CYP2C19, CYP2C9, CYP2D6, CYP2B6, CYP2A6, CYP1A2, or CYP2E1. Atazanavir is a weak inhibitor of CYP2C8. Caution should be used when APO-ATAZANAVIR without ritonavir is coadministered with drugs highly dependent on CYP2C8 with narrow therapeutic indecies (eg. paclitaxel, repaglinide). When atazanavir sulfate with ritonavir is coadministered with substrates of CYP2C8, clinically significant interactions are not expected.

Atazanavir has been shown *in vivo* not to induce its own metabolism, nor to increase the biotransformation of some drugs metabolized by CYP3A4. In a multiple-dose study, atazanavir decreased the urinary ratio of endogenous 6β-OH cortisol to cortisol versus baseline, indicating that CYP3A4 production was not induced.

Drug interaction studies were performed with atazanavir and other drugs likely to be coadministered and some drugs commonly used as probes for pharmacokinetic interactions.

The effects of coadministered drugs on the AUC, C_{max} and C_{min} of atazanavir are summarized in **Table 23**.

Table 23 Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
				C_{max}	AUC	C_{min}
Atenolol	50 mg once daily, d 7-11 and d19-23	400 mg once daily, d 1-11	19	1.00 (0.89, 1.12)	0.93 (0.85,1.01)	0.74 (0.65, 0.86)
clarithromycin	500 mg BID, d 7-10 and d 18-21	400 mg once daily, d 1-10	29	1.06 (0.93, 1.20)	1.28 (1.16, 1.43)	1.91 (1.66, 2.21)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose simultaneously with ddI and d4T	31	0.11 (0.06, 0.18)	0.13 (0.08, 0.21)	0.16 (0.10, 0.27)
	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose 1 hour after ddI + d4T	31	1.12 (0.67, 1.18)	1.03 (0.64, 1.67)	1.03 (0.61, 1.73)
didanosine (ddI) (enteric-coated [EC] capsules)[b]	400 mg d 8 (fed) 400 mg d 19 (fed)	400 mg once daily d 2-8 300 mg/ritonavir 100 mg once daily d 9-19	34 31	1.03 (0.93, 1.14) 1.04 (1.01, 1.07)	0.99 (0.91, 1.08) 1.00 (0.96, 1.03)	0.98 (0.89, 1.08) 0.87 (0.82, 0.92)
diltiazem	180 mg once daily, d 7-11 and d 19-23	400 mg once daily, d 1-11	30	1.04 (0.96, 1.11)	1.00 (0.95, 1.05)	0.98 (0.90, 1.07)
efavirenz	600 mg once daily, d 7-20	400 mg once daily, d 1-20	27	0.41 (0.33, 0.51)	0.26 (0.22, 0.32)	0.07 (0.05, 0.10)
efavirenz and ritonavir	efavirenz 600 mg once daily 2 h after atazanavir sulfate and ritonavir 100 mg once daily simultaneously with atazanavir sulfate, d 7-20	400 mg once daily, d 1-6 then 300 mg once daily d 7-20	13	1.14 (0.83, 1.58)	1.39 (1.02, 1.88)	1.48 (1.24, 1.76)

Table 23 Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
				C_{max}	AUC	C_{min}
efavirenz and ritonavir	600 mg once daily, d 11-24 (pm)	300 mg once daily / ritonavir 100 mg once daily, d 1-10 (pm), then 400 mg once daily / ritonavir 100 mg once daily, d 11-24 (pm), (simultaneous with efavirenz)	14	1.17 (1.08, 1.27)	1.00 (0.91, 1.10)	0.58 (0.49, 0.63)
famotidine	40 mg BID d 7-12 [c]	400 mg once daily d 1-12 [c]	15	0.53 (0.34, 0.82)	0.59 (0.40, 0.87)	0.58 (0.37, 0.89)
	40 mg BID d 7-12 [d]	400 mg once daily (pm) d 1-6, d 7-12 [d]	14	1.08 (0.82, 1.41)	0.95 (0.74, 1.21)	0.79 (0.60, 1.04)
	40 mg BID d 11-20 [c,e]	300 mg once daily / ritonavir 100 mg once daily d 1-20 [c,e]	14	0.86 (0.79, 0.94)	0.82 (0.75, 0.89)	0.72 (0.64, 0.81)
	20 mg BID, d 11-17	300 mg once daily /ritonavir 100 mg once daily /tenofovir DF 300 mg once daily, d 1-10 (am), then 300 mg once daily /ritonavir 100 mg once daily /tenofovir DF 300 mg once daily, d 11-17 (am) (simultaneous administration with am famotidine) [m, n]	18	0.91 (0.84, 0.99)	0.90 (0.82, 0.98)	0.81 (0.69, 0.94)
	40 mg once daily (pm), d 18-24	300 mg once daily /ritonavir 100 mg once daily /tenofovir DF 300 mg once daily, d 1-10 (am), then 300 mg once daily /ritonavir 100 mg once daily /tenofovir DF 300 mg once daily, d 18-24 (am) (12h after pm famotidine) [n]	20	0.89 (0.81, 0.97)	0.88 (0.80, 0.96)	0.77 (0.63, 0.93)
	40 mg BID, d 18-24	300 mg once daily /ritonavir 100 mg once	18	0.74	0.79	0.72

Table 23 Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
				C_{max}	AUC	C_{min}
		daily /tenofovir DF 300 mg once daily, d 1-10 (am), then 300 mg once daily /ritonavir 100 mg once daily /tenofovir DF 300 mg once daily, d 18-24 (am) (10h after pm famotidine and 2h before am famotidine)[n]		(0.66, 0.84)	(0.70, 0.88)	(0.63, 0.83)
fluconazole	200 mg once daily, d 11-20	300 mg once daily /ritonavir 100 mg once daily, d 1-10, then 300 mg once daily /ritonavir 100 mg once daily, d 11-20	29	1.03 (0.95, 1.11)	1.04 (0.95, 1.13)	0.98 (0.85, 1.13)
ketoconazole	200 mg once daily, d 7-13	400 mg once daily, d 1-13	14	0.99 (0.77, 1.28)	1.10 (0.89, 1.37)	1.03 (0.53, 2.01)
nevirapine[fg]	200 mg BID, d 1-23	300 mg once daily / ritonavir 100 mg once daily, d 4-13, then 400 mg once daily / ritonavir 100 mg once daily, d 14-23	23, 22[h]	0.72 (0.60, 0.86) 1.02 (0.85, 1.24)	0.58 (0.48, 0.71) 0.81 (0.65, 1.02)	0.28 (0.20, 0.40) 0.41 (0.27, 0.60)
omeprazole	40 mg once daily d 7-12 i	400 mg once daily d 1-12	16	0.04 (0.04, 0.05)	0.06 (0.05, 0.07)	0.05 (0.03, 0.07)
	40 mg once daily d 11-20 i	300 mg once daily/ ritonavir 100 mg once daily d 1-20	15	0.28 (0.24, 0.32)	0.24 (0.21, 0.27)	0.22 (0.19, 0.26)
	20 mg once daily, d 17-23 (am)	300 mg once daily /ritonavir 100 mg once daily, d 7-16 (pm), then 300 mg once daily /ritonavir 100 mg once daily, d 17-23 (pm)[o, p]	13	0.61 (0.46, 0.81)	0.58 (0.44, 0.75)	0.54 (0.41, 0.71)
	20 mg once daily, d 17-23 (am)	300 mg once daily /ritonavir 100 mg once daily, d 7-16 (am), then 400 mg once daily	14	0.69 (0.58, 0.83)	0.70 (0.57, 0.86)	0.69 (0.54, 0.88)

Table 23 Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
				C_{max}	AUC	C_{min}
		/ritonavir 100 mg once daily, d 17-23 (am) q, r				
rifabutin	150 mg once daily, d 15-28	400 mg once daily, d 1-28	7	1.34 (1.14, 1.59)	1.15 (0.98, 1.34)	1.13 (0.68, 1.87)
rifampin	600 mg once daily d 17-26	300 mg once daily/ ritonavir 100 mg once daily d 7-26	16	0.47 (0.41, 0.53)	0.28 (0.25, 0.32)	0.02 (0.02, 0.03)
ritonavir[j]	100 mg once daily, d 11-20	300 mg once daily, d 1-20	28	1.86 (1.69, 2.05)	3.38 (3.13, 3.63)	11.89 (10.23, 13.82)
tenofovir DF[k]	300 mg once daily with food d 9-16	400 mg once daily with food d 1-16	34	0.79 (0.73, 0.86)	0.75 (0.70, 0.81)	0.60 (0.52, 0.68)
tenofovir DF [k] and ritonavir	tenofovir DF [k] 300 mg once daily d 15-42	300 mg once daily with ritonavir 100 mg once daily d 1-42	10	0.72 l (0.50, 1.05)	0.75 l (0.58, 0.97)	0.77 l (0.54, 1.10)
voriconazole (Subjects with at least one functional CYP2C19 allele)	200 mg BID, d 2-3, 22-30; 400 mg BID d 1, 21	300 mg/ritonavir 100 mg QD, d 11–30	20	0.87 (0.80, 0.96)	0.88 (0.82, 0.95)	0.80 (0.72, 0.90)
voriconazole (Subjects without a functional CYP2C19 allele)	50 mg BID, d 2-3, 22-30; 100 mg BID d 1, 21	300 mg/ritonavir 100 mg QD, d 11–30	8	0.81 (0.66, 1.00)	0.80 (0.65, 0.97)	0.69 (0.54, 0.87)

[a] N = number of subjects
[b] 400 mg ddI EC and atazanavir sulfate were administered together with food on Days 8 and 19.
[c] Simultaneous administration
[d] 10 hr after, 2 hr before famotidine
[e] Atazanavir sulfate 300 mg plus ritonavir 100 mg once daily coadministered with famotidine 40 mg twice daily resulted in atazanavir geometric mean C_{max} that was similar and AUC and C_{min} values that were 1.79- and 4.46-fold higher relative to atazanavir sulfate 400 mg once daily alone.
[f] Study was conducted in HIV-infected individuals.

[g] Compared with atazanavir 400 mg historical data without nevirapine (n=13), the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 1.42 (0.98, 2.05), 1.64 (1.11, 2.42), and 1.25 (0.66, 2.36), respectively, for atazanavir/ritonavir 300/100 mg; and 2.02 (1.42, 2.87), 2.28 (1.54, 3.38), and 1.80 (0.94, 3.45), respectively, for atazanavir/ritonavir 400/100 mg.

[h] Parallel group design; n for atazanavir/ritonavir plus nevirapine, n for atazanavir 300 mg/ritonavir 100 mg without nevirapine. Subjects were treated with nevirapine prior to study entry.

[i] Omeprazole was administered on an empty stomach 2 hours before atazanavir sulfate.

[j] Compared with atazanavir 400 mg once daily historical data, administration of atazanavir/ritonavir 300/100 mg once daily increased the atazanavir geometric mean values of C_{max}, AUC, and C_{min} by 18%, 103%, and 671%, respectively. The geometric mean values of atazanavir pharmacokinetic parameters when coadministered with ritonavir were: C_{max} = 6129 ng/mL, AUC = 57039 ng●h/ml, and C_{min} = 1227 ng/mL.

[k] Tenofovir disoproxil fumarate. Note that similar results were observed in studies where administration of tenofovir DF and atazanavir sulfate was separated by 12 hours.

[l] Ratio of atazanavir plus ritonavir plus tenofovir DF to atazanavir plus ritonavir. Atazanavir 300 mg plus ritonavir 100 mg results in higher atazanavir exposure than atazanavir 400 mg (see footnote [g]).

[m] Similar results were noted when famotidine 20 mg BID was administered 2 hours after and 10 hours before atazanavir 300 mg and ritonavir 100 mg plus tenofovir DF 300 mg.

[n] Atazanavir/ritonavir/tenofovir DF was administered after a light meal.

[o] Omeprazole 20 mg was administered 30 minutes prior to a light meal in the morning and atazanavir sulfate 300 mg plus ritonavir 100 mg in the evening after a light meal, separated by 12 hours from omeprazole.

[p] Atazanavir sulfate 300 mg plus ritonavir 100 mg once daily separated by 12 hours from omeprazole 20 mg daily resulted in increases in atazanavir geometric mean AUC (10%) and C_{min} (2.4-fold), with a decrease in C_{max} (29%) relative to atazanavir sulfate 400 mg once daily in the absence of omeprazole (study days 1–6).

[q] Omeprazole 20 mg was given 30 min prior to a light meal in the morning and atazanavir sulfate 400 mg plus ritonavir 100 mg once daily after a light meal, 1 hour after omperazole. Effects on atazanavir concentrations were similar when atazanavir sulfate 400 mg plus ritonavir 100 mg was separated from omeprazole 20 mg by 12 hours.

[r] Atazanavir sulfate 400 mg plus ritonavir 100 mg once daily administered with omeprazole 20 mg once daily resulted in increases in atazanavir geometric mean AUC (32%) and C_{min} (3.3-fold), with a decrease in C_{max} (26%) relative to atazanavir sulfate 400 mg once daily in the absence of omeprazole (study days 1-6).

The effects of coadministration of atazanavir on the AUC, C_{max}, and C_{min} of other drugs are summarized in Table 24.

Table 24 Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Atazanavir

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Atazanavir; No Effect = 1.00		
				C_{max}	AUC	C_{min}
acetaminophen	1 gm BID, d 1-20	300 mg once daily /ritonavir 100 mg once daily, d 11-20	10	0.87 (0.77, 0.99)	0.97 (0.91, 1.03)	1.26 (1.08, 1.46)
atenolol	50 mg once daily, d 7-11 and d 19-23	400 mg once daily, d 1-11	19	1.34 (1.26, 1.42)	1.25 (1.16, 1.34)	1.02 (0.88, 1.19)

Table 24 Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Atazanavir

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Atazanavir; No Effect = 1.00		
				C_{max}	AUC	C_{min}
buprenorphine	16 mg once daily naloxone 4 mg once daily	300 mg once daily/ritonavir 100 mg once daily x 5 days	10	buprenorphine: 1.37 norbuprenorphine: 16.1	buprenorphine: 1.67 norbuprenorphine: 2.05	buprenorphine: 1.69 norbuprenorphine: 2.01
	once daily stable maintenance dose with naloxone	400 mg once daily x 5 days	10	buprenorphine: 1.64 norbuprenorphine: 1.36	buprenorphine: 1.93 norbuprenorphine: 1.76	buprenorphine: 1.99 norbuprenorphine: 1.64
clarithromycin	500 mg BID, d 7-10 and d 18-21	400 mg once daily, d 1-10	21	1.50 (1.32, 1.71) OH-clarithromycin: 0.28 (0.24, 0.33)	1.94 (1.75, 2.16) OH-clarithromycin: 0.30 (0.26, 0.34)	2.60(2.35, 2.88) OH-clarithromycin: 0.38 (0.34, 0.42)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)	ddI: 200 mg x 1 dose d4T: 40 mg x 1 dose	400 mg x 1 dose simultaneous with ddI and d4T	31	ddI: 0.92 (0.84, 1.02) d4T: 1.08 (0.96, 1.22)	ddI: 0.98 (0.92, 1.05) d4T: 1.00 (0.97, 1.03)	NA d4T: 1.04 (0.94, 1.16)
didanosine (ddI) (enteric coated [EC] capsules)[b]	400 mg d 1 (fasted), 8 (fed)	400 mg once daily, d 2-8	34	0.64 (0.55, 0.74)	0.66 (0.60, 0.74)	1.13 (0.91, 1.41)
	400 mg d 1 (fasted), 19 (fed)	300 mg once daily/ritonavir 100 mg once daily, d 9-19	31	0.62 (0.52, 0.74)	0.66 (0.59, 0.73)	1.25 (0.92, 1.69)
diltiazem	180 mg once daily, d 7-11 and d 19-23	400 mg once daily, d 1-11	28	1.98 (1.78, 2.19)	2.25 (2.09, 2.16) desacetyl-diltiazem: 2.65	2.42 (2.14, 2.73) desacetyl-diltiazem: 2.21

Table 24 Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Atazanavir

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Atazanavir; No Effect = 1.00		
				C_{max}	AUC	C_{min}
				desacetyl-diltiazem: 2.72 (2.44, 3.03)	(2.45, 2.87)	(2.02, 2.42)
ethinyl estradiol & norethindrone[c]	Ortho-Novum® 7/7/7 once daily, d 1-29	400 mg once daily, d 16-29	19	ethinyl estradiol: 1.15 (0.99, 1.32) norethindrone: 1.67 (1.42, 1.96)	ethinyl estradiol: 1.48 (1.31, 1.68) norethindrone: 2.10 (1.68, 2.62)	Ethinyl estradiol: 1.91 (1.57, 2.33) norethindrone: 3.62 (2.57, 5.09)
ethinyl estradiol & norgestimate[d]	Tri-Cyclen® once daily, d 1-28, then Tri-Cyclen® LO once daily, d 29-42[e]	300 mg once daily /ritonavir 100 mg once daily, d 29-42	13	ethinyl estradiol: 0.84 (0.74, 0.95) 17-deacetyl norgestimate[e:f] 1.68 (1.51, 1.88)	ethinyl estradiol: 0.81 (0.75, 0.87) 17-deacetyl norgestimate:[f] 1.85 (1.67, 2.05)	ethinyl estradiol: 0.63 (0.55, 0.71) 17-deacetyl norgestimate:[f] 2.02 (1.77, 2.31)
fluconazole	200 mg once daily, d 1-20	300 mg once daily /ritonavir 100 mg once daily, d 11-20	30	1.05 (0.99, 1.10)	1.08 (1.02, 1.15)	1.07 (1.00, 1.15)
Gelcaprevir/pibrentasvir	300 mg gelcaprevir	300 mg QD/ritonavir 100 mg QD	12	≥ 4.06[g] (3.15, 5.23)	≥ 6.53[g] (5.24, 8.14)	≥ 14.3[g] (9.85, 20.7)
	120 mg pibrentasvir	300 mg QD/ritonavir 100 mg QD	12	≥ 1.29[g] (1.15, 1.45)	≥ 1.64[g] (1.48, 1.82)	≥ 2.29[g] (1.95, 2.68)
methadone	stable maintenance dose, d 1-15	400 mg once daily, d 2-15	16	(R)-methadone[h] 0.91	(R)-methadone[h] 1.03	(R)-methadone[h] 1.11

Table 24 Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Atazanavir

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Atazanavir; No Effect = 1.00		
				C_{max}	AUC	C_{min}
				(0.84, 1.0) total: 0.85 (0.78, 0.93)	(0.95, 1.10) total: 0.94 (0.87, 1.02)	(1.02, 1.20) total: 1.02 (0.93, 1.12)
nevirapine[hi]	200 mg BID, d 1-23	300 mg once daily / ritonavir 100 mg once daily, d 4-13, then 400 mg once daily / ritonavir 100 mg once daily, d 14-23	23	1.17 (1.09, 1.25) 1.21 (1.11, 1.32)	1.25 (1.17, 1.34) 1.26 (1.17, 1.36)	1.32 (1.22, 1.43) 1.35 (1.25, 1.47)
omeprazole[j]	40 mg single dose d 7 and d 20	400 mg once daily d 1-12	16	1.24 (1.04, 1.47)	1.45 (1.20, 1.76)	NA
rifabutin	300 mg once daily, d 1-10 then 150 mg once daily, d 11-20	600 mg once daily k d 11-20	3	1.18 (0.94, 1.48) 25-O-desacetyl-rifabutin: 8.20 (5.90, 11.40)	2.10 (1.57, 2.79) 25-O-desacetyl-rifabutin: 22.01 (15.97, 30.34)	3.43 (1.98, 5.96) 25-O-desacetyl-rifabutin: 75.6 (30.1, 190.0)
	150 mg twice weekly, d 1-15	300 mg once daily / ritonavir 100 mg once daily, d 1-17	7	2.49 l (2.03, 3.06) 25-O-desacetyl-rifabutin: 7.77 (6.13, 9.83)	1.48 l (1.19, 1.84) 25-O-desacetyl-rifabutin: 10.90 (8.14, 14.61)	1.40 l (1.05, 1.87) 25-O-desacetyl-rifabutin: 11.45 (8.15, 16.10)
rosiglitazone[m]	4 mg single dose, d 1, 7, 17	400 mg once daily D 2-7, then 300 mg once daily / ritonavir	14	1.08 (1.03, 1.13) 0.97 (0.91, 1.04)	1.35 (1.26, 1.44) 0.83 (0.77, 0.89)	NA NA

Table 24 Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Atazanavir

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Atazanavir; No Effect = 1.00		
				C_{max}	AUC	C_{min}
		100 mg once daily, d 8-17				
saquinavir (soft gelatin capsules)	1200 mg once daily, d 1-13	400 mg once daily, d 7-13	7	4.39 (3.24, 5.95)	5.49 (4.04, 7.47)	6.86 (5.29, 8.91)
Sofosbuvir/velpatasvir/voxilaprevir	400 mg sofosbuvir single dose	300 mg/100 mg ritonavir single dose	15	1.29 (1.09, 1.52) sofosbuvir metabolite GS-331007 1.05 (0.99, 1.12)	1.40 (1.25, 1.57) sofosbuvir metabolite GS- 331007 1.25 (1.16, 1.36)	NA
	100 mg velpatasvir single dose	300 mg/100 mg ritonavir single dose	15	1.29 (1.07, 1.56)	1.93 (1.58, 2.36)	NA
	100 mg voxilaprevir single dose	300 mg/100 mg ritonavir single dose	15	4.42 (3.65, 5.35)	4.31 (3.76, 4.93)	NA
tenofovir DF [n]	300 mg once daily with food d 9-16 and d 24-30	400 mg once daily with food d 1-16	33	1.14 (1.08, 1.20)	1.24 (1.21, 1.28)	1.22 (1.15, 1.30)
	300 mg once daily d 1-7 (pm) d 25-34 (pm) n	300 mg once daily/ritonavir 100 mg once daily d 25-34 (am)[o]	12	1.34 (1.20, 1.51)	1.37 (1.30, 1.45)	1.29 (1.21, 1.36)
voriconazole (Subjects with at least one functional CYP2C19 allele)	200 mg BID, d 2-3, 22-30; 400 mg BID d 1, 21	300 mg/ritonavir 100 mg QD, d 11–30	20	0.90 (0.78, 1.04)	0.67 (0.58, 0.78)	0.61 (0.51, 0.72)
voriconazole (Subjects without a	50 mg BID, d 2-3, 22-30; 100 mg BID d 1, 21	300 mg/ritonavir 100 mg QD, d 11–30	8	4.38 (3.55, 5.39)	5.61 (4.51, 6.99)	7.65 (5.71, 10.2)

Table 24 Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Atazanavir

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Atazanavir; No Effect = 1.00		
				C_{max}	AUC	C_{min}
functional CYP2C19 allele)						
lamivudine + zidovudine	150 mg lamivudine + 300 mg zidovudine BID d 1-12	400 mg once daily, d 7-12	19	lamivudine: 1.04 (0.92, 1.16) Zidovudine: 1.05 (0.88, 1.24) Zidovudine glucuronide: 0.95 (0.88, 1.02)	Lamivudine: 1.03 (0.98, 1.08) Zidovudine: 1.05 (0.96, 1.14) Zidovudine glucuronide: 1.00 (0.97, 1.03)	Lamivudine: 1.12 (1.04, 1.21) zidovudine: 0.69 (0.57, 0.84) zidovudine glucuronide: 0.82 (0.62, 1.08)

[a] N = number of subjects
[b] 400 mg ddI EC and atazanavir sulfate were administered together with food on Days 8 and 19.
[c] Upon further dose normalization of ethinyl estradiol 25 mcg with atazanavir relative to ethinyl estradiol 35 mcg without atazanavir, the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 0.82 (0.73, 0.92), 1.06 (0.95, 1.17), and 1.35 (1.11, 1.63), respectively.
[d] Upon further dose normalization of ethinyl estradiol 35 mcg with atazanavir/ritonavir relative to ethinyl estradiol 25 mcg without atazanavir/ritonavir, the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 1.17 (1.03, 1.34), 1.13 (1.05, 1.22), and 0.88 (0.77, 1.00), respectively.
[e] All subjects were on a 28 day lead-in period; one full cycle of Ortho Tri-Cyclen® Ortho Tri-Cyclen® contains 35 mcg of ethinyl estradiol. Ortho Tri-Cyclen® LO contains 25 mcg of ethinyl estradiol. Results were dose normalized to an ethinyl estradiol dose of 35 mcg.
[f] 17-deacetyl norgestimate is the active component of norgestimate.
[g] Effect of atazanavir and ritonavir on the first dose of glecaprevir and pibrentasvir is reported.
[h] (R)-methadone is the active isomer of methadone.
[i] Study was conducted in HIV-infected individuals.
[j] Subjects were treated with nevirapine prior to study entry.
[k] Omeprazole was used as a metabolic probe for CYP2C19. Omeprazole was given 2 hours after atazanavir sulfate on Day 7; and was given alone 2 hours after a light meal on Day 20.
[l] Not the recommended therapeutic dose of atazanavir.
[m] When compared to rifabutin 150 mg once daily alone d1-10 (n=14). Total of rifabutin + 25-O-desacetyl-rifabutin: AUC 2.19 (1.78, 2.69).
[n] Rosiglitazone used as a probe substrate for CYP2C8.

[o] Tenofovir disoproxil fumarate. Note that similar results were observed in studies where administration of tenofovir DF and atazanavir sulfate was separated by 12 hours.
[p] Administration of tenofovir DF and atazanavir sulfate was temporally separated by 12 hours.
NA = Not available

MICROBIOLOGY

Antiviral activity *in vitro*

Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC_{50}) 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. ATV has activity against HIV-1 Group M subtype viruses A, B, C, D, AE, AG, F, G, and J isolates in cell culture. ATV has variable activity against HIV-2 isolates (1.9 to 32 nM), with EC_{50} values above the EC_{50} values of failure isolates. Two-drug combination studies with ATV showed additive to antagonistic antiviral activity *in vitro* with abacavir and the NNRTIs (delavirdine, efavirenz, and nevirapine) and additive antiviral activity *in vitro* with the PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir), NRTIs (didanosine, emtricitabine, lamivudine, stavudine, tenofovir DF, zalcitabine, and zidovudine), the HIV-1 fusion inhibitor enfuvirtide, and two compounds used in the treatment of viral hepatitis, adefovir and ribavirin, without enhanced cytotoxicity.

Resistance

Clinical Studies of Treatment-Naive Patients: Receiving Atazanavir sulfate 400 mg Without Ritonavir: ATV-resistant clinical isolates from treatment-naive patients who experienced virologic failure developed an I50L mutation (after an average of 50 weeks of ATV therapy), often in combination with an A71V mutation. In treatment-naive patients, viral isolates that developed the I50L mutation showed phenotypic resistance to ATV but retained *in vitro* susceptibility to other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir); however, there are no clinical data available to demonstrate the effect of the I50L mutation on the efficacy of subsequently administered PIs.

Clinical Studies of Treatment-Naive Patients Receiving Atazanavir sulfate 300 mg With Ritonavir 100 mg: In Phase III study AI424-138, an as-treated genotypic and phenotypic analysis was conducted on samples from patients who experienced virologic failure ≥400 copies/mL or discontinued before achieving suppression on ATV/RTV (n=39; 9%) and LPV/RTV (n=39; 9%) through 96 weeks of treatment. In the ATV/RTV arm, one virologic failure isolate had a 56-fold decrease in ATV susceptibility emerge on therapy with the development of PI substitutions L10F, V32I, K43T, M46I, A71I, G73S, I85I/V, and L90M. Five of the treatment failure isolates in the ATV/RTV arm developed emtricitabine resistance with the emergence of either the MI84I (1 patient) or the M184V (4 patients) substitution on therapy. In the LPV/RTV arm, one virologic failure isolate had a 69-fold decrease in LPV susceptibility emerge on therapy with the development of PI substitutions L10V and V11I in addition to baseline PI substitutions V32I, I54I/V, V82A, L90M, L10I, A71I, G73S and L89V. Six of the failure isolates in the LPV/RTV arm developed emtricitabine resistance with the emergence of the M184V substitution.

Clinical Studies of Treatment-Experienced Patients: In contrast, from studies of treatment-experienced patients treated with ATV or ATV/RTV, most ATV-resistant isolates from patients

who experienced virologic failure developed mutations that were associated with resistance to multiple PIs and displayed decreased susceptibility to multiple PIs. The most common protease mutations to develop in the viral isolates of patients who failed treatment with ATV 300 mg once daily and RTV 100 mg once daily (together with tenofovir DF and an NRTI) included V32I, L33F/V/I, E35D/G, M46I/L, I50L, F53L/V, I54V, A71V/T/I, G73S/T/C, V82A/T/L, I85V, and L89V/Q/M/T. Other mutations that developed on ATV/RTV treatment including E34K/A/Q, G48V, I84V, N88S/D/T, and L90M occurred in less than 10% of patient isolates. Generally, if multiple PI resistance mutations were present in the HIV-1 of the patient at baseline, ATV resistance developed through mutations associated with resistance to other PIs and could include the development of the I50L mutation. The I50L mutation has been detected in treatment-experienced patients experiencing virologic failure after long-term treatment. Protease cleavage site changes also emerged on ATV treatment but their presence did not correlate with the level of ATV resistance.

Clinical Studies of Treatment-Naive Patients: Comparison of Ritonavir-Boosted Atazanavir sulfate vs. Unboosted Atazanavir sulfate: Study AI424-089 compared atazanavir sulfate 300 mg once daily with ritonavir 100 mg vs. atazanavir sulfate 400 mg once daily when administered with lamivudine and extended release stavudine in HIV-infected treatment-naive patients. A summary of the number of virologic failures and virologic failure isolates with ATV resistance in each arm is shown in Table 25.

Table 25 Summary of Virologic Failures[a] at Week 96 in Study AI424-089: Comparison of Ritonavir Boosted Atazanavir sulfate vs. Unboosted Atazanavir sulfate: Randomized Patients

	atazanavir sulfate 300 mg + ritonavir 100 mg (n=95)	**atazanavir sulfate 400 mg (n=105)**
Virologic Failure (≥50 copies/mL) at Week 96	15 (16%)	34 (32%)
Virologic Failure with Genotypes and Phenotypes Data	5	17
Virologic Failure Isolates with ATV-resistance at Week 96	0/5 (0%)[b]	4/17 (24%)[b]
Virologic Failure Isolates with I50L Emergence at Week 96[c]	0/5 (0%)[b]	2/17 (12%)[b]
Virologic Failure Isolates with Lamivudine Resistance at Week 96	2/5 (40%)[b]	11/17 (65%)[b]

[a] Virologic failure includes patients who were never suppressed through Week 96 and on study at Week 96, had virologic rebound or discontinued due to insufficient viral load response.

[b] Percentage of Virologic Failure Isolates with genotypic and phenotypic data.

[c] Mixture of I50I/L emerged in 2 other ATV 400 mg-treated patients. Neither isolate was phenotypically resistant to ATV.

Cross-Resistance

An association between virologic response at 48 weeks and the number and type of primary PI-resistance-associated mutations detected in baseline HIV-1 isolates from antiretroviral-

experienced patients receiving ATV/RTV once daily or lopinavir (LPV)/RTV twice daily in Study AI424-045 is shown in Table 26.

Overall, both the number and type of baseline PI mutations affected response rates in treatment-experienced patients. In the ATV/RTV group, patients had lower response rates when 3 or more baseline PI mutations including a mutation at position 36, 71, 77, 82, or 90 were present compared to patients with 1-2 PI mutations including one of these mutations.

Table 26: HIV RNA Response by Number and Type of Baseline PI Mutation, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

	Virologic Response = HIV RNA <400 copies/mL[b]	
Number and Type of Baseline PI Mutations[a]	**ATV/RTV (n=110)**	**LPV/RTV (n=113)**
3 or more primary PI mutations including:[c]		
D30N	75% (6/8)	50% (3/6)
M36I/V	19% (3/16)	33% (6/18)
M46I/L/T	24% (4/17)	23% (5/22)
I54V/L/T/M/A	31% (5/16)	31% (5/16)
A71V/T/I/G	34% (10/29)	39% (12/31)
G73S/A/C/T	14% (1/7)	38% (3/8)
V77I	47% (7/15)	44% (7/16)
V82A/F/T/S/I	29% (6/21)	27% (7/26)
I84V/A	11% (1/9)	33% (2/6)
N88D	63% (5/8)	67% (4/6)
L90M	10% (2/21)	44% (11/25)
Number of baseline primary PI mutations[a]		
All patients, as-treated	58% (64/110)	59% (67/113)
0–2 PI mutations	75% (50/67)	75% (50/67)
3–4 PI mutations	41% (14/34)	43% (12/28)
5 or more PI mutations	0% (0/9)	28% (5/18)

[a] Primary mutations include any change at D30, V32, M36, M46, I47, G48, I50, I54, A71, G73, V77, V82, I84, N88, and L90.
[b] Results should be interpreted with caution because the subgroups were small.
[c] There were insufficient data (n<3) for PI mutations V32I, I47V, G48V, I50V, and F53L.

The response rates of antiretroviral-experienced patients in Study AI424-045 were analyzed by baseline phenotype (shift in in vitro susceptibility relative to reference, Table 27). The analyses are based on a select patient population with 62% of patients receiving an NNRTI-based regimen before study entry compared to 35% receiving a PI-based regimen. Additional data are needed to determine clinically relevant break points for atazanavir sulfate.

Table 27: Baseline Phenotype by Outcome, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

	Virologic Response = HIV RNA <400 copies/mL[b]	
Baseline Phenotype[a]	**ATV/RTV (n=111)**	**LPV/RTV (n=111)**
0–2	71% (55/78)	70% (56/80)
>2–5	53% (8/15)	44% (4/9)

Table 27: Baseline Phenotype by Outcome, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

	Virologic Response = HIV RNA <400 copies/mL[b]	
Baseline Phenotype[a]	**ATV/RTV (n=111)**	**LPV/RTV (n=111)**
>5–10	13% (1/8)	33% (3/9)
>10	10% (1/10)	23% (3/13)

[a] Fold change in *in vitro* susceptibility relative to the wild-type reference.
[b] Results should be interpreted with caution because the subgroups were small.

TOXICOLOGY

Acute Toxicity

The single-dose oral toxicity of atazanavir was evaluated in mice and rats at doses of 200 to 1600 mg/kg. In mice, doses of 800 and 1600 mg/kg produced death; clinical signs including tremors, hypoactivity, ptosis, scant stool, and/or urogenital staining; and transient group mean body weight loss (males). Additional clinical signs observed at 1600 mg/kg included loss of righting reflex, recumbency, and labored respiration. Clinical signs were generally first noted on Day 2 and resolved within 2 to 3 days. Doses up to 400 mg/kg were well tolerated in mice with only transient scant stool observed at 400 mg/kg. The no-effect dose in mice was 200 mg/kg. In rats, no atazanavir-related effects were observed after administration of single oral doses up to 1600 mg/kg.

Short- and Long-Term Toxicity

Repeat-dose oral toxicity studies were conducted in rats for 2 weeks to 6 months, and in dogs for 2 weeks to 9 months to evaluate the short- and long-term toxicity of atazanavir. Atazanavir-related findings were generally confined to the liver and included increases in serum total bilirubin in both species and liver enzymes in dogs, and hepatocellular vacuolation and hypertrophy in rats. These liver changes were observed at systemic exposures (AUC) of atazanavir that were 0.4 to 4 times in rats and 0.2 to 20 times in dogs the exposure in humans given atazanavir at 400 mg once daily. Similar liver changes were also observed in a 3-month oral toxicity study in mice at exposures 0.4 to 12 times the exposure in humans given 400 mg once daily. Additionally in mice, cytotoxic liver changes were observed in males (increased transaminases) and females (increased transaminases and single-cell necrosis) at exposures equivalent to and 12 times, respectively, that observed in humans given 400 mg once daily, whereas no effects were observed at exposures of 0.4 and 4 times, respectively, human exposure. Serum cholesterol and glucose were minimally to mildly increased in rats but not in mice. Similar increases were observed in an initial 2-week oral toxicity study performed in dogs. Subsequent 2-week and 9-month oral toxicity studies in dogs showed no drug-related changes in serum cholesterol and glucose.

Cardiotoxicity

Atazanavir minimally increased the duration of the rabbit Purkinje fiber action potential, weakly inhibited sodium and potassium IKr (HERG-encoded) and IKs currents (IC_{50} > 30 mcM), and moderately inhibited calcium current (IC_{50} = 10.4 mcM) *in vitro*. Electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prolongation of QT interval, and prolongation of

QRS complex) were observed only in an initial 2-week oral toxicity study performed in dogs and were considered secondary to the marked clinical toxicity and not a direct drug effect. Subsequent 2-week and 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes.

Reproduction and Teratology

In a fertility and early embryonic development study in rats, atazanavir altered oestrus cycling with no effects on mating or fertility. No teratogenic effects were observed in rats or rabbits at maternally toxic doses. In the pre- and postnatal development assessment in rats, atazanavir produced a transient reduction in body weight in the offspring at a maternally toxic dose. Systemic exposure to atazanavir at doses that resulted in maternal toxicity was at least equal to or slightly greater than that observed in humans given 400 mg once daily.

Carcinogenicity and Mutagenicity

Carcinogenicity studies with atazanavir were conducted in mice and rats. Mice were administered doses of 20, 40, and 80 mg/kg/day in males and 40, 120, and 360 mg/kg/day in females. In female mice, there was an increase in the incidence of benign hepatocellular adenomas at the highest dose. The exposure in female mice at the high dose is approximately seven times exposure in humans given atazanavir 400 mg once daily. No increase in the incidence of tumors was observed in female mice at lower doses or male mice at any dose. Exposures in male and female mice at nontumorigenic doses are approximately four times human exposure at 400 mg/day. In rats administered doses of 100, 350, and 1200 mg/kg/day, there was no increased incidence of any tumor type. Exposures in rats at the high dose are approximately two (males) and six (females) times exposure in humans given atazanavir 400 mg once daily. The clinical significance of benign hepatocellular adenomas in high-dose female mice is unknown as these benign tumors occurred in mice only at exposures (approximately seven times human exposure at 400 mg/day) causing significant liver damage. Atazanavir tested positive in an *in vitro* clastogenicity test using primary human lymphocytes, in the absence and presence of metabolic activation. Atazanavir tested negative in the *in vitro* Ames reverse-mutation assay, *in vivo* micronucleus and DNA repair tests in rats, and *in vivo* DNA damage test in rat duodenum (Comet assay).

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PART III: CONSUMER INFORMATION

PrAPO-ATAZANAVIR
Atazanavir capsules
Apotex Standard
150 mg, 200 mg and 300 mg

This leaflet is Part III of a three-part "Product Monograph" published when APO-ATAZANAVIR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-ATAZANAVIR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

ALERT: Find out about medicines that should NOT be taken with APO-ATAZANAVIR.

What the medication is used for:

APO-ATAZANAVIR is a prescription medicine used in combination with antiviral drugs to treat patients who are infected with HIV (the human immunodeficiency virus), the virus that causes AIDS. HIV infection destroys CD4 (T) cells, which are important to the immune system. The immune system helps fight infection. After a large number of T cells are destroyed, AIDS develops. APO-ATAZANAVIR helps to block HIV protease, an enzyme that is needed for the HIV virus to multiply. APO-ATAZANAVIR may lower the amount of HIV in your blood, helps your body keep its supply of CD4 (T) cells, and reduce the risk of death and illness associated with HIV.

What it does:

APO-ATAZANAVIR belongs to a family of medicines called protease inhibitors that control HIV infection by blocking a protease enzyme that HIV needs to multiply. Protease inhibitors work in two ways: they lower the number of HIV viruses in your body and allow the number of your CD4 T-cells that fight infection in your body to increase.

Your doctor prescribed APO-ATAZANAVIR for you because you are infected by the HIV virus that causes AIDS. APO-ATAZANAVIR helps by reducing the amount of HIV virus in your body and, therefore, reducing the risk of developing illnesses associated with HIV disease.

APO-ATAZANAVIR is prescribed together with other anti-viral medicines that also fight HIV infection. Your doctor will determine which combination of these medicines with APO-ATAZANAVIR is best for you.

You should know that APO-ATAZANAVIR is not a cure for HIV infection and that you may continue to develop infections or other illnesses associated with HIV infection. You should, therefore, remain under the care of your doctor while taking APO-ATAZANAVIR.

Treatment with APO-ATAZANAVIR does not reduce the risk of transmission of HIV to others through sexual contact or blood contamination. It is important to continue safe sex practices and not to share needles.

When it should not be used:

- APO-ATAZANAVIR, coadministered with ritonavir and one of the following anticoagulants: rivaroxaban (XARELTO*) or apixaban (ELIQUIS®).
- If you know that you are allergic to atazanavir or any of the other ingredients of APO-ATAZANAVIR (See "What the important non-medicinal ingredients are").
- If you have, or have had a severe liver disease.
- If you take rifampin (RIFADIN*, RIFATER*, or ROFACT*), triazolam, or ergot alkaloids (ex. dihydroergotamine, MIGRANAL NS*), irinotecan (CAMPTOSAR*), lovastatin (MEVACOR*), simvastatin (ZOCOR*), lurasidone (LATUDA*) with ritonavir (NORVIR*), pimozide (ORAP*), indinavir (CRIXIVAN*), elbasvir/grazoprevir (ZEPATIER *), glecaprevir/pibrentasvir (MAVIRET, quinidine (BIQUIN*) and vardenafil (LEVITRA*) when used for erectile dysfunction.
- Vosevi* (sofosbuvir/velpatasvir/voxilaprevir), used to treat HCV infection, is not recommended with APO-ATAZANAVIR.
- If you take medicinal products containing St. John's wort (*Hypericum perforatum*) as this may result in loss of efficacy and development of resistance to APO-ATAZANAVIR.
- VFEND* (voriconazole), used to treat fungal infections, is not recommended with APO-ATAZANAVIR.
- If you take VIRAMUNE* (nevirapine, used for HIV infection).
- If you take XATRAL* (alfuzosin, used to treat benign enlargement of the prostate).

- If you take REVATIO* (sildenafil, used to treat pulmonary arterial hypertension).

What the medicinal ingredient is:

Each capsule contains amounts of atazanavir sulfate corresponding to 150, 200 and 300 mg of atazanavir free base.

What the important non-medicinal ingredients are:

The non-medicinal ingredients include colloidal silicon dioxide, lactose monohydrate, magnesium stearate, and sodium starch glycolate.

The capsule shells contains black iron oxide (300 mg only), edible black ink, FD&C Blue #2 (for all strengths), gelatin and titanium dioxide (for all strengths), red iron oxide (300 mg only), and sodium lauryl sulfate (300 mg only).

Imprinting ink contains black iron oxide, potassium hydroxide, propylene glycol, shellac and strong ammonia solution.

What dosage forms it comes in:

Capsules for oral use.

WARNINGS AND PRECAUTIONS

BEFORE you use APO-ATAZANAVIR, talk to your doctor or pharmacist:

- If you suffer from liver disease because the dose of APO-ATAZANAVIR may need to be reduced.
- If you are intolerant to lactose because APO-ATAZANAVIR capsules contain small quantities of lactose. These small quantities are unlikely to induce specific symptoms of intolerance.
- If you are pregnant or planning to become pregnant, or breast feeding.
- If you have a heart problem.

Discuss the use of APO-ATAZANAVIR with your doctor because some conditions may require special attention before or while taking this medicine. In particular because:

- There have been changes in the way the heart beats (heart rhythm changes). Call your healthcare provider right away if you get dizzy or lightheaded. These could be symptoms of a heart problem.
- There is a possibility of increased bleeding if you have a type A or B haemophilia.
- There have been reports of increased sugar in the blood and development or worsening of diabetes mellitus when using protease inhibitors.
- Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck, breasts and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause or long-term health effects of these conditions are not known at this time.
- There have been reports of kidney stones. If you develop signs or symptoms of kidney stones (pain in your side, blood in your urine, pain when you urinate) call your healthcare provider right away.
- APO-ATAZANAVIR should not be used in combination with quetiapine. Serious and/or life-threatening reactions, including severe sedation and coma, have been reported for use of HIV protease inhibitors together with quetiapine. If co-administration is necessary, your doctor may need to monitor and adjust the dose of quetiapine.

See section on SIDE EFFECTS AND WHAT TO DO ABOUT THEM, for more information.

Can I take APO-ATAZANAVIR during pregnancy and breast-feeding?

- Pregnancy: It is not known if APO-ATAZANAVIR can harm your unborn baby.

  Pregnant women have experienced serious side effects when taking APO-ATAZANAVIR with other HIV medicines called nucleoside analogues. You and your healthcare provider will need to decide if APO-ATAZANAVIR is right for you. If you use APO-ATAZANAVIR while you are pregnant, talk to your healthcare provider about the Antiretroviral Pregnancy Registry.

- Breast-feeding: If you are breastfeeding, do not take APO-ATAZANAVIR unless specifically directed by your doctor. This is to avoid transmission of HIV to your infant through breast milk.

There have been reports of a condition called lactic acidosis syndrome (excess of lactic acid in the blood) with the use of APO-ATAZANAVIR in combination with other medicines used to treat HIV infection. This serious side effect has occasionally been fatal. Lactic acidosis occurs more often in women, particularly if very overweight. Frequent nausea, vomiting and stomach pain might indicate the development of lactic acidosis.

Ask your doctor for advice if you get pregnant or think you are pregnant or if you want to breast-feed.

Can APO-ATAZANAVIR be used in children?

APO-ATAZANAVIR capsules can be used in children 6 years of age and older. Dosing recommendations are not available for children from 3 months to less than 6 years of age. APO-ATAZANAVIR should not be used in babies under the age of 3 months.

INTERACTIONS WITH THIS MEDICATION

APO-ATAZANAVIR may interact with other drugs, including those you take without a prescription. You must tell your doctor or pharmacist about all drugs, including prescription and non-prescription drugs, herbal products and supplements and street drugs you are taking or planning to take before you take APO-ATAZANAVIR. APO-ATAZANAVIR should be taken in combination with other antiretroviral agents. Clinical trials have found that combination antiviral therapy is more effective than one drug alone at reducing the amount of HIV in the blood and at reducing the development of resistance.

APO-ATAZANAVIR should not be taken with indinavir (CRIXIVAN*) as both APO-ATAZANAVIR and CRIXIVAN* sometimes cause increased levels of bilirubin in the blood. Increased levels of bilirubin can cause yellowing of the skin and the white part of the eyes. APO-ATAZANAVIR should not be taken with the hepatitis C treatment glecaprevir/pibrentasvir (MAVIRET*) or grazoprevir-containing products including elbasvir/grazoprevir fixed-dose combination (ZEPATIER*) because of the potential increase in the risk of ALT elevations in the blood. Please see section "When it should not be used".

If you are taking didanosine (VIDEX®) buffered tablets or antacids, take APO-ATAZANAVIR with a meal one hour after or more than two hours before you take these medicines. Taking them together causes lower amounts of APO-ATAZANAVIR in the blood making it less effective.

The following medicines may require your healthcare provider to either monitor your therapy more closely or to change the dose or dose schedule of either APO-ATAZANAVIR or the other medicine:

- The anticoagulant warfarin (COUMADIN®).
- APO-ATAZANAVIR, coadministered with ritonavir and one of the following anticoagulants: dabigatran (PRADAXA*), edoxaban (LIXIANA*).
- Corticosteroids, given by nose or inhaled, such as fluticasone propionate (FLONASE* or FLOVENT*). Your doctor may choose not to keep you on fluticasone, especially if you are also taking ritonavir (KALETRA*, NORVIR*).
- Medicines to prevent organ transplant rejection: cyclosporine (SANDIMMUNE*, NEORAL*), tacrolimus (PROGRAF*) and sirolimus (RAPAMUNE*).
- Medicines for abnormal heart rhythm: lidocaine and quinidine (also known as BIQUIN*), amiodarone (CORDARONE*).
- The antidepressant trazodone.
- Tricyclic antidepressant such as amitriptyline (ELAVIL*), desipramine, imipramine (TOFRANIL*).
- Rifabutin (MYCOBUTIN*)
- Calcium channel blockers such as diltiazem (CARDIZEM* or TIAZAC*), felodipine (PLENDIL*), verapamil (COVERA-HS* or ISOPTIN SR*).
- Oral contraceptives; APO-ATAZANAVIR may affect the safety and effectiveness of hormonal contraceptives such as birth control pills. **Talk to your healthcare provider about choosing an effective method of contraception**. Hormonal contraceptives do not prevent the spread of HIV to others.
- Stomach acid reducing agents (eg, famotidine, also known as PEPCID AC*).
- Proton-pump inhibitors used for indigestion, heart burn or ulcers (ex. omeprazole, also known as LOSEC*).
- The antifungals ketoconazole (NIZORAL*) and itraconazole (SPORANOX*) if you are taking APO-ATAZANAVIR with ritonavir.
- Voriconazole (VFEND*), used to treat fungal infections: your doctor should monitor your therapy more closely for voriconazole-associated adverse events.
- The use of APO-ATAZANAVIR with the hepatitis C treatment

sofosbuvir/velpatasvir/voxilaprevir (VOSEVI*) is not recommended.
- Efavirenz
- Midazolam (when injected)
- Atorvastatin (LIPITOR*); there is an increased chance of serious side effects if you take APO-ATAZANAVIR with this cholesterol-lowering medicine.
- Sildenafil (VIAGRA*), or tadalafil (CIALIS*), used for erectile dysfunction: before you take sildenafil or, tadalafil with APO-ATAZANAVIR, talk to your doctor about possible drug interactions and side effects. Your doctor may lower your dose of sildenafil or tadalafil if you are taking APO-ATAZANAVIR. Vardenafil should not be coadministered with APO-ATAZANAVIR. If you take sildenafil or tadalafil and APO-ATAZANAVIR together, you may be at increased risk of side effects of sildenafil or tadalafil such as low blood pressure, visual changes, and penile erection lasting more than 4 hours. If you experience any of these side effects you should seek immediate medical assistance.
- Coadministration of APO-ATAZANAVIR and tadalafil (ADCIRCA*) for the treatment of pulmonary hypertension is not recommended.
- APO-ATAZANAVIR should not be coadministered with SEREVENT DISKUS* (salmeterol) and/or ADVAIR* (salmeterol with fluticasone) used to treat asthma, emphysema/ chronic obstructive pulmonary disease also known as COPD.
- Bosentan (TRACLEER*) when used to treat pulmonary arterial hypertension.
- Medicine to treat opioid dependence: buprenorphine (SUBOXONE*).
- The antibiotic clarithromycin (BIAXIN*).
- Colchicine, used to prevent or to treat gout.
- Antiepileptic medicines such as TEGRETOL* (carbamazepine), DILANTIN* (phenytoin), or phenobarbital, or LAMICTAL* (lamotrigine).
- Lurasidone (LATUDA*) when used with ritonavir.
- Quetiapine (SEROQUEL*), used to treat schizophrenia and bipolar disorder.

Other medicines may interact with APO-ATAZANAVIR. Remember to tell your healthcare provider all the medicines (prescription, non-prescription) and herbal supplements you are taking or planning to take.

PROPER USE OF THIS MEDICATION

Usual dose:

For adults, who have never taken anti-HIV medicines before, the recommended dose of APO-ATAZANAVIR is

- 300 mg (one 300-mg capsule or two 150-mg capsules) once daily taken with ritonavir 100 mg once daily taken with food.

OR

- 400 mg (two 200-mg capsules), or as prescribed by physician, once a day with food (without ritonavir).

For adults who have taken anti-HIV medicines in the past, the usual dose is:
- 300 mg (one 300-mg capsule or two 150-mg capsules) once daily taken with ritonavir 100 mg once daily taken with food.

For children from 6 to 18 years of age, the recommended dose is based on weight. Your child's physician will provide you with the correct dosing instructions. **Do not exceed the adult dose**.

It is important that you take APO-ATAZANAVIR with food to achieve higher, more consistent APO-ATAZANAVIR levels. APO-ATAZANAVIR capsules should not be opened, they should be swallowed whole with water.

APO-ATAZANAVIR must be taken every day exactly as your doctor prescribes because it gives you the best chance to slow down resistance to the medicine. Therefore do not change or stop your daily dose of APO-ATAZANAVIR without first asking your doctor.

APO-ATAZANAVIR should always be taken with other antiretrovirals.

APO-ATAZANAVIR should be taken at about the same time each day with a meal.

If a side effect prevents you from taking APO-ATAZANAVIR as directed, tell your doctor right away.

Always keep APO-ATAZANAVIR on hand so you don't run out. When you travel or need to stay in the hospital, make sure you will have enough APO-ATAZANAVIR to last until you can get a new supply.

Overdose:

If you think you have taken too much APO-ATAZANAVIR, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

It is important to take the daily dose prescribed by your doctor to ensure that you get maximum benefit. If you forget to take a dose, take the dose you missed as soon as possible with some food, and then return to your normal schedule. However, if a dose is skipped, do not double the next dose. Continue as normal with your next dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, APO-ATAZANAVIR can have side effects.

When treating HIV infection, it is not always easy to tell what side effects are caused by APO-ATAZANAVIR, by the other medicines you take, or by the HIV infection itself. For this reason, it is important that you inform your doctor of any change in your health.

Some of the most common side effects of APO-ATAZANAVIR taken with other anti-HIV medicines include nausea, headache, rash, abdominal pain, and yellowing of the skin or whites of the eyes.

APO-ATAZANAVIR can cause the following side effects:

- **Yellowing of the skin or eyes**. These effects may be due to increases in bilirubin levels in the blood. Call your healthcare provider if your skin or the white part of your eyes turn yellow. Although these effects may not be damaging to your liver, skin, or eyes, it is important to tell your healthcare provider promptly if they occur.

- **If you have liver disease** including hepatitis B or C, your liver disease may get worse when you take anti-HIV medicines like APO-ATAZANAVIR.

- **Rash**. Rash (redness and itching) sometimes occurs in patients taking APO-ATAZANAVIR, most often in the first few weeks after the medicine is started. Tell your healthcare provider if rash occurs. If severe rash occurs or if severe rash with swelling of the face or tongue occur, seek immediate medical attention.

- **Diabetes and high blood sugar (hyperglycemia)** sometimes happen in patients taking protease inhibitor medicines like APO-ATAZANAVIR. Some patients had diabetes before taking protease inhibitors while others did not. Some patients may need changes in their diabetes medicine.

- **A change in the way your heart beats (heart rhythm change)**. Call your healthcare provider right away if you get dizzy or lightheaded. These could be symptoms of a heart problem.

- **Gallbladder disorders** (which may include gallstones and gallbladder inflammation) and includes symptoms such as severe abdominal pain, nausea, vomiting, itching, jaundice (yellowing of the skin and eyes), pale stool and dark urine. If these symptoms occur, contact your doctor immediately.

- Your immune system may get stronger when you start taking HIV medicines. It may begin to fight infections that have been hidden in your body for a long time or your immune system could react against your own body (autoimmune disease). Examples are Grave's disease (which affects the thyroid gland), Guillain-Barre syndrome (which affects the nervous system) or polymyositis (which affects the muscles). Autoimmune disease may develop at any time, sometimes months after the start of HIV therapy. Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling, or fatigue or any new symptoms contact your doctor straight away.

Other side effects may occur with APO-ATAZANAVIR. Ask your doctor or pharmacist for more information about side effects. Inform your doctor promptly about these or any other symptoms. If the condition persists or worsens, seek medical attention.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

This summary does not include everything there is to know about APO-ATAZANAVIR. If you have questions or concerns, or want more information about APO-ATAZANAVIR, your physician and pharmacist have the complete prescribing

information upon which this leaflet was based. You may want to read it and discuss it with your doctor or other healthcare professional. Remember, no written summary can replace careful discussion with your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug & call your doctor or pharmacist
		Only if severe	In all cases	
Common	Rash (redness & itching)	√		
	Yellowing of the skin or eyes		√	
Uncommon	Frequent nausea, vomiting & stomach pain (occurs more often in women, particularly if very overweight)		√	
Postmarket-ing cases of unknown frequency	Diabetes and high blood sugar		√	
	Heart rhythm changes		√	
	Gall bladder disorders	√		
	Kidney stones (pain in your side, blood in your urine, pain when you urinate)			√
Postmarket-ing cases of unknown frequency	Rash with swelling of the face or tongue			√

This is not a complete list of side effects. If you have any unexpected effects while taking APO-ATAZANAVIR, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.

Store at 15°C to 30°C. Protect from moisture.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about APO-ATAZANAVIR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this patient medication information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp) Find the Consumer Information on the manufacturer's websitehttp://www.apotex.ca/products , or by calling 1-800-667-4708.

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