HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ATAZANAVIR CAPSULES safely and effectively. See full prescribing information for ATAZANAVIR CAPSULES.

ATAZANAVIR capsules, for oral use

Initial U.S. Approval: 2003

----------RECENT MAJOR CHANGES----------

Contraindications (4) 09/2020

Warnings and Precautions

Immune Reconstituted Syndrome (5.10) 09/2020

----------INDICATIONS AND USAGE----------

Atazanavir capsules are a protease inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and in pediatric patients 6 years of age and older weighing at least 15 kg. (1)

----------DOSAGE AND ADMINISTRATION----------

- *Pretreatment testing:* Renal laboratory testing should be performed in all patients prior to initiation of atazanavir capsules and continued during treatment with atazanavir capsules. Hepatic testing should be performed in patients with underlying liver disease prior to initiation of atazanavir capsules and continued during treatment with atazanavir capsules. (2.2)
- *Treatment-naive adults:* Atazanavir capsules 300 mg with ritonavir 100 mg once daily with food or atazanavir capsules 400 mg once daily with food. (2.3)
- *Treatment-experienced adults:* Atazanavir capsules 300 mg with ritonavir 100 mg once daily with food. (2.3)
- *Pediatric patients:* Atazanavir capsule dosage is based on body weight not to exceed the adult dose and must be taken with food. (2.4)
- *Pregnancy:* Atazanavir capsules 300 mg with ritonavir 100 mg once daily with food, with dosing modifications for some concomitant medications. (2.6)
- *Dosing modifications:* may be required for concomitant therapy (2.3, 2.4, 2.6), renal impairment (2.7), and hepatic impairment (2.8).

----------DOSAGE FORMS AND STRENGTHS----------

- Capsules: 150 mg, 200 mg, 300 mg. (3, 16)

----------CONTRAINDICATIONS----------

- Atazanavir capsules are contraindicated in patients with previously demonstrated hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product. (4)
- Coadministration with alfuzosin, amiodarone (if atazanavir is coadministered with ritonavir), quinidine (if atazanavir is coadministered with ritonavir), triazolam, orally administered midazolam, ergot derivatives, rifampin, irinotecan, lurasidone (if atazanavir is coadministered with ritonavir), lovastatin, simvastatin, lomitapide, indinavir, cisapride, pimozide, St. John's wort, nevirapine, elbasvir/grazoprevir, glecaprevir/pibrentasvir, and sildenafil when dosed as REVATIO®. (4)

----------WARNINGS AND PRECAUTIONS----------

- *Cardiac conduction abnormalities:* PR interval prolongation may occur in some patients. ECG monitoring should be considered in patients with preexisting conduction system disease or when administered with other drugs that may prolong the PR interval. (5.1, 7.3, 12.2, 17)
- Severe Skin Reactions: Discontinue if severe rash develops. (5.2, 17)
- *Hyperbilirubinemia:* Most patients experience asymptomatic increases in indirect bilirubin, which is reversible upon discontinuation. Do not dose reduce. If a concomitant transaminase increase occurs, evaluate for alternative etiologies. (5.8)
- *Hepatotoxicity:* Patients with hepatitis B or C infection are at risk of increased transaminases or hepatic decompensation. Monitor hepatic laboratory tests prior to therapy and during treatment. (2.8, 5.4, 8.8)
- *Chronic kidney disease* has been reported during postmarketing surveillance in patients with HIV-1 infection treated with atazanavir, with or without ritonavir. Consider alternatives in patients at high risk for renal disease or with preexisting renal disease. Monitor renal laboratory tests prior to therapy and during treatment. Consider discontinuation of atazanavir in patients with progressive renal disease. (5.5)
- *Nephrolithiasis and cholelithiasis* have been reported. Consider temporary interruption or discontinuation. (5.6)
- The concomitant use of atazanavir with ritonavir and certain other medications may result in known or potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.7, 7.3)
- Patients receiving atazanavir may develop new onset or exacerbations of diabetes mellitus/hyperglycemia (5.9), immune reconstitution syndrome (5.10), and redistribution/accumulation of body fat (5.11).
- *Hemophilia:* Spontaneous bleeding may occur and additional factor VIII may be required. (5.12)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥2%) are nausea, jaundice/scleral icterus, rash, headache, abdominal pain, vomiting, insomnia, peripheral neurologic symptoms, dizziness, myalgia, diarrhea, depression, and fever. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Laurus Generics Inc. at 1-833-3-LAURUS (1-833-352-8787) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

Coadministration of atazanavir can alter the concentration of other drugs and other drugs may alter the concentration of atazanavir. The potential drug-drug interactions must be considered prior to and during therapy. (4, 7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy:* Available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate. (8.1)
- *Lactation:* Breastfeeding is not recommended. (8.2)
- *Hepatitis B or C co-infection:* Monitor liver enzymes. (5.4, 6.1)
- *Renal impairment:* Atazanavir is not recommended for use in treatment-experienced patients with end-stage renal disease managed with hemodialysis. (2.7, 8.7)
- *Hepatic impairment:* Atazanavir is not recommended in patients with severe hepatic impairment. Atazanavir with ritonavir is not recommended in patients with any degree of hepatic impairment. (2.8, 8.8)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Atazanavir capsules are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and in pediatric patients 6 years of age and older weighing at least 15 kg.

Limitations of Use:

- Atazanavir is not recommended for use in pediatric patients below the age of 3 months due to the risk of kernicterus *[see Use in Specific Populations (8.4)]*.
- Use of atazanavir with ritonavir in treatment-experienced patients should be guided by the number of baseline primary protease inhibitor resistance substitutions *[see Microbiology (12.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Overview

- Atazanavir capsules must be taken with food.
- Do not open the capsules.
- The recommended oral dosage of atazanavir capsules depends on the treatment history of the patient and the use of other coadministered drugs. When coadministered with H$_2$-receptor antagonists or proton-pump inhibitors, dose separation may be required *[see Dosage and Administration (2.3, 2.4, and 2.6) and Drug Interactions (7)]*.
- Atazanavir capsules without ritonavir are not recommended for treatment-experienced adult or pediatric patients with prior virologic failure *[see Clinical Studies (14)]*.
- Efficacy and safety of atazanavir capsules with ritonavir when ritonavir is administered in doses greater than 100 mg once daily have not been established. The use of higher ritonavir doses may alter the safety profile of atazanavir (cardiac effects, hyperbilirubinemia) and, therefore, is not recommended. Prescribers should consult the complete prescribing information for ritonavir when using ritonavir.

2.2 Testing Prior to Initiation and During Treatment with Atazanavir Capsules

Renal laboratory testing should be performed in all patients prior to initiation of atazanavir capsules and continued during treatment with atazanavir capsules. Renal laboratory testing should include serum creatinine, estimated creatinine clearance, and urinalysis with microscopic examination *[see Warnings and Precautions (5.5, 5.6)]*.

Hepatic laboratory testing should be performed in patients with underlying liver disease prior to initiation of atazanavir capsules and continued during treatment with atazanavir capsules *[see Warnings and Precautions (5.4)]*.

2.3 Dosage of Atazanavir Capsules in Adult Patients

Table 1 displays the recommended dosage of atazanavir capsules in treatment-naive and treatment-experienced adults. Table 1 also displays recommended dosage of atazanavir capsules and ritonavir when given concomitantly with other antiretroviral drugs and H$_2$-receptor antagonists (H2RA). Ritonavir is required with several atazanavir capsules dosage regimens (see the ritonavir complete prescribing information about the safe and effective use of ritonavir). The use of atazanavir capsules in treatment-experienced adult patients without ritonavir is not recommended.

Table 1: Recommended Atazanavir Capsules and Ritonavir Dosage in Adults[a]

	Atazanavir Capsules Once Daily Dosage	Ritonavir Once Daily Dosage
Treatment-Naive Adult Patients		
recommended regimen	300 mg	100 mg
unable to tolerate ritonavir	400 mg	N/A
in combination with efavirenz	400 mg	100 mg
Treatment-Experienced Adult Patients		
recommended regimen	300 mg	100 mg
in combination with both H2RA and tenofovir DF	400 mg	100 mg

[a] See *Drug Interactions (7)* for instructions concerning coadministration of acid-reducing medications (eg, H2RA or proton pump inhibitors [PPIs]), and other antiretroviral drugs (eg, efavirenz, tenofovir DF, and didanosine).

2.4 Dosage of Atazanavir Capsules in Pediatric Patients

The recommended daily dosage of atazanavir capsules and ritonavir in pediatric patients (6 years of age to less than 18 years of age) is based on body weight (see Table 2).

Table 2: Recommended Dosage of Atazanavir Capsules and Ritonavir in Pediatric Patients (6 to less than 18 years of age)[a,b]

Body weight	Atazanavir Capsules Daily Dosage	Ritonavir Daily Dosage
Treatment-Naive and Treatment-Experienced[c]		
Less than 15 kg	Capsules not recommended	N/A
At least 15 kg to less than 35 kg	200 mg	100 mg
At least 35 kg	300 mg	100 mg
Treatment-Naive, at least 13 years old and cannot tolerate ritonavir		
At least 40 kg	400 mg	N/A

[a] Administer atazanavir capsules and ritonavir simultaneously with food.
[b] The same recommendations regarding the timing and maximum doses of concomitant PPIs and H2RAs in adults also apply to pediatric patients. See *Drug Interactions (7)* for instructions concerning coadministration of acid-reducing medications (eg, H2RA or PPIs), and other antiretroviral drugs (eg, efavirenz, tenofovir DF, and didanosine).
[c] In treatment-experienced patients, atazanavir capsules must be administered with ritonavir.

When transitioning between formulations, a change in dose may be needed. Consult the dosing table for the specific formulation.

2.6 Dosage Adjustments in Pregnant Patients

Table 4 includes the recommended dosage of atazanavir capsules and ritonavir in treatment-naive and treatment-experienced pregnant patients. In these patients, atazanavir capsules must be administered with ritonavir. There are no dosage adjustments for postpartum patients (see Table 1 for the recommended atazanavir capsules dosage in adults) *[see Use in Specific Populations (8.1)]*.

Table 4: Recommended Dosage of Atazanavir Capsules and Ritonavir in Pregnant Patients[a]

	Atazanavir Capsules Once Daily Dosage	Ritonavir Once Daily Dosage
Treatment-Naive and Treatment-Experienced		
Recommended Regimen	300 mg	100 mg
Treatment-Experienced During the Second or Third Trimester When Coadministered with either H2RA or Tenofovir DF[b]		
In combination with **EITHER** H2RA **OR** tenofovir DF	400 mg	100 mg

[a] See *Drug Interactions (7)* for instructions concerning coadministration of acid-reducing medications (eg, H2RA or PPIs), and other antiretroviral drugs (eg, efavirenz, tenofovir DF, and didanosine).
[b] Atazanavir capsules are not recommended for treatment-experienced pregnant patients during the second and third trimester taking atazanavir capsules with **BOTH** tenofovir DF and H2RA.

2.7 Dosage in 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 atazanavir capsules. Treatment-naive patients with end-stage renal disease managed with hemodialysis should receive atazanavir capsules 300 mg with ritonavir 100 mg. Atazanavir capsules are not recommended in treatment-experienced patients with HIV-1 infection who have end-stage renal disease managed with hemodialysis *[see Use in Specific Populations (8.7)]*.

2.8 Dosage Adjustments in Patients with Hepatic Impairment

Table 5 displays the recommended atazanavir capsules dosage in treatment-naive patients with hepatic impairment. The use of atazanavir capsules in patients with severe hepatic impairment (Child-Pugh Class C) is not recommended. The coadministration of atazanavir capsules with ritonavir in patients with any degree of hepatic impairment is not recommended.

Table 5: Recommended Dosage of Atazanavir Capsules in Treatment-Naive Adults with Hepatic Impairment

	Atazanavir Capsules Once Daily Dosage
Mild hepatic impairment (Child-Pugh Class A)	400 mg
Moderate hepatic impairment (Child-Pugh Class B)	300 mg
Severe hepatic impairment (Child-Pugh Class C)	Atazanavir capsules with or without ritonavir is not recommended

3 DOSAGE FORMS AND STRENGTHS

- **150 mg:** Off-white to Pale yellow colored granular powder filled in size "1" empty hard gelatin capsule shell with Opaque green colored cap imprinted with AT150 in white ink and Opaque light green colored body.
- **200 mg:** Off-white to Pale yellow colored granular powder filled in size "0" empty hard gelatin capsule shell with Opaque green colored cap imprinted with AT200 in white ink and Opaque green colored body.
- **300 mg:** Off-white to Pale yellow colored granular powder filled in size "00" empty hard gelatin capsule shell with Opaque orange colored cap imprinted with AT300 in white ink and Opaque green colored body.

4 CONTRAINDICATIONS

Atazanavir capsules are contraindicated:

- in patients with previously demonstrated clinically significant hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of atazanavir capsules *[see Warnings and Precautions (5.2)]*.
- when coadministered with drugs that are highly dependent on CYP3A or UGT1A1 for clearance, and for which elevated plasma concentrations of the interacting drugs are associated with serious and/or life-threatening events (see Table 6).
- when coadministered with drugs that strongly induce CYP3A and may lead to lower exposure and loss of efficacy of atazanavir capsules (see Table 6).

Table 6 displays drugs that are contraindicated with atazanavir capsules.

Table 6: Drugs Contraindicated with Atazanavir Capsules (Information in the table applies to atazanavir capsules with or without ritonavir, unless otherwise indicated)

Drug Class	Drugs within class that are contraindicated with Atazanavir capsules
Alpha 1-adrenoreceptor antagonist	Alfuzosin
Antiarrhythmics	Amiodarone (with ritonavir), quinidine (with ritonavir)
Antimycobacterials	Rifampin
Antineoplastics	Irinotecan
Antipsychotics	Lurasidone (with ritonavir), pimozide
Benzodiazepines	Triazolam, orally administered midazolam[a]
Ergot Derivatives	Dihydroergotamine, ergotamine, ergonovine, methylergonovine
GI Motility Agent	Cisapride
Hepatitis C DirectActing Antivirals	Elbasvir/grazoprevir; glecaprevir/pibrentasvir
Herbal Products	St. John's wort (*Hypericum perforatum*)
Lipid-Modifying Agents:	Lovastatin, simvastatin, lomitapide
Phosphodiesterase-5 (PDE-5) Inhibitor	Sildenafil[b] when dosed as REVATIO® for the treatment of pulmonary arterial hypertension
Protease Inhibitors	Indinavir
Non-nucleoside Reverse Transcriptase Inhibitors	Nevirapine

[a] See *Drug Interactions, Table 16 (7)* for parenterally administered midazolam.
[b] See *Drug Interactions, Table 16 (7)* for sildenafil when dosed as VIAGRA® for erectile dysfunction.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiac Conduction Abnormalities

Atazanavir has been shown to prolong the PR interval of the electrocardiogram in some subjects. In healthy subjects and in subjects with HIV-1 infection treated with atazanavir, abnormalities in atrioventricular (AV) conduction were asymptomatic and generally limited to first-degree AV block. There have been reports of second-degree AV block and other conduction abnormalities *[see Adverse Reactions (6.2) and Overdosage (10)]*. In clinical trials that included electrocardiograms, asymptomatic first-degree AV block was observed in 5.9% of atazanavir-treated subjects (n=920), 5.2% of lopinavir/ritonavir-treated subjects (n=252), 10.4% of nelfinavir-treated subjects (n=48), and 3.0% of efavirenz-treated subjects (n=329). In Study AI424-045, asymptomatic first-degree AV block was observed in 5% (6/118) of atazanavir with ritonavir-treated subjects and 5% (6/116) of lopinavir/ritonavir-treated subjects who had on-study electrocardiogram measurements. Because of limited clinical experience in those with preexisting conduction system disease (eg, marked first-degree AV block or second- or third-degree AV block), ECG monitoring should be considered in these patients *[see Clinical Pharmacology (12.2)]*.

5.2 Severe Skin Reactions

In controlled clinical trials, rash (all grades, regardless of causality) occurred in approximately 20% of subjects with HIV-1 infection treated with atazanavir. 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 (6.1)]*. Dosing with atazanavir was often continued without interruption in patients who developed rash. The discontinuation rate for rash in clinical trials was <1%. 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 *[see Contraindications (4) and Adverse Reactions (6.1)]*. Atazanavir should be discontinued if severe rash develops.

5.4 Hepatotoxicity

Patients with underlying hepatitis B or C viral infections or marked elevations in transaminases before treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. In these patients, hepatic laboratory testing should be conducted prior to initiating therapy with atazanavir and during treatment *[see Dosage and Administration (2.2), Adverse Reactions (6.1), and Use in Specific Populations (8.8)]*.

5.5 Chronic Kidney Disease

Chronic kidney disease in patients with HIV-1 infection treated with atazanavir, with or without ritonavir, has been reported during postmarketing surveillance. Reports included biopsy-proven cases of granulomatous interstitial nephritis associated with the deposition of atazanavir drug crystals in the renal parenchyma. Consider alternatives to atazanavir in patients at high risk for renal disease or with preexisting renal disease. Renal laboratory testing (including serum creatinine, estimated creatinine clearance, and urinalysis with microscopic examination) should be conducted in all patients prior to initiating therapy with atazanavir and continued during treatment with atazanavir. Expert consultation is advised for patients who have confirmed renal laboratory abnormalities while taking atazanavir. In patients with progressive kidney disease, discontinuation of atazanavir may be considered *[see Dosage and Administration (2.2 and 2.7) and Adverse Reactions (6.2)]*.

5.6 Nephrolithiasis and Cholelithiasis

Cases of nephrolithiasis and/or cholelithiasis have been reported during postmarketing surveillance in patients with HIV-1 infection 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 *[see Adverse Reactions (6.2)]*.

5.7 Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of atazanavir with ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving atazanavir with ritonavir, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of atazanavir with ritonavir, respectively. These interactions may lead to:

- clinically significant adverse reactions potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications.
- clinically significant adverse reactions from greater exposures of atazanavir with ritonavir.
- loss of therapeutic effect of atazanavir with ritonavir and possible development of resistance.

See Table 16 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions (7)]*. Consider the potential for drug interactions prior to and during therapy containing atazanavir with ritonavir; and monitor for the adverse reactions associated with concomitant medications *[see Contraindications (4) and Drug Interactions (7)]*.

5.8 Hyperbilirubinemia

Most patients taking atazanavir experience asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT). This hyperbilirubinemia is reversible upon discontinuation of atazanavir. Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies. No long-term safety data are available for patients experiencing persistent elevations in total bilirubin >5 times the upper limit of normal (ULN). Alternative antiretroviral therapy to atazanavir may be considered if jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for patients. Dose reduction of atazanavir is not recommended since long-term efficacy of reduced doses has not been established *[see Adverse Reactions (6.1)]*.

5.9 Diabetes Mellitus/Hyperglycemia

New-onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in patients with HIV-1 infection receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established *[see Adverse Reactions (6.2)]*.

5.10 Immune Reconstitution Syndrome

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

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome, and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.11 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.

5.12 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.

5.13 Resistance/Cross-Resistance

Various degrees of cross-resistance among protease inhibitors have been observed. Resistance to atazanavir may not preclude the subsequent use of other protease inhibitors *[see Microbiology (12.4)]*.

6 ADVERSE REACTIONS

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

- cardiac conduction abnormalities *[see Warnings and Precautions (5.1)]*
- rash *[see Warnings and Precautions (5.2)]*
- hyperbilirubinemia *[see Warnings and Precautions (5.8)]*
- chronic kidney disease *[see Warnings and Precautions (5.5)]*
- nephrolithiasis and cholelithiasis *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trial Experience

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

Adverse Reactions in Treatment-Naive Adult Subjects

The safety profile of atazanavir in treatment-naive adults is based on 1,625 subjects with HIV-1 infection in clinical trials. 536 subjects received atazanavir 300 mg with ritonavir 100 mg and 1,089 subjects received atazanavir 400 mg or higher (without ritonavir).

The most common adverse reactions were nausea, jaundice/scleral icterus, and rash.

Selected clinical adverse reactions of moderate or severe intensity reported in ≥2% of treatment-naive subjects receiving combination therapy including atazanavir 300 mg with ritonavir 100 mg and atazanavir 400 mg (without ritonavir) are presented in Tables 7 and 8, respectively.

Table 7: Selected Adverse Reactions[a] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-Naive Subjects with HIV-1 Infection,[b] Study AI424-138

	96 weeks[c] Atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir DF/emtricitabine[d] (n=441)	96 weeks[c] lopinavir/ritonavir[e] 400 mg/100 mg (twice daily) and tenofovir DF/emtricitabine[e] (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.
[c] Median time on therapy.
[d] Administered as a fixed-dose
[e] As a fixed-dose product: 300 mg tenofovir DF, 200 mg emtricitabine once daily.

Table 8: Selected Adverse Reactions[a] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-Naive Subjects with HIV-1 Infection,[b] Studies AI424-034, AI424-007, and AI424-008

	Study AI424-034		Studies AI424-007, -008	
	64 weeks[c] atazanavir 400 mg (once daily) with lamivudine/ zidovudine[e] (n=404)	64 weeks[c] efavirenz 600 mg (once daily) with lamivudine/ zidovudine[e] (n=401)	120 weeks[c,d] Atazanavir 400 mg (once daily) with stavudine and lamivudine or didanosine (n=279)	73 weeks[c,d] nelfinavir 750 mg TID or 1,250 mg BID with stavudine and lamivudine or didanosine (n=191)
Body as a Whole				
Headache	6%	6%	1%	2%
Digestive System				
Nausea	14%	12%	6%	4%
Jaundice/scleral icterus	7%	*	7%	*
Vomiting	4%	7%	3%	3%
Abdominal pain	4%	4%	4%	2%
Diarrhea	1%	2%	3%	16%
Nervous System				
Insomnia	3%	3%	<1%	*
Dizziness	2%	7%	<1%	*
Peripheral neurologic symptoms	<1%	1%	4%	3%
Skin and Appendages				
Rash	7%	10%	5%	1%

* None reported in this treatment arm.
[a] Includes events of possible, probable, certain, or unknown relationship to treatment regimen.
[b] Based on regimens containing atazanavir.
[c] Median time on therapy.
[d] Includes long-term follow-up.
[e] As a fixed-dose product: 150 mg lamivudine/300 mg zidovudine twice daily.

Adverse Reactions in Treatment-Experienced Adult Subjects

The safety profile of atazanavir in treatment-experienced adults with HIV-1 infection is based on 119 subjects with HIV-1 infection in clinical trials.

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

Selected clinical adverse reactions of moderate or severe intensity reported in ≥2% of treatment-experienced subjects receiving atazanavir with ritonavir are presented in Table 9.

Table 9: Selected Adverse Reactions[a] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-Experienced Subjects with HIV-1 Infection,[b] Study AI424-045

	48 weeks[c] Atazanavir with ritonavir 300/100 mg (once daily) and tenofovir DF and NRTI (n=119)	48 weeks[c] lopinavir/ritonavir 400/100 mg (twice daily[d]) and tenofovir DF and NRTI (n=118)
Body as a Whole		
Fever	2%	*
Digestive System		
Jaundice/scleral icterus	9%	*
Diarrhea	3%	11%
Nausea	3%	2%
Nervous System		
Depression	2%	<1%
Musculoskeletal System		
Myalgia	4%	*

* None reported in this treatment arm.
[a] Includes events of possible, probable, certain, or unknown relationship to treatment regimen.
[b] Based on the regimen containing atazanavir.
[c] Median time on therapy.
[d] As a fixed-dose product.

Laboratory Abnormalities in Treatment-Naive Subjects

The percentages of adult treatment-naive subjects with HIV-1 infection treated with combination therapy, including atazanavir 300 mg with ritonavir 100 mg or atazanavir 400 mg (without ritonavir) with Grade 3 to 4 laboratory abnormalities, are presented in Tables 10 and 11, respectively.

Table 10: Grade 3 to 4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Naive Subjects with HIV-1 Infection,[a] Study AI424-138

Variable	Limit[e]	96 weeks[b] atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir DF/emtricitabine[c] (n=441)	96 weeks[b] lopinavir/ritonavir 400 mg/100 mg[c] (twice daily) and tenofovir DF/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%

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

Table 11: Grade 3 to 4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Naive Subjects with HIV-1 Infection,[a] Studies AI424-034, AI424-007, and AI424-008

		Study AI424-034		Studies AI424-007, -008	
Variable	Limit[d]	64 weeks[b] atazanavir 400 mg once daily and lamivudine/ zidovudine[e] (n=404)	64 weeks[b] efavirenz 600 mg once daily and lamivudine/ zidovudine[e] (n=401)	120 weeks[b,c] atazanavir 400 mg once daily with stavudine and lamivudine or with stavudine and didanosine (n=279)	73 weeks[b,c] nelfinavir 750 mg TID or 1,250 mg BID with stavudine and lamivudine or with stavudine and didanosine (n=191)
Chemistry	High				
SGOT/AST	≥5.1 x ULN	2%	2%	7%	5%
SGPT/ALT	≥5.1 x ULN	4%	3%	9%	7%
Total Bilirubin	≥2.6 x ULN	35%	<1%	47%	3%
Amylase	≥2.1 x ULN	*	*	14%	10%
Lipase	≥2.1 x ULN	<1%	1%	4%	5%
Creatine Kinase	≥5.1 x ULN	6%	6%	11%	9%
Total Cholesterol	≥240 mg/dL	6%	24%	19%	48%
Triglycerides	≥751 mg/dL	<1%	3%	4%	2%
Hematology	Low				
Hemoglobin	<8.0 g/dL	5%	3%	<1%	4%
Neutrophils	<750 cells/mm^3	7%	9%	3%	7%

* None reported in this treatment arm.
[a] Based on regimen(s) containing atazanavir.
[b] Median time on therapy.
[c] Includes long-term follow-up.
[d] ULN = upper limit of normal.
[e] As a fixed-dose product: 150 mg lamivudine, 300 mg zidovudine twice daily.

Change in Lipids from Baseline in Treatment-Naive Subjects with HIV-1 Infection

For Study AI424-138 and Study AI424-034, changes from baseline in LDL-cholesterol, HDL- cholesterol, total cholesterol, and triglycerides are shown in Tables 12 and 13, respectively.

Table 12: Lipid Values, Mean Change from Baseline, Study AI424-138

	Atazanavir with ritonavir[a,b]					lopinavir/ritonavir[b,c]				
	Baseline	Week 48		Week 96		Baseline	Week 48		Week 96	
	mg/dL (n=428[e])	mg/dL (n=372[e])	Change[d] (n=372[e])	mg/dL (n=342[e])	Change[d] (n=342[e])	mg/dL (n=424[e])	mg/dL (n=335[e])	Change[d] (n=335[e])	mg/dL (n=291[e])	Change[d] (n=291[e])
LDL-Cholesterol[f]	92	105	+14%	105	+14%	93	111	+19%	110	+17%
HDL-Cholesterol[f]	37	46	+29%	44	+21%	36	48	+37%	46	+29%
Total Cholesterol[f]	149	169	+13%	169	+13%	150	187	+25%	186	+25%
Triglycerides[f]	126	145	+15%	140	+13%	129	194	+52%	184	+50%

[a] Atazanavir 300 mg with ritonavir 100 mg once daily with the fixed-dose product: 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. At baseline, serum lipid-reducing agents were used in 1% in the lopinavir/ritonavir treatment arm and 1% in the atazanavir with ritonavir arm. Through Week 48, serum lipid-reducing agents were used in 8% in the lopinavir/ritonavir treatment arm and 2% in the atazanavir with ritonavir arm. Through Week 96, serum lipid-reducing agents were used in 10% in the lopinavir/ritonavir treatment arm and 3% in the atazanavir with ritonavir arm.
[c] Lopinavir/ritonavir (400 mg/100 mg) twice daily with the fixed-dose product 300 mg tenofovir DF/200 mg emtricitabine once daily.
[d] The change from baseline is the mean of within-subject changes from baseline for subjects 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 subjects with LDL-cholesterol measured.
[f] Fasting.

Table 13: Lipid Values, Mean Change from Baseline, Study AI424-034

	atazanavir[a,b]			efavirenz[b,c]		
	Baseline mg/dL (n=383[e])	Week 48 mg/dL (n=283[e])	Week 48 Change[d] (n=272[e])	Baseline mg/dL (n=378[e])	Week 48 mg/dL (n=264[e])	Week 48 Change[d] (n=253[e])
LDL-Cholesterol[f]	98	98	+1%	98	114	+18%
HDL-Cholesterol	39	43	+13%	38	46	+24%
Total Cholesterol	164	168	+2%	162	195	+21%
Triglycerides[f]	138	124	-9%	129	168	+23%

[a] Atazanavir 400 mg once daily with the fixed-dose product: 150 mg lamivudine, 300 mg zidovudine twice daily.
[b] Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 0% in the efavirenz treatment arm and <1% in the atazanavir arm. Through Week 48, serum lipid-reducing agents were used in 3% in the efavirenz treatment arm and 1% in the atazanavir arm.
[c] Efavirenz 600 mg once daily with the fixed-dose product: 150 mg lamivudine/300 mg zidovudine twice daily.
[d] The change from baseline is the mean of within-subject changes from baseline for patients with both baseline and Week 48 values and is not a simple difference of the baseline and Week 48 mean values.
[e] Number of subjects with LDL-cholesterol measured.
[f] Fasting.

Laboratory Abnormalities in Treatment-Experienced Subjects with HIV-1 Infection

The percentages of adult treatment-experienced subjects with HIV-1 infection treated with combination therapy, including atazanavir with ritonavir having Grade 3 to 4 laboratory abnormalities are presented in Table 14.

Table 14: Grade 3 to 4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Experienced Subjects with HIV-1 Infection, Study AI424-045[a]

Variable	Limit[c]	48 weeks[b] atazanavir with ritonavir 300/100 mg (once daily) and tenofovir DF and NRTI (n=119)	48 weeks[b] lopinavir/ritonavir 400/100 mg (twice daily[d]) and tenofovir DF and NRTI (n=118)
Chemistry	High		
SGOT/AST	≥5.1 x ULN	3%	3%
SGPT/ALT	≥5.1 x ULN	4%	3%
Total Bilirubin	≥2.6 x ULN	49%	<1%
Lipase	≥2.1 x ULN	5%	6%
Creatine Kinase	≥5.1 x ULN	8%	8%
Total Cholesterol	≥240 mg/dL	25%	26%
Triglycerides	≥751 mg/dL	8%	12%
Glucose	≥251 mg/dL	5%	<1%
Hematology	Low		
Platelets	<50,000 cells/mm^3	2%	3%
Neutrophils	<750 cells/mm^3	7%	8%

[a] Based on regimen(s) containing atazanavir.
[b] Median time on therapy.
[c] ULN = upper limit of normal.
[d] As a fixed-dose product.

Change in Lipids from Baseline in Treatment-Experienced Subjects with HIV-1 Infection

For Study AI424-045, changes from baseline in LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglycerides are shown in Table 15. The observed magnitude of dyslipidemia was less with atazanavir with ritonavir than with lopinavir/ritonavir. However, the clinical impact of such findings has not been demonstrated.

Table 15: Lipid Values, Mean Change from Baseline, Study AI424-045

	atazanavir with ritonavir[a,b]			lopinavir/ritonavir[b,c]		
	Baseline mg/dL (n=111[e])	Week 48 mg/dL (n=75[e])	Week 48 Change[d] (n=74[e])	Baseline mg/dL (n=108[e])	Week 48 mg/dL (n=76[e])	Week 48 Change[d] (n=73[e])
LDL-Cholesterol[f]	108	98	–10%	104	103	+1%
HDL-Cholesterol	40	39	–7%	39	41	+2%
Total Cholesterol	188	170	–8%	181	187	+6%
Triglycerides[f]	215	161	–4%	196	224	+30%

[a] Atazanavir 300 mg once daily with ritonavir and tenofovir DF, and 1 NRTI.
[b] Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 4% in the lopinavir/ritonavir treatment arm and 4% in the atazanavir with ritonavir arm. Through Week 48, serum lipid-reducing agents were used in 19% in the lopinavir/ritonavir treatment arm and 8% in the atazanavir with ritonavir arm.
[c] Lopinavir/ritonavir (400/100 mg), as a fixed dose regimen, BID with tenofovir DF and 1 NRTI.
[d] The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 48 values and is not a simple difference of the baseline and Week 48 mean values.
[e] Number of subjects with LDL-cholesterol measured.
[f] Fasting.

Adverse Reactions in Pediatric Subjects with HIV-1 Infection: Atazanavir Capsules

The safety and tolerability of atazanavir capsules with and without ritonavir have been established in pediatric subjects with HIV-1 infection, at least 6 years of age from the open-label, multicenter clinical trial PACTG 1020A.

The safety profile of atazanavir in pediatric subjects with HIV-1 infection (6 to less than 18 years of age) taking the capsule formulation was generally similar to that observed in clinical studies of atazanavir in adults. The most common Grade 2 to 4 adverse events (≥5%, regardless of causality) reported in pediatric subjects were cough (21%), fever (18%), jaundice/scleral icterus (15%), rash (14%), vomiting (12%), diarrhea (9%), headache (8%), peripheral edema (7%), extremity pain (6%), nasal congestion (6%), oropharyngeal pain (6%), wheezing (6%), and rhinorrhea (6%). Asymptomatic second-degree atrioventricular block was reported in <2% of subjects. The most common Grade 3 to 4 laboratory abnormalities occurring in pediatric subjects taking the capsule formulation were elevation of total bilirubin (≥3.2 mg/dL, 58%), neutropenia (9%), and hypoglycemia (4%). All other Grade 3 to 4 laboratory abnormalities occurred with a frequency of less than 3%.

Adverse Reactions in Subjects with HIV-1 Infection, Co-Infected with Hepatitis B and/or Hepatitis C Virus

In Study AI424-138, 60 subjects administered atazanavir 300 mg with ritonavir 100 mg once daily, and 51 subjects treated with lopinavir/ritonavir 400 mg/100 mg (as fixed-dose product) 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 subjects administered atazanavir with ritonavir and 8% (4/50) of the subjects treated with lopinavir/ritonavir. AST levels >5 times ULN developed in 10% (6/60) of the subjects administered atazanavir with ritonavir and none (0/50) of the subjects treated with lopinavir/ritonavir.

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

In Studies AI424-008 and AI424-034, 74 subjects treated with atazanavir 400 mg once daily, 58 who received efavirenz, and 12 who received nelfinavir were seropositive for hepatitis B and/or C at study entry. ALT levels >5 times ULN developed in 15% the subjects treated with atazanavir, 14% of the subjects treated with efavirenz, and 17% of the subjects treated with nelfinavir. AST levels >5 times ULN developed in 9% of the subjects treated with atazanavir, 5% of the subjects treated with efavirenz, and 17% of the subjects treated with nelfinavir. Within atazanavir and control regimens, no difference in frequency of bilirubin elevations was noted between seropositive and seronegative subjects *[see Warnings and Precautions (5.8)]*.

6.2 Postmarketing Experience

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

Body as a Whole: edema

Cardiovascular System: second-degree AV block, third-degree AV block, left bundle branch block, QTc prolongation *[see Warnings and Precautions (5.1)]*

Gastrointestinal System: pancreatitis

Hepatic System: hepatic function abnormalities

Hepatobiliary Disorders: cholelithiasis *[see Warnings and Precautions (5.6)]*, cholecystitis, cholestasis

Metabolic System and Nutrition Disorders: diabetes mellitus, hyperglycemia *[see Warnings and Precautions (5.9)]*

Musculoskeletal System: arthralgia

Renal System: nephrolithiasis *[see Warnings and Precautions (5.6)]*, interstitial nephritis, granulomatous interstitial nephritis, chronic kidney disease *[see Warnings and Precautions (5.5)]*

Skin and Appendages: alopecia, maculopapular rash *[see Contraindications (4) and Warnings and Precautions (5.2)]*, pruritus, angioedema

7 DRUG INTERACTIONS

7.1 Potential for Atazanavir to Affect Other Drugs

Atazanavir is an inhibitor of CYP3A and UGT1A1. Coadministration of 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. Use of atazanavir without ritonavir is not recommended when coadministered with drugs highly dependent on CYP2C8 with narrow therapeutic indices (eg, paclitaxel, repaglinide). When atazanavir with ritonavir is coadministered with substrates of CYP2C8, clinically significant interactions are not expected *[see Clinical Pharmacology, Table 22 (12.3)]*.

The magnitude of CYP3A-mediated drug interactions on coadministered drug may change when atazanavir is coadministered with ritonavir. See the complete prescribing information for ritonavir for information on drug interactions with ritonavir.

7.2 Potential for Other Drugs to Affect Atazanavir

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

Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir are expected if proton-pump inhibitors, antacids, buffered medications, or H$_2$-receptor antagonists are administered with atazanavir *[see Dosage and Administration (2.3, 2.4, and 2.6)]*.

7.3 Established and Other Potentially Significant Drug Interactions

Table 16 provides dosing recommendations in adults as a result of drug interactions with atazanavir. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 16: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions (Information in the table applies to atazanavir with or without ritonavir, unless otherwise indicated)

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir or Concomitant Drug	Clinical Comment
HIV Antiviral Agents		
Nucleoside Reverse Transcriptase Inhibitors (NRTIs): didanosine buffered formulations enteric-coated (EC) capsules	↓ atazanavir ↓ didanosine	Coadministration of atazanavir with didanosine buffered tablets resulted in a marked decrease in atazanavir exposure. It is recommended that atazanavir be given (with food) 2 h before or 1 h after didanosine buffered formulations. Simultaneous administration of didanosine EC and atazanavir with food results in a decrease in didanosine exposure. Thus, atazanavir and didanosine EC should be administered at different times.
Nucleotide Reverse Transcriptase Inhibitors: tenofovir disoproxil fumarate (DF)	↓ atazanavir ↑ tenofovir	Tenofovir DF may decrease the AUC and C_{min} of atazanavir. When coadministered with tenofovir DF in adults, it is recommended that atazanavir 300 mg be given with ritonavir 100 mg and tenofovir DF 300 mg (all as a single daily dose with food). Atazanavir increases tenofovir concentrations. The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse reactions, including renal disorders. Patients receiving atazanavir and tenofovir DF should be monitored for tenofovir-associated adverse reactions. For pregnant patients taking atazanavir with ritonavir and tenofovir DF, see *Dosage and Administration (2.6)*.
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs): efavirenz	↓ atazanavir	Efavirenz decreases atazanavir exposure. ***In treatment-naive adult patients:*** If atazanavir is combined with efavirenz, atazanavir 400 mg (two 200-mg capsules) should be administered with ritonavir 100 mg simultaneously once daily with food, and efavirenz 600 mg should be administered once daily on an empty stomach, preferably at bedtime. ***In treatment-experienced adult patients:*** Coadministration of atazanavir with efavirenz in treatment-experienced patients is not recommended due to decreased atazanavir exposure.
nevirapine	↓ atazanavir ↑ nevirapine	Coadministration of atazanavir with nevirapine is contraindicated. This is due to substantial decreases in atazanavir exposure, which may result in loss of therapeutic effect and development of resistance. Potential risk for nevirapine-associated adverse reactions due to increased nevirapine exposures *[see Contraindications (4)]*.
Protease Inhibitors: saquinavir (soft gelatin capsules)	↑ saquinavir	Appropriate dosing recommendations for this combination, with or without ritonavir, with respect to efficacy and safety have not been established. In a clinical study, saquinavir 1,200 mg coadministered with atazanavir 400 mg and tenofovir DF 300 mg (all given once daily), and nucleoside analogue reverse transcriptase inhibitors did not provide adequate efficacy *[see Clinical Studies (14.2)]*.
indinavir		Coadministration of atazanavir with indinavir is contraindicated. Both atazanavir and indinavir are associated with indirect (unconjugated) hyperbilirubinemia *[see Contraindications (4)]*.
ritonavir	↑ atazanavir	If atazanavir is coadministered with ritonavir, it is recommended that atazanavir 300 mg once daily be given with ritonavir 100 mg once daily with food in adults. See the complete prescribing information for ritonavir for information on drug interactions with ritonavir.
Others	↑ other protease inhibitor	Although not studied, the coadministration of atazanavir with ritonavir and an additional protease inhibitor would be expected to increase exposure to the other protease inhibitor. Such coadministration is not recommended.
Hepatitis C Antiviral Agents		
elbasvir/grazoprevir	↑ grazoprevir	Coadministration of atazanavir with grazoprevir is contraindicated. The resulting increase in grazoprevir plasma concentrations can lead to an increased risk of ALT elevations *[see Contraindications (4)]*.
glecaprevir/pibrentasvir	↑ glecaprevir ↑ pibrentasvir	Coadministration of atazanavir with glecaprevir/pibrentasvir is contraindicated. It may increase the risk of ALT elevations due to an increase in glecaprevir and pibrentasvir concentrations *[see Contraindications (4)]*.
voxilaprevir/ sofosbuvir/ velpatasvir	↑ voxilaprevir	Coadministration with atazanavir is not recommended.
Other Agents		
Alpha 1-Adrenoreceptor Antagonist: alfuzosin	↑ alfuzosin	Coadministration of atazanavir with alfuzosin is contraindicated. The resulting increase in alfuzosin plasma concentrations can lead to hypotension *[see Contraindications (4)]*.
Antacids and buffered medications	↓ atazanavir	Reduced plasma concentrations of atazanavir are expected if antacids, including buffered medications, are administered with atazanavir. Atazanavir should be administered 2 hours before or 1 hour after these medications.
Antiarrhythmics: amiodarone, quinidine	↑ amiodarone, bepridil, lidocaine (systemic), quinidine	Concomitant use of atazanavir with ritonavir and either quinidine or amiodarone is contraindicated. This is due to the potential for substantial increase in systemic exposure of either quinidine or amiodarone, which may result in serious or life-threatening reactions such as cardiac arrhythmias *[(see Contraindications (4)]*.
amiodarone, bepridil, lidocaine (systemic), quinidine		Coadministration with atazanavir has the potential to produce serious and/or life-threatening adverse events but has not been studied. Caution is warranted and therapeutic concentration monitoring of these drugs is recommended if they are used concomitantly with atazanavir.
Anticoagulants: warfarin	↑ warfarin	Coadministration with atazanavir has the potential to produce serious and/or life-threatening bleeding and has not been studied. It is recommended that International Normalized Ratio (INR) be monitored.
Direct-Acting Oral Anticoagulants: betrixaban, dabigatran, edoxaban	↑ betrixaban ↑ dabigatran ↑ edoxaban	Concomitant use of atazanavir with ritonavir, a strong CYP3A4/P-gp inhibitor, with either betrixaban, dabigatran, or edoxaban may result in increased exposure of the respective DOAC that could lead to an increased risk of bleeding. Refer to the respective DOAC prescribing information regarding dosing instructions for coadministration with P-gp inhibitors.
rivaroxaban	***Atazanavir with ritonavir*** ↑ rivaroxaban	Coadministration of atazanavir with ritonavir and rivaroxaban is not recommended. Concomitant treatment with agents that are combined P-glycoprotein (P-gp) strong CYP3A4 inhibitors, such as ritonavir, increase exposure to rivaroxaban and may increase risk of bleeding.
	Atazanavir ↑ rivaroxaban	Coadministration of atazanavir, a CYP3A4 inhibitor, and rivaroxaban may result in increased increase exposure to rivaroxaban and may increase risk of bleeding. Close monitoring is recommended when atazanavir is coadministered with rivaroxaban.
apixaban	***Atazanavir with ritonavir*** ↑ apixaban	Concomitant use of atazanavir with ritonavir, a strong CYP3A4/P-gp inhibitor, with apixaban may result in increased exposure of apixaban, which could lead to an increased risk of bleeding. Refer to apixaban dosing instructions for coadministration with strong CYP3A4 and P-gp inhibitors in the apixaban prescribing information.
	Atazanavir ↑ apixaban	Concomitant use of 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 atazanavir.
Antidepressants: tricyclic antidepressants	↑ tricyclic antidepressants	Coadministration with atazanavir has the potential to produce serious and/or life-threatening adverse events and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with atazanavir.
trazodone	↑ trazodone	Concomitant use of trazodone and atazanavir with or without ritonavir may increase plasma concentrations of trazodone. Nausea, dizziness, hypotension, and syncope have been observed following coadministration of trazodone with ritonavir. If trazodone is used with a CYP3A4 inhibitor such as atazanavir, the combination should be used with caution and a lower dose of trazodone should be considered.
Antiepileptics: carbamazepine	↓ atazanavir ↑ carbamazepine	Plasma concentrations of atazanavir may be decreased when carbamazepine is administered with atazanavir without ritonavir. Coadministration of carbamazepine and atazanavir without ritonavir is not recommended. Ritonavir may increase plasma levels of carbamazepine. If patients beginning atazanavir with 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 without ritonavir. Coadministration of phenytoin or phenobarbital and atazanavir without ritonavir is not recommended. Ritonavir may decrease plasma levels of phenytoin and phenobarbital. When 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 atazanavir ***with*** ritonavir may decrease lamotrigine plasma concentrations, and may require dosage adjustment of lamotrigine. Coadministration of lamotrigine and atazanavir ***without*** ritonavir is not expected to decrease lamotrigine plasma concentrations. No dose adjustment of lamotrigine is required when coadministered with atazanavir without ritonavir.
Antifungals: ketoconazole, itraconazole	***Atazanavir with ritonavir:*** ↑ ketoconazole ↑ itraconazole	Coadministration of ketoconazole has only been studied with atazanavir without ritonavir (negligible increase in atazanavir AUC and C_{max}). Due to the effect of ritonavir on ketoconazole, high doses of ketoconazole and itraconazole (>200 mg/day) should be used cautiously when administering with atazanavir with ritonavir.
voriconazole	***Atazanavir with ritonavir in subjects with a functional CYP2C19 allele:*** ↓ voriconazole ↓ atazanavir ***Atazanavir with ritonavir in subjects without a functional CYP2C19 allele:*** ↑ voriconazole ↓ atazanavir	The use of voriconazole in patients receiving atazanavir with ritonavir is not recommended unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Patients should be carefully monitored for voriconazole-associated adverse reactions and loss of either voriconazole or atazanavir efficacy during the coadministration of voriconazole and atazanavir with ritonavir. Coadministration of voriconazole with atazanavir (without ritonavir) may affect atazanavir concentrations; however, no data are available.
Antigout: colchicine	↑ colchicine	The coadministration of atazanavir with colchicine in patients with renal or hepatic impairment is not recommended. ***Recommended adult dosage of colchicine when administered with 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*. ***Treatment of familial Mediterranean fever (FMF):*** Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimycobacterials: rifampin	↓ atazanavir	Coadministration of atazanavir with rifampin is contraindicated. Rifampin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect and development of resistance *[see Contraindications (4)]*.
rifabutin	↑ rifabutin	A rifabutin dose reduction of up to 75% (eg, 150 mg every other day or 3 times per week) is recommended. Increased monitoring for rifabutin-associated adverse reactions including neutropenia is warranted.
Antineoplastics: irinotecan	↑ irinotecan	Coadministration of atazanavir with irinotecan is contraindicated. Atazanavir inhibits UGT1A1 and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities *[see Contraindications (4)]*.
Antipsychotics: pimozide	↑ pimozide	Coadministration of atazanavir with pimozide is contraindicated. This is due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias *[see Contraindications (4)]*
lurasidone	***Atazanavir with ritonavir*** ↑ lurasidone ***Atazanavir*** ↑ lurasidone	***Atazanavir with ritonavir*** Coadministration of lurasidone with atazanavir with ritonavir is contraindicated. This is due to the potential for serious and/or life-threatening reactions *[see Contraindications (4)]*. ***Atazanavir without ritonavir*** If coadministration is necessary, reduce the lurasidone dose. Refer to the lurasidone prescribing information for concomitant use with moderate CYP3A4 inhibitors.
quetiapine	↑ quetiapine	***Initiation of atazanavir with ritonavir in patients taking quetiapine:*** Consider alternative antiretroviral therapy to avoid increases in quetiapine exposures. If coadministration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring. ***Initiation of quetiapine in patients taking atazanavir with ritonavir:*** Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
Benzodiazepines: midazolam (oral) triazolam	↑ midazolam ↑ triazolam	Coadministration of atazanavir with either orally administered midazolam or triazolam is contraindicated. Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Atazanavir may cause large increases in the concentration of these benzodiazepines that can lead to the potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression *[see Contraindications (4)]*.
parenterally administered midazolam[b]	↑ midazolam	Concomitant use of parenteral midazolam with atazanavir may increase plasma concentrations of midazolam. Coadministration should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.
Calcium channel blockers: diltiazem	↑ diltiazem and desacetyl-diltiazem	Caution is warranted. A dose reduction of diltiazem by 50% should be considered. ECG monitoring is recommended. Coadministration of diltiazem and atazanavir with ritonavir has not been studied.
felodipine, nifedipine, nicardipine, and verapamil	↑ calcium channel blocker	Caution is warranted. Dose titration of the calcium channel blocker should be considered. ECG monitoring is recommended.
Endothelin receptor antagonists: bosentan	↓ atazanavir ↑ bosentan	Plasma concentrations of atazanavir may be decreased when bosentan is administered with atazanavir without ritonavir. Coadministration of bosentan and atazanavir without ritonavir is not recommended. ***Coadministration of bosentan in adult patients on atazanavir with ritonavir:*** For patients who have been receiving atazanavir with ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based on individual tolerability. ***Coadministration of atazanavir with ritonavir in adult patients on bosentan:*** Discontinue bosentan at least 36 hours before starting atazanavir with ritonavir. At least 10 days after starting atazanavir with ritonavir, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.
Ergot derivatives: dihydroergotamine, ergotamine, ergonovine, methylergonovine	↑ ergot derivatives	Coadministration of atazanavir with ergot derivatives is contraindicated. This is due to the 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 *[see Contraindications (4)]*.
GI Motility Agents: cisapride	↑ cisapride	Coadministration of atazanavir with cisapride is contraindicated. This is due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias *[see Contraindications (4)]*.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ atazanavir	Coadministration of products containing St. John's wort with atazanavir is contraindicated. This may result in loss of therapeutic effect of atazanavir and the development of resistance *[see Contraindications (4)]*.
Lipid-modifying agents HMG-CoA reductase inhibitors: lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Coadministration of atazanavir with lovastatin or simvastatin is contraindicated. This is due to the potential for serious reactions such as myopathy, including rhabdomyolysis *[see Contraindications (4)]*.
atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Titrate atorvastatin dose carefully and use the lowest necessary dose. Rosuvastatin dose should not exceed 10 mg/day. The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including atazanavir, are used in combination with these drugs.
Other Lipid Modifying Agents: lomitapide	↑ lomitapide	Coadministration of atazanavir with lomitapide is contraindicated. This is due to the potential for risk of markedly increased transaminase levels and hepatotoxicity associated with increased plasma concentrations of lomitapide. The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir *[see Contraindications (4)]*.
H$_2$-*Receptor antagonists*	↓ atazanavir	Plasma concentrations of atazanavir were substantially decreased when atazanavir 400 mg once daily was administered simultaneously with famotidine 40 mg twice daily in adults, which may result in loss of therapeutic effect and development of resistance. ***In treatment-naive adult patients:*** Atazanavir 300 mg with ritonavir 100 mg once daily with food should be administered simultaneously with, and/or at least 10 hours after, a dose of the H$_2$-receptor antagonist (H2RA). An H2RA dose comparable to famotidine 20 mg once daily up to a dose comparable to famotidine 40 mg twice daily can be used with atazanavir 300 mg with ritonavir 100 mg in treatment-naive patients. OR For patients unable to tolerate ritonavir, atazanavir 400 mg once daily with food should be administered at least 2 hours before and at least 10 hours after a dose of the H2RA. No single dose of the H2RA should exceed a dose comparable to famotidine 20 mg, and the total daily dose should not exceed a dose comparable to famotidine 40 mg. The use of atazanavir without ritonavir in pregnant patients is not recommended. ***In treatment-experienced adult patients:*** Whenever an H2RA is given to a patient receiving atazanavir with ritonavir, the H2RA dose should not exceed a dose comparable to famotidine 20 mg twice daily, and the atazanavir with ritonavir doses should be administered simultaneously with, and/or at least 10 hours after, the dose of the H2RA. • Atazanavir 300 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with an H2RA. • Atazanavir 400 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with both tenofovir DF and an H2RA. • Atazanavir 400 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with either tenofovir DF or an H2RA for pregnant patients during the second and third trimester. Atazanavir is not recommended for pregnant patients during the second and third trimester taking atazanavir with both tenofovir DF and an H2RA.
Hormonal contraceptives: ethinyl estradiol and norgestimate or norethindrone	↓ ethinyl estradiol ↑ norgestimate[c] ↑ ethinyl estradiol ↑ norethindrone[d]	Use caution if considering coadministration of oral contraceptives with atazanavir or atazanavir with ritonavir. If atazanavir with ritonavir is coadministered with an oral contraceptive, it is recommended that the oral contraceptive contain at least 35 mcg of ethinyl estradiol. If atazanavir is administered without ritonavir, the oral contraceptive should contain no more than 30 mcg of ethinyl estradiol. Potential safety risks include substantial increases in progesterone exposure. The long-term effects of increases in concentration of the progestational agent are unknown and could increase the risk of insulin resistance, dyslipidemia, and acne. Coadministration of atazanavir or atazanavir with ritonavir and other hormonal contraceptives (eg, contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestogens other than norethindrone or norgestimate, or less than 25 mcg of ethinyl estradiol, has not been studied; therefore, alternative methods of contraception are recommended.
Immunosuppressants: cyclosporine, sirolimus, tacrolimus	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for these immunosuppressants when coadministered with atazanavir.
Inhaled beta agonist: salmeterol	↑ salmeterol	Coadministration of salmeterol with atazanavir is not recommended. Concomitant use of salmeterol and atazanavir may result in increased risk of cardiovascular adverse reactions associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Inhaled/nasal steroid: fluticasone	***Atazanavir*** ↑ fluticasone ***Atazanavir with ritonavir*** ↑ fluticasone	Concomitant use of fluticasone propionate and atazanavir (without ritonavir) may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use. Concomitant use of fluticasone propionate and atazanavir with ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression, have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Coadministration of fluticasone propionate and atazanavir with ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects *[see Warnings and Precautions (5.1)]*.
Macrolide antibiotics: clarithromycin	↑ 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 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. Coadministration of atazanavir with ritonavir with clarithromycin has not been studied.
Opioids: buprenorphine	↑ buprenorphine ↑ norbuprenorphine	Coadministration of buprenorphine and atazanavir with or without ritonavir increases the plasma concentration of buprenorphine and norbuprenorphine. Coadministration of atazanavir with ritonavir and buprenorphine warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered. Coadministration of buprenorphine and atazanavir with ritonavir is not expected to decrease atazanavir plasma concentrations. Coadministration of buprenorphine and atazanavir without ritonavir may decrease atazanavir plasma concentrations. The coadministration of atazanavir and buprenorphine without ritonavir is not recommended.
PDE5 inhibitors: sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Coadministration with atazanavir has not been studied but may result in an increase in PDE5 inhibitor-associated adverse reactions, including hypotension, syncope, visual disturbances, and priapism. ***Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH):*** Coadministration of atazanavir with REVATIO® (sildenafil) for the treatment of pulmonary hypertension (PAH) is contraindicated *[see Contraindications (4)]*. The following dose adjustments are recommended for the use of ADCIRCA® (tadalafil) with atazanavir: Coadministration of ADCIRCA® in patients on atazanavir (with or without ritonavir): • For patients receiving atazanavir (with or without ritonavir) for at least one week, start ADCIRCA® at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability. Coadministration of atazanavir (with or without ritonavir) in patients on ADCIRCA®: • Avoid the use of ADCIRCA® when starting atazanavir (with or without ritonavir). Stop ADCIRCA® at least 24 hours before starting atazanavir (with or without ritonavir). At least one week after starting atazanavir (with or without ritonavir), resume ADCIRCA® at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability. ***Use of PDE5 inhibitors for erectile dysfunction:*** Use VIAGRA® (sildenafil) with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Use CIALIS® (tadalafil) with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. ***Atazanavir with ritonavir:*** Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse reactions. ***Atazanavir:*** Use vardenafil with caution at reduced doses of no more than 2.5 mg every 24 hours with increased monitoring for adverse reactions.
Proton-pump inhibitors: omeprazole	↓ atazanavir	Plasma concentrations of atazanavir were substantially decreased when atazanavir 400 mg or atazanavir 300 mg with ritonavir 100 mg once daily was administered with omeprazole 40 mg once daily in adults, which may result in loss of therapeutic effect and development of resistance. ***In treatment-naive adult patients:*** The proton-pump inhibitor (PPI) dose should not exceed a dose comparable to omeprazole 20 mg and must be taken approximately 12 hours prior to the atazanavir 300 mg with ritonavir 100 mg dose. ***In treatment-experienced adult patients:*** The use of PPIs in treatment-experienced patients receiving atazanavir is not recommended.

[a] For magnitude of interactions see *Clinical Pharmacology, Tables 21* and *22 (12.3)*.
[b] See *Contraindications (4), Table 6* for orally administered midazolam.
[c] In combination with atazanavir 300 mg with ritonavir 100 mg once daily.
[d] In combination with atazanavir 400 mg once daily.

7.4 Drugs with No Observed Interactions with Atazanavir

No clinically significant drug interactions were observed when atazanavir was coadministered with methadone, fluconazole, acetaminophen, atenolol, or the nucleoside reverse transcriptase inhibitors lamivudine or zidovudine *[see Clinical Pharmacology, Tables 21 and 22 (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in patients exposed to atazanavir during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Atazanavir has been evaluated in a limited number of women during pregnancy. Available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate *[see Data]*. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. No treatment-related malformations were observed in rats and rabbits, for which the atazanavir exposures were 0.7 to 1.2 times of those at the human clinical dose (300 mg/day atazanavir boosted with 100 mg/day ritonavir). When atazanavir was administered to rats during pregnancy and throughout lactation, reversible neonatal growth retardation was observed *[see Data]*.

Clinical Considerations

Dose Adjustments during Pregnancy and the Postpartum Period

- Atazanavir must be administered with ritonavir in pregnant patients.
- For pregnant patients, no dosage adjustment is required for atazanavir with the following exceptions:
  - For treatment-experienced pregnant women during the second or third trimester, when atazanavir is coadministered with either an H$_2$-receptor antagonist **or** tenofovir DF, atazanavir 400 mg with ritonavir 100 mg once daily is recommended. There are insufficient data to recommend a atazanavir dose for use with both an H$_2$-receptor antagonist and tenofovir DF in treatment-experienced pregnant patients.
- No dosage 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 *[see Dosage and Administration (2.6) and Clinical Pharmacology (12.3)]*.

Maternal Adverse Reactions

Cases of lactic acidosis syndrome, sometimes fatal, and symptomatic hyperlactatemia have occurred in pregnant women using atazanavir in combination with nucleoside analogues, which are associated with an increased risk of lactic acidosis syndrome.

Hyperbilirubinemia occurs frequently in patients who take atazanavir *[see Warnings and Precautions (5.8)]*, including those who are pregnant *[see Data]*.

Advise pregnant women of the potential risks of lactic acidosis syndrome and hyperbilirubinemia.

Fetal/Neonatal Adverse Reactions

All infants, including neonates exposed to atazanavir *in utero*, should be monitored for the development of severe hyperbilirubinemia during the first few days of life *[see Data]*.

Data

Human Data

In Study AI424-182, atazanavir with ritonavir (300/100 mg or 400/100 mg) coadministered with lamivudine/zidovudine (150 mg/300 mg, as fixed-dose product) was administered to 41 pregnant women with HIV-1 infection, during the second or third trimester. Among the 39 women who completed the study, 38 women achieved an HIV-1 RNA less than 50 copies/mL at time of delivery. Six of 20 (30%) women on atazanavir with ritonavir 300/100 mg and 13 of 21 (62%) women on atazanavir with ritonavir 400/100 mg experienced hyperbilirubinemia (total bilirubin greater than or equal to 2.6 times ULN). There were no cases of lactic acidosis observed in clinical trial AI424-182.

Atazanavir drug concentrations in fetal umbilical cord blood were approximately 12% to 19% of maternal concentrations. Among the 40 infants born to 40 pregnant women with HIV-1 infection, all 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. No evidence of severe hyperbilirubinemia (total bilirubin levels greater than 20 mg/dL) or acute or chronic bilirubin encephalopathy was observed among neonates in this study. However, 10/36 (28%) infants (6 greater than or equal to 38 weeks gestation and 4 less than 38 weeks gestation) had bilirubin levels of 4 mg/dL or greater within the first day of life.

Lack of ethnic diversity was a study limitation. In the study population, 33/40 (83%) infants were Black/African American, who have a lower incidence of neonatal hyperbilirubinemia than Caucasians and Asians. In addition, women with Rh incompatibility were excluded, as well as women who had a previous infant who developed hemolytic disease and/or had neonatal pathologic jaundice (requiring phototherapy).

Additionally, of the 38 infants who had glucose samples collected in the first day of life, 3 had adequately collected serum glucose samples with values of less than 40 mg/dL that could not be attributed to maternal glucose intolerance, difficult delivery, or sepsis.

Based on prospective reports from the APR of approximately 1,600 live births following exposure to atazanavir-containing regimens (including 1,037 live births in infants exposed in the first trimester and 569 exposed in second/third trimesters), there was no difference between atazanavir and overall birth defects compared with the background birth defect rate. In the U.S. general population, the estimated background risk of major birth defects in clinically recognized pregnancies is 2 to 4%.

PATIENT INFORMATION
Atazanavir (A-ta-ZAN-a-vir) Capsules

Important: Ask your healthcare provider or pharmacist about medicines that should not be taken with atazanavir capsules. For more information, see "Do not take atazanavir if you" and "Before taking atazanavir capsules".

What are atazanavir capsules?

Atazanavir capsules are a prescription medicine that is used to treat human immunodeficiency virus-1 (HIV-1) infection, in combination with other HIV-1 medicines in adults and children 6 years of age and older who weigh at least 15 kg.

HIV-1 is the virus that causes AIDS (Acquired Immunodeficiency Syndrome).

Atazanavir should not be used in children younger than 3 months of age.

Do not take atazanavir capsules if you:

- are allergic to atazanavir or any of the ingredients in atazanavir capsules. See the end of this leaflet for a complete list of ingredients in atazanavir capsules.
- are taking any of the following medicines. Taking atazanavir capsules with these medicines may affect how atazanavir capsules works. Atazanavir capsules may cause serious or life-threatening side effects, or death when used with these medicines:
  - alfuzosin
  - amiodarone (when atazanavir is used with ritonavir)
  - cisapride
  - elbasvir/grazoprevir
  - ergot medicines including:
    - dihydroergotamine
    - ergonovine
    - ergonovine ergotamine
    - methylergonovine
  - glecaprevir/pibrentasvir
  - indinavir
  - irinotecan
  - lurasidone (when atazanavir is used with ritonavir)
  - lomitapide
  - lovastatin
  - midazolam, when taken by mouth for sedation
  - nevirapine
  - pimozide
  - quinidine (when atazanavir is used with ritonavir)
  - rifampin
  - sildenafil, when used for the treatment of pulmonary arterial hypertension
  - simvastatin
  - St. John's wort
  - triazolam

Before taking atazanavir capsules, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems
- have liver problems, including hepatitis B or C virus infection
- have kidney problems
- are receiving dialysis treatment
- have diabetes
- have hemophilia
- are pregnant or plan to become pregnant.
  - **Atazanavir capsules must be taken with ritonavir during pregnancy.**
  - **Hormonal forms of birth control, such as injections, vaginal rings or implants, contraceptive patch, and some birth control pills may not work during treatment with atazanavir capsules.** Talk to your healthcare provider about forms of birth control that may be used during treatment with atazanavir capsules.
  - **Pregnancy Exposure Registry.** There is a pregnancy exposure registry for people who take atazanavir capsules during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
  - **After your baby is born,** tell your healthcare provider if your baby's skin or the white part of their eyes turns yellow.
- are breastfeeding or plan to breastfeed. **Do not breastfeed if you are taking atazanavir capsules.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby. Atazanavir can pass into your breast milk.
  - Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines interact with atazanavir capsules. **Keep a list of your medicines to show your healthcare provider and pharmacist.**

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with atazanavir capsules.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take atazanavir capsules with other medicines.

How should I take atazanavir capsules?

- **Take atazanavir capsules exactly as your healthcare provider tells you to.**
- Do not change your dose or stop taking atazanavir capsules unless your healthcare provider tells you to.
- Stay under the care of your healthcare provider during treatment with atazanavir capsules.
- Atazanavir capsules must be used with other HIV-1 medicines.
- Take atazanavir capsule 1 time each day.
- Atazanavir comes as capsules.
- Take atazanavir capsules with food.
- Swallow the capsules whole. Do not open the capsules.
- Your child's healthcare provider will prescribe the right dose of atazanavir capsules based on your child's weight.
- If you miss a dose of atazanavir capsules, take it as soon as you remember. Then take the next dose at your regular time. Do not take 2 doses at the same time.
- If you take too much atazanavir capsules, call your healthcare provider or go to the nearest hospital emergency room right away.

When your supply of atazanavir capsules starts to run low, get more from your healthcare provider or pharmacy. It is important not to run out of atazanavir capsules. The amount of HIV-1 in your blood may increase if the medicine is stopped for even a short time. The virus may become resistant to atazanavir capsules and harder to treat.

What are the possible side effects of atazanavir capsules?

Atazanavir capsules can cause serious side effects, including:

- **A change in the way your heart beats (heart rhythm change).** Tell your healthcare provider right away if you get dizzy or lightheaded. These could be symptoms of a heart problem.
- **Skin rash.** Skin rash is common with atazanavir capsules but can sometimes be severe. Severe rash may develop with other symptoms which could be serious. If you develop a severe rash or a rash with any of the following symptoms, stop taking atazanavir capsules and call your healthcare provider or go to the nearest hospital emergency room right away:
  - general feeling of discomfort or "flu- like" symptoms
  - fever
  - blisters
  - mouth sores

Animal Data

In animal reproduction studies, there was no evidence of mortality or teratogenicity in offspring born to animals at systemic drug exposure levels (AUC) 0.7 (in rabbits) to 1.2 (in rats) times those observed at the human clinical dose (300 mg/day atazanavir boosted with 100 mg/day ritonavir). In pre- and postnatal development studies in the rat, atazanavir caused neonatal growth retardation during lactation that reversed after weaning. Maternal drug exposure at this dose was 1.3 times the human exposure at the recommended clinical exposure. Minimal maternal toxicity occurred at this exposure level.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that patients with HIV-1 infection, not breastfeed their infants to avoid risking postnatal transmission of HIV-1. Atazanavir has been detected in human milk. No data are available regarding atazanavir effects on milk production. Atazanavir was present in the milk of lactating rats and was associated with neonatal growth retardation that reversed after weaning.

Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in breastfed infants, advise women not to breastfeed.

8.4 Pediatric Use

Atazanavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients 6 years of age and older weighing at least 15 kg. Atazanavir is not recommended for use in pediatric patients below the age of 3 months due to the risk of kernicterus *[see Indications and Usage (1)]*. All atazanavir contraindications, warnings, and precautions apply to pediatric patients *[see Contraindications (4) and Warnings and Precautions (5)]*.

The safety, pharmacokinetic profile, and virologic response of atazanavir in pediatric patients 6 years of age and older weighing at least 15 kg were established in an open-label, multicenter clinical trial: PACTG 1020A [*see Clinical Pharmacology (12.3) and Clinical Studies (14.3)*]. The safety profile in pediatric patients was generally similar to that observed in adults [*see Adverse Reactions (6.1)*]. *See Dosage and Administration (2.4)* for dosing recommendations for the use of atazanavir capsules in pediatric patients.

8.5 Geriatric Use

Clinical studies of atazanavir did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Based on a comparison of mean single-dose pharmacokinetic values for C_{max} and AUC, a dose adjustment based upon age is not recommended. In general, appropriate caution should be exercised in the administration and monitoring of atazanavir in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Age/Gender

A study of the pharmacokinetics of atazanavir was performed in young (n=29; 18 to 40 years) and elderly (n=30; ≥65 years) healthy subjects. There were no clinically significant pharmacokinetic differences observed due to age or gender.

8.7 Impaired Renal Function

Atazanavir is not recommended for use in treatment-experienced patients with HIV-1 infection, who have end-stage renal disease managed with hemodialysis *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)]*.

8.8 Impaired Hepatic Function

Atazanavir is not recommended for use in patients with severe hepatic impairment. Atazanavir with ritonavir is not recommended in patients with any degree of hepatic impairment *[see Dosage and Administration (2.8) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

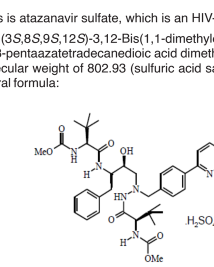
Human experience of acute overdose with atazanavir is limited. Single doses up to 1,200 mg (three times the 400 mg maximum recommended dose) have been taken by healthy subjects without symptomatic untoward effects. A single self-administered overdose of 29.2 g of atazanavir in a patient with HIV-1 infection (73 times the 400-mg recommended dose) was associated with asymptomatic bifascicular block and PR interval prolongation. These events resolved spontaneously. At atazanavir doses resulting in high atazanavir exposures, jaundice due to indirect (unconjugated) hyperbilirubinemia (without associated liver function test changes) or PR interval prolongation may be observed *[see Warnings and Precautions (5.1, 5.8) and Clinical Pharmacology (12.2)]*.

Treatment of overdosage with atazanavir should consist of general supportive measures, including monitoring of vital signs and ECG, and observations of the patient's clinical status. If indicated, elimination of unabsorbed atazanavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with atazanavir. Since atazanavir is extensively metabolized by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicine.

11 DESCRIPTION

The active ingredient in atazanavir capsules is atazanavir sulfate, which is an HIV-1 protease inhibitor.

The chemical name for atazanavir sulfate is (3*S*,8*S*,9*S*,12*S*)-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). Its molecular formula is $C_{38}H_{54}N_6O_{11}S$, which corresponds to a molecular weight of 802.93 (sulfuric acid salt). The free base molecular weight is 704.9. Atazanavir sulfate has the following structural formula:



Atazanavir sulfate is a white to pale yellow crystalline powder. It is freely soluble in methanol and practically insoluble in water.

Atazanavir capsules are available for oral administration in strengths of 150 mg, 200 mg, or 300 mg of atazanavir, which are equivalent to 170.8 mg, 227.8 mg, or 341.69 mg of atazanavir sulfate, respectively. The capsules also contain the following inactive ingredients: crospovidone, lactose monohydrate, and magnesium stearate. The capsule shells contain the following inactive ingredients: gelatin, FD&C Blue No. 2, FD & C Yellow 6, iron oxide yellow, and titanium dioxide. The capsules are printed with ink containing butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, shellac, strong ammonia solution, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atazanavir is an HIV-1 antiretroviral drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Concentration- and dose-dependent prolongation of the PR interval in the electrocardiogram has been observed in healthy subjects receiving atazanavir. In placebo-controlled Study AI424-076, the mean (±SD) maximum change in PR interval from the predose 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 a pharmacodynamic interaction in humans between atazanavir and other drugs that prolong the PR interval of the electrocardiogram *[see Warnings and Precautions (5.1)]*.

Electrocardiographic effects of atazanavir were determined in a clinical pharmacology study of 72 healthy subjects. Oral doses of 400 mg (maximum recommended dosage) and 800 mg (twice the maximum recommended dosage) were compared with placebo; there was no concentration-dependent effect of atazanavir on the QTc interval (using Fridericia's correction). In 1,793 subjects with HIV-1 infection, receiving antiretroviral regimens, QTc prolongation was comparable in the atazanavir and comparator regimens. No atazanavir-treated healthy subject or subject with HIV-1 infection in clinical trials had a QTc interval >500 msec *[see Warnings and Precautions (5.1)]*.

12.3 Pharmacokinetics

The pharmacokinetics of atazanavir were evaluated in adult subjects who either were healthy, or with HIV infection, after administration of atazanavir 400 mg once daily and after administration of atazanavir 300 mg with ritonavir 100 mg once daily (see Table 17).

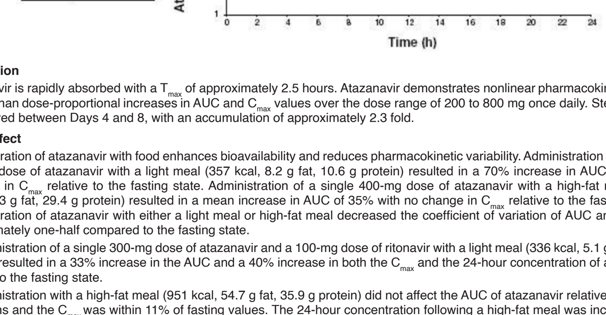
Table 17: Steady-State Pharmacokinetics of Atazanavir in Healthy Subjects or Subjects with HIV-1 Infection in the Fed State

Parameter	400 mg once daily		300 mg with ritonavir 100 mg once daily	
	Healthy Subjects (n=14)	Subjects with HIV-1 Infection (n=13)	Healthy Subjects (n=28)	Subjects with HIV-1 Infection (n=10)
C_{max} (ng/mL)				
Geometric mean (CV%)	5,199 (26)	2,298 (71)	6,129 (31)	4,422 (58)
Mean (SD)	5,358 (1,371)	3,152 (2,231)	6,450 (2,031)	5,233 (3,033)
T_{max} (h)				
Median	2.5	2.0	2.7	3.0
AUC (ng•h/mL)				
Geometric mean (CV%)	28,132 (28)	14,874 (91)	57,039 (37)	46,073 (66)
Mean (SD)	29,303 (8,263)	22,262 (20,159)	61,435 (22,911)	53,761 (35,294)
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)	1,227 (53)	636 (97)
Mean (SD)	218 (191)	273 (298)[b]	1,441 (757)	862 (838)

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

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

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 Subjects with HIV-1 infection.



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 to 800 mg once daily. Steady state is achieved between Days 4 and 8, with an accumulation of approximately 2.3 fold.

Food Effect

Administration of atazanavir with food enhances bioavailability and reduces pharmacokinetic variability. 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.

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

Coadministration with a high-fat meal (951 kcal, 54.7 g fat, 35.9 g protein) did not affect the AUC of atazanavir relative to fasting conditions and the C_{max} was within 11% of fasting values. The 24-hour concentration following a high-fat meal was increased by approximately 33% due to delayed absorption; the median T_{max} increased from 2.0 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 subjects with HIV-1 infection dosedwith 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

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

Elimination

Following a single 400-mg dose of ^{14}C-atazanavir, 79% and 13% of the total radioactivity was recovered in the feces and 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 subjects (n=214) and adult subjects with HIV-1 infection (n=13) was approximately 7 hours at steady state following a dose of 400 mg daily with a light meal.

Specific Populations

Renal Impairment

In healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. 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. In a 4-hour dialysis session, 2.1% of the administered dose was removed. When atazanavir was administered either prior to, or following hemodialysis (n=10), the geometric means for C_{max}, AUC, and C_{min} were approximately 25% to 43% lower compared to subjects with normal renal function. The mechanism of this decrease is unknown. Atazanavir is not recommended for use in treatment-experienced patients with HIV-1 who have end-stage renal disease managed with hemodialysis *[see Dosage and Administration (2.7)]*.

Hepatic Impairment

Atazanavir has been studied in adult subjects with moderate-to-severe hepatic impairment (14 Child-Pugh B and 2 Child-Pugh C subjects) after a single 400-mg dose. The mean $AUC_{(0-\infty)}$ was 42% greater in subjects with impaired hepatic function than in healthy subjects. The mean half-life of atazanavir in hepatically impaired subjects was 12.1 hours compared to 6.4 hours in healthy subjects. A dose reduction to 300 mg is recommended for patients with moderate hepatic impairment (Child-Pugh Class B) who have not experienced prior virologic failure as increased concentrations of atazanavir are expected. Atazanavir is not recommended for use in patients with severe hepatic impairment. The pharmacokinetics of atazanavir in combination with ritonavir has not been studied in subjects with hepatic impairment; thus, coadministration of atazanavir with ritonavir is not recommended for use in patients with any degree of hepatic impairment *[see Dosage and Administration (2.8)]*.

Pediatrics

The pharmacokinetic parameters for atazanavir at steady state in pediatric subjects taking the capsule formulation were predicted by a population pharmacokinetic model and are summarized in Table 19 by weight ranges that correspond to the recommended doses *[see Dosage and Administration (2.4)]*.

Table 19: Predicted Steady-State Pharmacokinetics of Atazanavir (capsule formulation) with Ritonavir in Pediatric Subjects with HIV-1 Infection

Body Weight (range in kg)	atazanavir with ritonavir Dose (mg)	C_{max} ng/mL Geometric Mean (CV%)	AUC ng•h/mL Geometric Mean (CV%)	C_{min} ng/mL Geometric Mean (CV%)
15 to <35	200/100	3,303 (86%)	37,235 (84%)	538 (99%)
≥35	300/100	2,980 (82%)	37,643 (83%)	653 (89%)

Pregnancy

The pharmacokinetic data from pregnant women with HIV-1 infection receiving atazanavir capsules with ritonavir are presented in Table 20.

Table 20: Steady-State Pharmacokinetics of Atazanavir with Ritonavir in Pregnant Women with HIV-1 Infection in the Fed State

Pharmacokinetic Parameter	Atazanavir 300 mg with ritonavir 100 mg		
	2nd Trimester (n=5[a])	3rd Trimester (n=20)	Postpartum[b] (n=34)
C_{max} ng/mL	3,078.85	3,291.46	5,721.21
Geometric mean (CV%)	(50)	(48)	(31)
AUC ng•h/mL	27,657.1	34,251.5	61,990.4
Geometric mean (CV%)	(43)	(43)	(32)
C_{min} ng/mL[c]	538.70	668.48	1,462.59
Geometric mean (CV%)	(46)	(50)	(45)

[a] Available data during the 2nd trimester are limited.
[b] Atazanavir peak concentrations and AUCs were found to be approximately 28% to 43% higher during the postpartum period (4 to 12 weeks) than those observed historically in, non-pregnant patients with HIV-1 infection. Atazanavir plasma trough concentrations were approximately 2.2-fold higher during the postpartum period when compared to those observed historically in non-pregnant patients with HIV-1 infection.
[c] C_{min} is concentration 24 hours post-dose.

Drug Interaction Data

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) and CYP2C8 (K_i=2.1 mcM).

Atazanavir has been shown *in vivo* not to induce its own metabolism nor to increase the biotransformation of some drugs metabolized by CYP3A. In a multiple-dose study, atazanavir decreased the urinary ratio of endogenous 6β-OH cortisol to cortisol versus baseline, indicating that CYP3A production was not induced.

Clinically significant interactions are not expected between atazanavir and substrates of CYP2C19, CYP2C9, CYP2D6, CYP2B6, CYP2A6, CYP1A2, or CYP2E1. Clinically significant interactions are not expected between atazanavir when administered with ritonavir and substrates of CYP2C8. See the complete prescribing information for ritonavir for information on other potential drug interactions with ritonavir.

Based on known metabolic profiles, clinically significant drug interactions are not expected between atazanavir and dapsone, trimethoprim/sulfamethoxazole, azithromycin, or erythromycin. Atazanavir does not interact with substrates of CYP2D6 (eg, nortriptyline, desipramine, metoprolol).

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 coadministration of atazanavir on the AUC, C_{max}, and C_{min} are summarized in Tables 21 and 22. Neither didanosine EC nor diltiazem had a significant effect on atazanavir exposures (see Table 22 for effect of atazanavir on didanosine EC or diltiazem exposures). Atazanavir did not have a significant effect on the exposures of didanosine (when administered as the buffered tablet), stavudine, or fluconazole. For information regarding clinical recommendations, see *Drug Interactions (7)*.

Table 21: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}
atenolol	50 mg QD, d 7 to 11 (n=19) and d 19 to 23	400 mg QD, d 1 to 11 (n=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 to 10 (n=29) and d 18 to 21	400 mg QD, d 1 to 10 (n=29)	1.06 (0.93, 1.20)	1.28 (1.16, 1.43)	1.91 (1.66, 2.21)
didanosine (ddI) (buffered tablets) and stavudine (d4T)[b]	ddI: 200 mg × 1 dose, d4T: 40 mg × 1 dose (n=31)	400 mg × 1 dose simultaneously with ddI and d4T (n=31)	0.11 (0.06, 0.18)	0.13 (0.08, 0.21)	0.16 (0.10, 0.27)
	ddI: 200 mg × 1 dose, d4T: 40 mg × 1 dose (n=32)	400 mg × 1 dose 1 h after ddI + d4T (n=32)	1.12 (0.67, 1.18)	1.03 (0.64, 1.67)	1.03 (0.61, 1.73)
efavirenz	600 mg QD, d 7 to 20 (n=27)	400 mg QD, d 1 to 20 (n=27)	0.41 (0.33, 0.51)	0.26 (0.22, 0.32)	0.07 (0.05, 0.10)
	600 mg QD, d 7 to 20 (n=13)	400 mg QD, d 1 to 6 (n=23) then 300 mg with ritonavir 100 mg QD, 2 h before efavirenz, d 7 to 20 (n=13)	1.14 (0.83, 1.58)	1.39 (1.02, 1.88)	1.48 (1.24, 1.76)
	600 mg QD, d 11 to 24 (pm) (n=14)	300 mg QD with ritonavir 100 mg QD, d 1 to 10 (pm) (n=22), then 400 mg QD with ritonavir 100 mg QD, d 11 to 24 (pm), (simultaneously with efavirenz) (n=14)	1.17 (1.08, 1.27)	1.00 (0.91, 1.10)	0.58 (0.49, 0.69)
famotidine	40 mg BID, d 7 to 12 (n=15)	400 mg QD, d 1 to 6 (n=45), d 7 to 12 (simultaneous administration) (n=15)	0.53 (0.34, 0.82)	0.59 (0.40, 0.87)	0.58 (0.37, 0.89)
	40 mg BID, d 7 to 12 (n=14)	400 mg QD (pm), d 1 to 6 (n=14), d 7 to 12 (10 h after, 2 h before famotidine) (n=14)	1.08 (0.82, 1.41)	0.95 (0.74, 1.21)	0.79 (0.60, 1.04)
	40 mg BID, d 11 to 20 (n=14)[c]	300 mg QD with ritonavir 100 mg QD, d 1 to 10 (n=46), d 11 to 20[d] (simultaneous administration) (n=14)	0.86 (0.79, 0.94)	0.82 (0.75, 0.89)	0.72 (0.64, 0.81)
	20 mg BID, d 11 to 17 (n=18)	300 mg QD with ritonavir 100 mg QD and tenofovir DF 300 mg QD, d 1 to 10 (am) (n=39), d 11 to 17 (am) (simultaneous administration with am famotidine) (n=18)[d,e]	0.91 (0.84, 0.99)	0.90 (0.82, 0.98)	0.81 (0.69, 0.94)
	40 mg QD (pm), d 18 to 24 (n=20)	300 mg QD with ritonavir 100 mg QD and tenofovir DF 300 mg QD, d 1 to 10 (am) (n=39), d 18 to 24 (am) (12 h after pm famotidine) (n=20)[e]	0.89 (0.81, 0.97)	0.88 (0.80, 0.96)	0.77 (0.63, 0.93)
	40 mg BID, d 18 to 24 (n=18)	300 mg QD with ritonavir 100 mg QD and tenofovir DF 300 mg QD, d 1 to 10 (am) (n=39), d 18 to 24 (am) (10 h after pm famotidine and 2 h before am famotidine) (n=18)[e]	0.74 (0.66, 0.84)	0.79 (0.70, 0.88)	0.72 (0.63, 0.83)
	40 mg BID, d 11 to 20 (n=15)	300 mg QD with ritonavir 100 mg QD, d 1 to 10 (am) (n=46), then 400 mg QD with ritonavir 100 mg QD, d 11 to 20 (am) (n=15)	1.02 (0.87, 1.18)	1.03 (0.86, 1.22)	0.86 (0.68, 1.08)
grazoprevir/elbasvir	grazoprevir 200 mg QD d 1 to 35 (n = 11)	300 mg QD with ritonavir 100 mg QD, d 1 to 35 (n = 11)	1.12 (1.01, 1.24)	1.43 (1.30, 1.57)	1.23 (1.13, 1.34)
	elbasvir 50 mg QD d 1 to 35 (n = 8)	300 mg QD with ritonavir 100 mg QD, d 1 to 35 (n = 8)	1.02 (0.96, 1.08)	1.07 (0.98, 1.17)	1.15 (1.02, 1.29)
ketoconazole	200 mg QD, d 7 to 13 (n=14)	400 mg QD, d 1 to 13 (n=14)	0.99 (0.77, 1.28)	1.10 (0.89, 1.37)	1.03 (0.53, 2.01)
nevirapine[f,g]	200 mg BID, d 1 to 23 (n=23)	300 mg QD with ritonavir 100 mg QD, d 4 to 13, then 400 mg QD with ritonavir 100 mg QD, d 14 to 23 (n=23)[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 QD, d 7 to 12 (n=16)[i]	400 mg QD, d 1 to 6 (n=48), d 7 to 12 (n=16)	0.04 (0.04, 0.05)	0.06 (0.05, 0.07)	0.05 (0.03, 0.07)
	40 mg QD, d 11 to 20 (n=15)[i]	300 mg QD with ritonavir 100 mg QD, d 1 to 20 (n=15)	0.28 (0.24, 0.32)	0.24 (0.21, 0.27)	0.22 (0.19, 0.26)
	20 mg QD, d 17 to 23 (am) (n=13)	300 mg QD with ritonavir 100 mg QD, d 7 to 16 (pm) (n=27), d 17 to 23 (pm) (n=13)[j,k]	0.61 (0.46, 0.81)	0.58 (0.44, 0.75)	0.54 (0.41, 0.71)
	20 mg QD, d 17 to 23 (am) (n=14)	300 mg QD with ritonavir 100 mg QD, d 7 to 16 (am) (n=27), then 400 mg QD with ritonavir 100 mg QD, d 17 to 23 (am) (n=14)[l,m]	0.69 (0.58, 0.83)	0.70 (0.57, 0.86)	0.69 (0.54, 0.88)
pitavastatin	4 mg QD for 5 days	300 mg QD for 5 days	1.13 (0.96, 1.32)	1.06 (0.90, 1.26)	NA
rifabutin	150 mg QD, d 15 to 28 (n=7)	400 mg QD, d 1 to 28 (n=7)	1.34 (1.14, 1.59)	1.15 (0.98, 1.34)	1.13 (0.68, 1.87)
rifampin	600 mg QD, d 17 to 26 (n=16)	300 mg QD with ritonavir 100 mg QD, d 7 to 16 (n=48), d 17 to 26 (n=16)	0.47 (0.41, 0.53)	0.28 (0.25, 0.32)	0.02 (0.02, 0.03)
ritonavir[n]	100 mg QD, d 11 to 20 (n=28)	300 mg QD, d 1 to 20 (n=28)	1.86 (1.69, 2.05)	3.38 (3.13, 3.63)	11.89 (10.23, 13.82)
tenofovir DF[o]	300 mg QD, d 9 to 16 (n=34)	400 mg QD, d 2 to 16 (n=34)	0.79 (0.73, 0.86)	0.75 (0.70, 0.81)	0.60 (0.52, 0.68)
	300 mg QD, d 15 to 42 (n=10)	300 mg with ritonavir 100 mg QD, d 1 to 42 (n=10)	0.72[p] (0.50, 1.05)	0.75[p] (0.58, 0.97)	0.77[p] (0.54, 1.10)
voriconazole (Subjects with at least one functional CYP2C19 allele)	200 mg BID, d 2 to 3, 22 to 30; 400 mg BID, d 1, 21 (n=20)	300 mg with ritonavir 100 mg QD, d 11 to 30 (n=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 to 3, 22 to 30; 100 mg BID, d 1, 21 (n=8)	300 mg with ritonavir 100 mg QD, d 11 to 30 (n=8)	0.81 (0.66, 1.00)	0.80 (0.65, 0.97)	0.69 (0.54, 0.87)

[a] Data provided are under fed conditions unless otherwise noted.
[b] All drugs were given under fasted conditions.
[c] Atazanavir 300 mg with 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 400 mg once daily alone.
[d] Similar results were noted when famotidine 20 mg BID was administered 2 hours after and 10 hours before atazanavir 300 mg with ritonavir 100 mg and tenofovir DF 300 mg.
[e] Coadministration of atazanavir with ritonavir and tenofovir DF was administered after a light meal.
[f] Study was conducted in subjects with HIV-1 infection.
[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 with 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 with ritonavir 400/100 mg.
[h] Parallel group design; n=23 for atazanavir with ritonavir and nevirapine, n=22 for atazanavir 300 mg/ritonavir 100 mg without nevirapine. Subjects were treated with nevirapine prior to study entry.
[i] Omeprazole 40 mg was administered on an empty stomach 2 hours before atazanavir.
[j] Omeprazole 20 mg was administered 30 minutes prior to a light meal in the morning and atazanavir 300 mg with ritonavir 100 mg in the evening after a light meal, separated by 12 hours from omeprazole.
[k] Atazanavir 300 mg with 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 400 mg once daily in the absence of omeprazole (study days 1 to 6).
[l] Omeprazole 20 mg was given 30 minutes prior to a light meal in the morning and atazanavir 400 mg with ritonavir 100 mg once daily after a light meal, 1hour after omeprazole. Effects on atazanavir concentrations were similar when atazanavir 400 mg plus ritonavir 100 mg was separated from omeprazole 20 mg by 12 hours.
[m] Atazanavir 400 mg with 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 400 mg once daily in the absence of omeprazole (study days 1 to 6).
[n] Compared with atazanavir 400 mg QD historical data, administration of atazanavir with ritonavir 300/100 mg QD increased the atazanavir geometric mean values of C_{max}, AUC, and C_{min} by 18%, 103%, and 671%, respectively.
[o] Note that similar results were observed in studies where administration of tenofovir DF and atazanavir was separated by 12 hours.
[p] Ratio of atazanavir with ritonavir and tenofovir DF to atazanavir with ritonavir. Atazanavir 300 mg with ritonavir 100 mg results in higher atazanavir exposure than atazanavir 400 mg (see footnote [o]). The geometric mean values of atazanavir pharmacokinetic parameters when coadministered with ritonavir and tenofovir DF were: C_{max} = 3,190 ng/mL, AUC = 34,459 ng•h/mL, and C_{min} = 491 ng/mL. Study was conducted in subjects with HIV-1 infection.
NA = not available.

Table 22: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Atazanavir[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/ Schedule	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 to 20 (n=10)	300 mg QD with ritonavir 100 mg QD, d 11 to 20 (n=10)	0.87 (0.77, 0.99)	0.97 (0.91, 1.03)	1.26 (1.08, 1.46)
atenolol	50 mg QD, d 7 to 11 (n=19) and d 19 to 23	400 mg QD, d 1 to 11 (n=19)	1.34 (1.26, 1.42)	1.25 (1.16, 1.34)	1.02 (0.88, 1.19)
clarithromycin	500 mg BID, d 7 to 10 (n=21) and d 18 to 21	400 mg QD, d 1 to 10 (n=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)
ddI (enteric-coated [EC] capsules)[b]	400 mg d 1 (fasted), d 8 (fed) (n=34)	400 mg QD, d 2 to 8 (n=34)	0.64 (0.55, 0.74)	0.66 (0.60, 0.74)	1.13 (0.91, 1.41)
	400 mg d 1 (fasted), d 19 (fed) (n=31)	300 mg QD with ritonavir 100 mg QD, d 9 to 19 (n=31)	0.62 (0.52, 0.74)	0.66 (0.59, 0.73)	1.25 (0.92, 1.69)
diltiazem	180 mg QD, d 7 to 11 (n=28) and d 19 to 23	400 mg QD, d 1 to 11 (n=28)	1.98 (1.78, 2.19) desacetyl-diltiazem: 2.72 (2.44, 3.03)	2.25 (2.09, 2.16) desacetyl-diltiazem: 2.65 (2.45, 2.87)	2.42 (2.14, 2.73) desacetyl-diltiazem: 2.21 (2.02, 2.42)
ethinyl estradiol & norethindrone[c]	Ortho-Novum® 7/7/7 QD, d 1 to 29 (n=19)	400 mg QD, d 16 to 29 (n=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]	Ortho Tri-Cyclen® QD, d 1 to 28 (n=18), then Ortho Tri Cyclen® LO QD, d 29 to 42[e] (n=14)	300 mg QD with ritonavir 100 mg QD, d 29 to 42 (n=14)	ethinyl estradiol: 0.84 (0.74, 0.95) 17-deacetyl norgestimate:[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)
glecaprevir/pibrentasvir	300 mg glecaprevir (n=12)	300 mg QD with ritonavir 100 mg QD (n=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 (n=12)	300 mg QD with ritonavir 100 mg QD (n=12)	≥1.29[g] (1.15, 1.45)	≥1.64[g] (1.48, 1.82)	≥2.29[g] (1.95, 2.68)
grazoprevir/elbasvir	grazoprevir 200 mg QD d 1 to 35 (n=12)	300 mg QD with ritonavir 100 mg QD d 1 to 35 (n=12)	6.24 (4.42, 8.81)	10.58 (7.78, 14.39)	11.64 (7.96, 17.02)
	elbasvir 50 mg QD d 1 to 35 (n=10)	300 mg QD with ritonavir 100 mg QD d 1 to 35 (n=10)	4.15 (3.46, 4.97)	4.76 (4.07, 5.56)	6.45 (5.51 7.54)
methadone	Stable maintenance dose, d 1 to 15 (n=16)	400 mg QD, d 2 to 15 (n=16)	(R)-methadone[h] 0.91 (0.84, 1.0) total: 0.85 (0.78, 0.93)	(R)-methadone[h] 1.03 (0.95, 1.10) total: 0.94 (0.87, 1.02)	(R)-methadone[h] 1.11 (1.02, 1.20) total: 1.02 (0.93, 1.12)
nevirapine[i, j]	200 mg BID, d 1 to 23 (n=23)	300 mg QD with ritonavir 100 mg QD, d 4 to 13, then 400 mg QD with ritonavir 100 mg QD, d 14 to 23 (n=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[k]	40 mg single dose, d 7 and d 20 (n=16)	400 mg QD, d 1 to 12 (n=16)	1.24 (1.04, 1.47)	1.45 (1.20, 1.76)	NA
rifabutin	300 mg QD, d 1 to 10 then 150 mg QD, d 11 to 20 (n=3)	600 mg QD,[l] d 11 to 20 (n=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 to 15 (n=7)	300 mg QD with ritonavir 100 mg QD, d 1 to 17 (n=7)	2.49[m] (2.03, 3.06) 25-O-desacetyl rifabutin: 7.77 (6.13, 9.83)	1.48[m] (1.19, 1.84) 25-O-desacetyl rifabutin: 10.90 (8.14, 14.61)	1.40[m] (1.05, 1.87) 25-O-desacetyl rifabutin: 11.45 (8.15, 16.10)
pitavastatin	4 mg QD for 5 days	300 mg QD for 5 days	1.60 (1.39, 1.85)	1.31 (1.23, 1.39)	NA
rosiglitazone[n]	4 mg single dose, d 1, 7, 17 (n=14)	400 mg QD, d 2 to 7, then 300 mg QD with ritonavir 100 mg QD, d 8 to 17 (n=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
rosuvastatin	10 mg single dose	300 mg QD with ritonavir 100 mg QD for 7 days	↑ 7-fold[o]	↑ 3-fold[o]	NA
saquinavir[p] (soft gelatin capsules)	1,200 mg QD, d 1 to 13 (n=7)	400 mg QD, d 7 to 13 (n=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 (n=15)	300 mg with 100 mg ritonavir single dose (n=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 (n=15)	300 mg with 100 mg ritonavir single dose (n=15)	1.29 (1.07, 1.56)	1.93 (1.58, 2.36)	NA
	100 mg voxilaprevir single dose (n=15)	300 mg with 100 mg ritonavir single dose (n=15)	4.42 (3.65, 5.35)	4.31 (3.76, 4.93)	NA
tenofovir DF[q]	300 mg QD, d 9 to 16 (n=33) and d 24 to 30 (n=33)	400 mg QD, d 2 to 16 (n=33)	1.14 (1.08, 1.20)	1.24 (1.21, 1.28)	1.22 (1.15, 1.30)
	300 mg QD, d 1 to 7 (pm) (n=14) d 25 to 34 (pm) (n=12)	300 mg QD with ritonavir 100 mg QD, d 25 to 34 (am) (n=12)[r]	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 to 3, 22 to 30; 400 mg BID, d 1, 21 (n=20)	300 mg with ritonavir 100 mg QD, d 11 to 30 (n=20)	0.90 (0.78, 1.04)	0.67 (0.58, 0.78)	0.61 (0.51, 0.72)
voriconazole (Subjects without a functional CYP2C19 allele)	50 mg BID, d 2 to 3, 22 to 30; 100 mg BID, d 1, 21 (n=8)	300 mg with ritonavir 100 mg QD, d 11 to 30 (n=8)	4.38 (3.55, 5.39)	5.61 (4.51, 6.99)	7.65 (5.71, 10.2)
lamivudine and zidovudine	150 mg lamivudine and 300 mg zidovudine BID, d 1 to 12 (n=19)	400 mg QD, d 7 to 12 (n=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] Data provided are under fed conditions unless otherwise noted.
[b] 400 mg ddI EC and atazanavir 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 with ritonavir relative to ethinyl estradiol 25 mcg without atazanavir with 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 with 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 subjects with HIV-1 infection.
[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 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 QD alone d1 to 10 (n=14). Total of rifabutin and 25-O-desacetyl-rifabutin: AUC 2.19 (1.78, 2.69).
[n] Rosiglitazone used as a probe substrate for CYP2C8.
[o] Mean ratio (with/without coadministered drug). ↑ indicates an increase in rosuvastatin exposure.
[p] The combination of atazanavir and saquinavir 1,200 mg QD produced daily saquinavir exposures similar to the values produced by the standard therapeutic dosing of saquinavir at 1,200 mg TID. However, the C_{max} is about 79% higher than that for thestandard dosing of saquinavir (soft gelatin capsules) alone at 1,200 mg TID.
[q] Note that similar results were observed in a study where administration of tenofovir DF and atazanavir was separated by 12 hours.
[r] Administration of tenofovir DF and atazanavir was temporally separated by 12 hours.

NA = not available.

12.4 Microbiology

Mechanism of Action

Atazanavir (ATV) is an azapeptide HIV-1 protease inhibitor (PI). 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.

Antiviral Activity in Cell Culture

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. Atazanavir has activity against HIV-1 Group M subtype viruses A, B, C, D, AE, AG, F, G, and J isolates in cell culture. Atazanavir 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 antiviral activity studies with atazanavir showed no antagonism in cell culture with PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir), NNRTIs (delavirdine, efavirenz, and nevirapine), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir DF, 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

In Cell Culture: HIV-1 isolates with a decreased susceptibility to atazanavir have been selected in cell culture and obtained from patients treated with atazanavir or atazanavir with ritonavir. HIV-1 isolates with 93- to 183-fold reduced susceptibility to atazanavir from three different viral strains were selected in cell culture by 5 months. The substitutions in these HIV-1 viruses that contributed to atazanavir resistance include I50L, N88S, I84V, A71V, and M46I. Changes were also observed at the protease cleavage sites following drug selection. Recombinant viruses containing the I50L substitution without other major PI substitutions were growth impaired and displayed increased susceptibility in cell culture to other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). The I50L and I50V substitutions yielded selective resistance to atazanavir and amprenavir, respectively, and did not appear to be cross-resistant.

Clinical Studies of Treatment-Naive Subjects: Comparison of Ritonavir-Boosted Atazanavir vs. Unboosted Atazanavir: Study AI424-089 compared atazanavir 300 mg once daily with ritonavir 100 mg vs. atazanavir 400 mg once daily when administered with lamivudine and extended-release stavudine in treatment-naive subjects with HIV-1 infection. A summary of the number of virologic failures and virologic failure isolates with atazanavir resistance in each arm is shown in Table 23.

Table 23: Summary of Virologic Failures[a] at Week 96 in Study AI424-089: Comparison of Ritonavir Boosted Atazanavir vs. Unboosted Atazanavir: Randomized Subjects

	atazanavir 300 mg with ritonavir 100 mg (n=95)	atazanavir 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 atazanavir -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 subjects 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 atazanavir 400 mg-treated subjects. Neither isolate was phenotypically resistant to atazanavir.

Clinical Studies of Treatment-Naive Subjects Receiving Atazanavir 300 mg with Ritonavir 100 mg: In Phase 3 Study AI424-138, an as-treated genotypic and phenotypic analysis was conducted on samples from subjects who experienced virologic failure (HIV-1 RNA ≥400 copies/mL) or discontinued before achieving suppression on atazanavir with ritonavir (n=39; 9%) and lopinavir/ritonavir (n=39; 9%) through 96 weeks of treatment. In the atazanavir with ritonavir arm, one of the virologic failure isolates had a 56-fold decrease in atazanavir susceptibility emerge on therapy with the development of PI resistance-associated substitutions L10F, V32I, K43T, M46I, A71I, G73S, I85I/V, and L90M. The NRTI resistance-associated substitution M184V also emerged on treatment in this isolate conferring emtricitabine resistance. Two atazanavir with ritonavir-virologic failure isolates had baseline phenotypic atazanavir resistance and IAS-defined major PI resistance-associated substitutions at baseline. The I50L substitution emerged on study in one of these failure isolates and was associated with a 17-fold decrease in atazanavir susceptibility from baseline and the other failure isolate with baseline atazanavir resistance and PI substitutions (M46M/I and I84I/V) had additional IAS-defined major PI substitutions (V32I, M46I, and I84V) emerge on atazanavir treatment associated with a 3-fold decrease in atazanavir susceptibility from baseline. Five of the treatment failure isolates in the atazanavir with ritonavir arm developed phenotypic emtricitabine resistance with the emergence of either the M184I (n=1) or the M184V (n=4) substitution on therapy and none developed phenotypic tenofovir disoproxil resistance. In the lopinavir/ritonavir arm, one of the virologic failure subject isolates had a 69-fold decrease in lopinavir susceptibility emerge on therapy with the development of PI substitutions L10V, V11I, I54V, G73S, and V82A in addition to baseline PI substitutions L10L/I, V32I, I54I/V, A71I, G73G/S, V82V/A, L89V, and L90M. Six lopinavir/ritonavir virologic failure isolates developed the M184V substitution and phenotypic emtricitabine resistance and two developed phenotypic tenofovir disoproxil resistance.

Clinical Studies of Treatment-Naive Subjects Receiving Atazanavir 400 mg without Ritonavir: atazanavir-resistant clinical isolates from treatment-naive subjects who experienced virologic failure on atazanavir 400 mg treatment without ritonavir often developed an I50L substitution (after an average of 50 weeks of atazanavir therapy), often in combination with an A71V substitution, but also developed one or more other PI substitutions (eg, V32I, L33F, G73S, V82A, I85V, or N88S) with or without the I50L substitution. In treatment-naive subjects, viral isolates that developed the I50L substitution, without other major PI substitutions, showed phenotypic resistance to atazanavir but retained in cell culture 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 substitution on the efficacy of subsequently administered PIs.

Clinical Studies of Treatment-Experienced Subjects: In studies of treatment-experienced subjects treated with atazanavir or atazanavir with ritonavir, most atazanavir-resistant isolates from subjects who experienced virologic failure developed substitutions that were associated with resistance to multiple PIs and displayed decreased susceptibility to multiple PIs. The most common protease substitutions to develop in the viral isolates of subjects who failed treatment with atazanavir 300 mg once daily and ritonavir 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 substitutions that developed on atazanavir with ritonavir treatment including E34K/A/Q, G48V, I84V, N88S/D/T, and L90M occurred in less than 10% of subject isolates. Generally, if multiple PI resistance substitutions were present in the HIV-1 virus of the subject at baseline, atazanavir resistance developed through substitutions associated with resistance to other PIs and could include the development of the I50L substitution. The I50L substitution has been detected in treatment-experienced subjects experiencing virologic failure after long-term treatment. Protease cleavage site changes also emerged on atazanavir treatment but their presence did not correlate with the level of atazanavir resistance.

Cross-Resistance

Cross-resistance among PIs has been observed. Baseline phenotypic and genotypic analyses of clinical isolates from atazanavir clinical trials of PI-experienced subjects showed that isolates cross- resistant to multiple PIs were cross-resistant to atazanavir. Greater than 90% of the isolates with substitutions that included I84V or G48V were resistant to atazanavir. Greater than 60% of isolates containing L90M, G73S/T/C, A71V/T, I54V, M46I/L, or a change at V82 were resistant to atazanavir, and 38% of isolates containing a D30N substitution in addition to other changes were resistant to atazanavir. Isolates resistant to atazanavir 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 subjects, PI-resistant viral isolates that developed the I50L substitution in addition to other PI resistance-associated substitution were also cross-resistant to other PIs.

Baseline Genotype/Phenotype and Virologic Outcome Analyses

Genotypic and/or phenotypic analysis of baseline virus may aid in determining atazanavir susceptibility before initiation of atazanavir with ritonavir therapy. An association between virologic response at 48 weeks and the number and type of primary PI resistance-associated substitutions detected in baseline HIV-1 isolates from antiretroviral-experienced subjects receiving atazanavir with ritonavir once daily or lopinavir/ritonavir (fixed-dose product) twice daily in Study AI424-045 is shown in Table 24.

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

Table 24: HIV-1 RNA Response by Number and Type of Baseline PI Substitution, Antiretroviral-Experienced Subjects in Study AI424-045, As-Treated Analysis

Number and Type of Baseline PI Substitutions[a]	Virologic Response = HIV RNA <400 copies/mL[b]	
	atazanavir with ritonavir (n=110)	lopinavir/ ritonavir[c] (n=113)
3 or more primary PI substitutions including[d]:		
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 substitutions[a]		
All patients, as-treated	58% (64/110)	59% (67/113)
0 to 2 PI substitutions	75% (50/67)	75% (50/67)
3 to 4 PI substitutions	41% (14/34)	43% (12/28)
5 or more PI substitutions	0% (0/9)	28% (5/18)

[a] Primary substitutions 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] Administered as a fixed-dose product.
[d] There were insufficient data (n<3) for PI substitutions V32I, I47V, G48V, I50V, and F53L.

The response rates of antiretroviral-experienced subjects in Study AI424-045 were analyzed by baseline phenotype (shift in susceptibility in cell culture relative to reference, Table 25). The analyses are based on a select patient population with 62% of subjects 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.

Table 25: Baseline Phenotype by Outcome, Antiretroviral-Experienced Subjects in Study AI424-045, As-Treated Analysis

Baseline Phenotype[a]	Virologic Response = HIV-1 RNA <400 copies/mL[b]	
	atazanavir with ritonavir (n=111)	lopinavir/ ritonavir[c] (n=111)
0 to 2	71% (55/78)	70% (56/80)
>2 to 5	53% (8/15)	44% (4/9)
>5 to 10	13% (1/8)	33% (3/9)
>10	10% (1/10)	23% (3/13)

[a] Fold change susceptibility in cell culture relative to the wild-type reference.
[b] Results should be interpreted with caution because the subgroups were small.
[c] Administered as a fixed-dose product.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term carcinogenicity studies in mice and rats were carried out with atazanavir for two years. In the mouse study, drug-related increases in hepatocellular adenomas were found in females at 360 mg/kg/day. The systemic drug exposure (AUC) at the NOAEL (no observable adverse effect level) in females, (120 mg/kg/day) was 2.8 times and in males (80 mg/kg/day) was 2.9 times higher than those in humans at the clinical dose (300 mg/day atazanavir boosted with 100 mg/day ritonavir, non-pregnant patients). In the rat study, no drug-related increases in tumor incidence were observed at doses up to 1,200 mg/kg/day, for which AUCs were 1.1 (males) or 3.9 (females) times those measured in humans at the clinical dose.

Mutagenesis

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).

Impairment of Fertility

At the systemic drug exposure levels (AUC) 0.9 (in male rats) or 2.3 (in female rats) times that of the human clinical dose, (300 mg/day atazanavir boosted with 100 mg/day ritonavir) significant effects on mating, fertility, or early embryonic development were not observed.

14 CLINICAL STUDIES

14.1 Adult Subjects without Prior Antiretroviral Therapy

Study AI424-138: a 96-week study comparing the antiviral efficacy and safety of either atazanavir or lopinavir/ritonavir, each in combination with fixed-dose tenofovir DF-emtricitabine in treatment-naive subjects with HIV-1 infection. Study AI424-138 (NCT 00272779) was a 96-week, open-label, randomized, multicenter study, comparing atazanavir (300 mg once daily) with ritonavir (100 mg once daily) to lopinavir/ritonavir (400/100 mg twice daily as a fixed-dose product), each in combination with the fixed-dose product, tenofovirDF/emtricitabine (300/200 mg once daily), in 878 antiretroviral treatment-naive treated subjects. Subjects had a mean age of 36 years (range: 19 to 72), 49% were Caucasian, 18% Black, 9% Asian, 23% Hispanic/Mestizo/mixed race, and 68% were male. The median baseline plasma CD4+ cell count was 204 cells/mm³ (range: 2 to 810 cells/mm³) and the mean baseline plasma HIV-1 RNA level was 4.94 log_{10} copies/mL (range: 2.60 to 5.88 log_{10} copies/mL). Treatment response and outcomes through Week 96 are presented in Table 26.

Table 26: Outcomes of Treatment Through Week 96 in Treatment-Naive Adults (Study AI424-138)

Outcome	atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir DF/emtricitabine (once daily)[a] (n=441) 96 Weeks	lopinavir/ritonavir[b] 400 mg/100 mg (twice daily) with tenofovir DF/emtricitabine (once daily)[a] (n=437) 96 Weeks
Responder[c,d,e]	75%	68%
Virologic failure[f]	17%	19%
Rebound	8%	10%
Never suppressed through Week 96	9%	9%
Death	1%	1%
Discontinued due to adverse event	3%	5%
Discontinued for other reasons[g]	4%	7%

[a] As a fixed-dose product: 300 mg tenofovir DF/200 mg emtricitabine once daily.
[b] As a fixed-dose product: 400 mg lopinavir/100 mg ritonavir (twice daily).
[c] Subjects achieved HIV-1 RNA <50 copies/mL at Week 96. Roche Amplicor®, v1.5 ultra-sensitive assay.
[d] Pre-specified ITT analysis at Week 48 using as-randomized cohort: atazanavir with ritonavir 78% and lopinavir/ritonavir 76% (difference estimate: 1.7% [95% confidence interval: –3.8%, 7.1%]).
[e] Pre-specified ITT analysis at Week 96 using as-randomized cohort: atazanavir with ritonavir 74% and lopinavir/ritonavir 68% (difference estimate: 6.1% [95% confidence interval: 0.3%, 12.0%]).
[f] Includes viral rebound and failure to achieve confirmed HIV-1 RNA <50 copies/mL through Week 96.
[g] Includes lost to follow-up, subject's withdrawal, noncompliance, protocol violation, and other reasons.

Through 96 weeks of therapy, the proportion of responders among subjects with high viral loads (i.e., baseline HIV-1 RNA ≥100,000 copies/mL) was comparable for the atazanavir with ritonavir (165 of 223 subjects, 74%) and lopinavir/ritonavir (148 of 222 subjects, 67%) arms. At 96 weeks, the median increase from baseline in CD4+ cell count was 261 cells/mm³ for the atazanavir with ritonavir arm and 273 cells/mm³ for the lopinavir/ritonavir arm.

Study AI424-034: Atazanavir once daily compared to efavirenz once daily, each in combination with fixed-dose lamivudine/zidovudine twice daily. Study AI424-034 *(NCT00013897)* was a randomized, double-blind, multicenter trial comparing atazanavir (400 mg once daily) to efavirenz (600 mg once daily), each in combination with the fixed-dose product of lamivudine/zidovudine (150 mg/300 mg) given twice daily, in 810 antiretroviral treatment-naive subjects. Subjects 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/mm³ (range: 64 to 1,424 cells/mm³) 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). Treatment response and outcomes through Week 48 are presented in Table 27.

Table 27: Outcomes of Randomized Treatment Through Week 48 in Treatment-Naive Adults (Study AI424-034)

Outcome	atazanavir 400 mg once daily and lamivudine/ zidovudine[d] (n=405)	efavirenz 600 mg once daily and lamivudine/ zidovudine[d] (n=405)
Responder[a]	67% (32%)	62% (37%)
Virologic failure[b]	20%	21%
Rebound	17%	16%
Never suppressed through Week 48	3%	5%
Death	–	<1%
Discontinued due to adverse event	5%	7%
Discontinued for other reasons[c]	8%	10%

[a] Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL (<50 copies/mL) through Week 48. Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.0 or 1.5 as geographically appropriate.
[b] Includes viral rebound and failure to achieve confirmed HIV-1 RNA <400 copies/mL through Week 48.
[c] Includes lost to follow-up, subject's withdrawal, noncompliance, protocol violation, and other reasons.
[d] As a fixed-dose product: 150 mg lamivudine/300 mg zidovudine twice daily.

Through 48 weeks of therapy, the proportion of responders among subjects with high viral loads (i.e., baseline HIV-1 RNA ≥100,000 copies/mL) was comparable for the atazanavir and efavirenz arms. The mean increase from baseline in CD4+ cell count was 176 cells/mm³ for the atazanavir arm and 160 cells/mm³ for the efavirenz arm.

Study AI424-008: Atazanavir 400 mg once daily compared to atazanavir 600 mg once daily, and compared to nelfinavir 1,250 mg twice daily, each in combination with stavudine and lamivudine twice daily. Study AI424-008 (NCT identifier not available) was a 48-week, randomized, multicenter trial, blinded to dose of atazanavir, comparing atazanavir at two dose levels (400 mg and 600 mg once daily) to nelfinavir (1,250 mg twice daily), each in combination with stavudine (40 mg) and lamivudine (150 mg) given twice daily, in 467 antiretroviral treatment-naive subjects. Subjects 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/mm³ (range: 4 to 1,003 cells/mm³) 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). Treatment response and outcomes through Week 48 are presented in Table 28.

Table 28: Outcomes of Randomized Treatment Through Week 48 in Treatment-Naive Adults (Study AI424-008)

Outcome	atazanavir 400 mg once daily with lamivudine and stavudine (n=181)	nelfinavir 1,250 mg twice daily with lamivudine and stavudine (n=91)
Responder[a]	67% (33%)	59% (38%)
Virologic failure[b]	24%	27%
Rebound	14%	14%
Never suppressed through Week 48	10%	13%
Death	<1%	–
Discontinued due to adverse event	1%	3%
Discontinued for other reasons[c]	7%	10%

[a] Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL (<50 copies/mL) through Week 48. Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.0 or 1.5 as geographically appropriate.
[b] Includes viral rebound and failure to achieve confirmed HIV-1 RNA <400 copies/mL through Week 48.
[c] Includes lost to follow-up, subject's withdrawal, noncompliance, protocol violation, and other reasons.

Through 48 weeks of therapy, the mean increase from baseline in CD4+ cell count was 234 cells/mm³ for the atazanavir 400-mg arm and 211 cells/mm³ for the nelfinavir arm.

14.2 Adult Subjects with Prior Antiretroviral Therapy

Study AI424-045: Atazanavir once daily with ritonavir once daily compared to atazanavir once daily and saquinavir (soft gelatin capsules) once daily, and compared to lopinavir/ritonavir twice daily, each in combination with tenofovir DF and one NRTI. Study AI424-045 *(NCT00035932):* was a randomized, multicenter trial comparing atazanavir (300 mg once daily) with ritonavir (100 mg once daily) to atazanavir (400 mg once daily) with saquinavir soft gelatin capsules (1,200 mg once daily), and to lopinavir/ritonavir (400/100 mg twice daily as fixed-dose product), each in combination with tenofovir DF and one NRTI, in 347 (of 358 randomized) subjects who experienced virologic failure on highly active antiretroviral therapy regimens containing PIs, NNRTIs, and NRTIs. The mean time of prior exposure to antiretrovirals was 139 weeks for PIs, 85 weeks for NNRTIs, and 283 weeks for NRTIs. The mean age was 41 years (range: 24 to 74); 60% were Caucasian, and 78% were male. The mean baseline CD4+ cell count was 338 cells/mm³ (range: 14 to 1,543 cells/mm³) and the mean baseline plasma HIV-1 RNA level was 4.4 log_{10} copies/mL (range: 2.6 to 5.88 log_{10} copies/mL).

Treatment outcomes through Week 48 for the atazanavir with ritonavir and lopinavir/ritonavir treatment arms are presented in Table 29. Atazanavir with ritonavir and lopinavir/ritonavir were similar for the primary efficacy outcome measure of time-averaged difference in change from baseline in HIV-1 RNA level. Study AI424-045 was not large enough to reach a definitive conclusion that atazanavir with ritonavir and lopinavir/ritonavir are equivalent on the secondary efficacy outcome measure of proportions below the HIV-1 RNA lower limit of quantification *[see Microbiology, Tables 24 and 25 (12.4)]*.

Table 29: Outcomes of Treatment Through Week 48 in Study AI424-045 (Subjects with Prior Antiretroviral Experience)

Outcome	atazanavir 300 mg with ritonavir 100 mg once daily and tenofovir DF and 1 NRTI (n=119)	lopinavir/ritonavir (400/100 mg) twice daily and tenofovir DF and 1 NRTI (n=118)	Difference[a] (atazanavir- lopinavir/ ritonavir)[b] (CI)
HIV-1 RNA Change from Baseline (log_{10} copies/mL)[c]	–1.58	–1.70	+0.12[c] (–0.17, 0.41)
CD4+ Change from Baseline (cells/ mm³)[e]	116	123	–7 (–67, 52)
Percent of Subjects Responding[e]			
HIV-1 RNA <400 copies/mL[c]	55%	57%	–2.2% (–14.8%, 10.5%)
HIV-1 RNA <50 copies/mL[c]	38%	45%	–7.1% (–19.6%, 5.4%)

[a] Time-averaged difference through Week 48 for HIV-1 RNA; Week 48 difference in HIV-1 RNA percentages and CD4+ mean changes, atazanavir with ritonavir vs lopinavir/ritonavir; CI = 97.5% confidence interval for change in HIV-1 RNA; 95% confidence interval otherwise.
[b] Administered as a fixed-dose product
[c] Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.5.
[d] Protocol-defined primary efficacy outcome measure.
[e] Based on subjects with baseline and Week 48 CD4+ cell count measurements (atazanavir with ritonavir, n=85; lopinavir/ritonavir, n=93).
[f] Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL (<50 copies/mL) through Week 48.

No subjects in the atazanavir with ritonavir treatment arm and three subjects in the lopinavir/ritonavir treatment arm experienced a new-onset CDC Category C event during the study.

In Study AI424-045, the mean change from baseline in plasma HIV-1 RNA for atazanavir 400 mg with saquinavir (n=115) was –1.55 log_{10} copies/mL, and the time-averaged difference in change in HIV-1 RNA levels versus lopinavir/ritonavir was 0.33. The corresponding mean increase in CD4+ cell count was 72 cells/mm³. Through 48 weeks of treatment, the proportion of subjects in this treatment arm with plasma HIV-1 RNA <400 (<50) copies/mL was 38% (26%). In this study, coadministration of atazanavir and saquinavir did not provide adequate efficacy *[see Drug Interactions (7)]*.

Study AI424-045 also compared changes from baseline in lipid values. *[See Adverse Reactions (6.1).]*

Study AI424-043 (NCT00028301): Study AI424-043 was a randomized, open-label, multicenter trial comparing atazanavir (400 mg once daily) to lopinavir/ritonavir (400/100 mg twice daily as fixed-dose product), each in combination with two NRTIs, in 300 subjects who experienced virologic failure to only one prior PI-containing regimen. Through 48 weeks, the proportion of subjects with plasma HIV-1 RNA <400 (<50) copies/mL was 49% (35%) for subjects randomized to atazanavir (n=144) and 69% (53%) for subjects randomized to lopinavir/ritonavir (n=146). The mean change from baseline was –1.59 log_{10} copies/mL in the atazanavir treatment arm and –2.02 log_{10} copies/mL in the lopinavir/ritonavir arm. Based on the results of this study, atazanavir without ritonavir was inferior to lopinavir/ritonavir in PI-experienced subjects with prior virologic failure and is not recommended for such patients.

14.3 Pediatric Subjects

Pediatric Trials with Atazanavir Capsules

Study AI424-040; PACTG 1020A (NCT00006604): Assessment of the pharmacokinetics, safety, tolerability, and virologic response of atazanavir capsules was based on data from this open-label, multicenter clinical trial which included subjects from 6 years to 21 years of age. In this study, 105 subjects (43 antiretroviral-naive and 62 antiretroviral-experienced) received once daily atazanavir capsule formulation, with or without ritonavir, in combination with two NRTIs.

One-hundred five (105) subjects (6 to less than 18 years of age) treated with the atazanavir capsule formulation, with or without ritonavir, were evaluated. Using an intent-to-treat (ITT) analysis, the overall proportions of antiretroviral-naive and -experienced subjects with HIV-1 RNA <400 copies/mL at Week 96 were 51% (22/43) and 34% (21/62), respectively. The overall proportions of antiretroviral-naive and -experienced subjects with HIV-1 RNA <50 copies/mL at Week 96 were 47% (20/43) and 24% (15/62), respectively. The median increase from baseline in absolute CD4 count at 96 weeks of therapy was 335 cells/mm³ in antiretroviral-naive subjects and 220 cells/mm³ in antiretroviral-experienced subjects.

16 HOW SUPPLIED/STORAGE AND HANDLING

Atazanavir capsules are available in 150 mg, 200 mg and 300 mg strengths and supplied as follows:

150 mg Capsules: Off-white to Pale yellow colored granular powder filled in size "1" empty hard gelatin capsule shell with Opaque green colored cap imprinted with AT150 in white ink and Opaque light green colored body.

Bottles of 60	NDC 42385-920-60
Carton with 60 (10 x 6) Unit-Dose Capsules	NDC 42385-920-48

200 mg Capsules: Off-white to Pale yellow colored granular powder filled in size "0" empty hard gelatin capsule shell with Opaque green colored cap imprinted with AT200 in white ink and Opaque green colored body.

Bottles of 60	NDC 42385-921-60
Carton with 60 (10 x 6) Unit-Dose Capsules	NDC 42385-921-48

300 mg Capsules: Off-white to Pale yellow colored granular powder filled in size "00" empty hard gelatin capsule shell with Opaque orange colored cap imprinted with AT300 in white ink and Opaque green colored body.

Bottles of 30	NDC 42385-922-30
Carton with 30 (5 x 6) Unit-Dose Capsules	NDC 42385-922-37

Keep capsules in a tightly closed container.

Store atazanavir capsules at 20° to 25°C (68° to 77°F), excursions permitted between 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling *(Patient Information)*.

Atazanavir is not a cure for HIV-1 infection. Advise patients to remain under the care of a healthcare provider while using atazanavir.

Cardiac Conduction Abnormalities

Inform patients that atazanavir may produce changes in the electrocardiogram (eg, PR prolongation). Tell patients to consult their healthcare provider if they are experiencing symptoms such as dizziness or lightheadedness *[see Warnings and Precautions (5.1)]*.

Severe Skin Reaction

Inform patients that there have been reports of severe skin reactions (eg, Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions) with atazanavir use. Advise patients that if signs or symptoms of severe skin reactions or hypersensitivity reactions develop, they must discontinue atazanavir and seek medical evaluation immediately *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

Hyperbilirubinemia

Inform patients that asymptomatic elevations in indirect bilirubin have occurred in patients receiving atazanavir. This may be accompanied by yellowing of the skin or whites of the eyes and alternative antiretroviral therapy may be considered if the patient has cosmetic concerns *[see Warnings and Precautions (5.8)]*.

Chronic Kidney Disease

Inform patients that treatment with atazanavir may lead to the development of chronic kidney disease, and to maintain adequate hydration while taking atazanavir *[see Warnings and Precautions (5.5)]*.

Nephrolithiasis and Cholelithiasis

Inform patients that kidney stones and/or gallstones have been reported with atazanavir use. Some patients with kidney stones and/or gallstones required hospitalization for additional management and some had complications. Discontinuation of atazanavir may be necessary as part of the medical management of these adverse events *[see Warnings and Precautions (5.6)]*.

Drug Interactions

Atazanavir may lead to significant interaction with some drugs; therefore, advise patients to report the use of any other prescription, nonprescription medication, or herbal products, particularly St. John's wort, to their healthcare provider prior to use *[see Contraindications (4), Warnings and Precautions (5.7)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started *[see Warnings and Precautions (5.10)]*.

Fat Redistribution

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy including protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.11)]*.

Dosing Instructions

Advise patients to take atazanavir with food every day and take other concomitant antiretroviral therapy as prescribed. Atazanavir must always be used in combination with other antiretroviral drugs. Advise patients that they should not alter the dose or discontinue therapy without consulting with their healthcare provider. Tell patients if a dose of atazanavir is missed, they 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.

Pregnancy

Inform pregnant patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in pregnant patients exposed to atazanavir during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry *[see Use in Specific Populations (8.1)]*.

Lactation

Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk. Atazanavir can also be passed to the baby in breast milk and it is not known whether it could harm the baby *[see Use in Specific Populations (8.2)]*.

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PATIENT INFORMATION
Atazanavir (A-ta-ZAN-a-vir)
Capsules

Important: Ask your healthcare provider or pharmacist about medicines that should not be taken with atazanavir capsules. For more information, see "Do not take atazanavir if you" and "Before taking atazanavir capsules".

What are atazanavir capsules?

Atazanavir capsules are a prescription medicine that is used to treat human immunodeficiency virus-1 (HIV-1) infection, in combination with other HIV-1 medicines in adults and children 6 years of age and older who weigh at least 15 kg.

HIV-1 is the virus that causes AIDS (Acquired Immunodeficiency Syndrome).

Atazanavir should not be used in children younger than 3 months of age.

Do not take atazanavir capsules if you:

- are allergic to atazanavir or any of the ingredients in atazanavir capsules. See the end of this leaflet for a complete list of ingredients in atazanavir capsules.
- are taking any of the following medicines. Taking atazanavir capsules with these medicines may affect how atazanavir capsules works. Atazanavir capsules may cause serious or life-threatening side effects, or death when used with these medicines:
  - alfuzosin
  - amiodarone (when atazanavir is used with ritonavir)
  - cisapride
  - elbasvir/grazoprevir
  - ergot medicines including:
    - dihydroergotamine
    - ergonovine
    - ergonovine ergotamine
    - methylergonovine
  - glecaprevir/pibrentasvir
  - indinavir
  - irinotecan
  - lurasidone (when atazanavir is used with ritonavir)
  - lomitapide
  - lovastatin
  - midazolam, when taken by mouth for sedation
  - nevirapine
  - pimozide
  - quinidine (when atazanavir is used with ritonavir)
  - rifampin
  - sildenafil, when used for the treatment of pulmonary arterial hypertension
  - simvastatin
  - St. John's wort
  - triazolam

Before taking atazanavir capsules, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems
- have liver problems, including hepatitis B or C virus infection
- have kidney problems
- are receiving dialysis treatment
- have diabetes
- have hemophilia
- are pregnant or plan to become pregnant.
  - **Atazanavir capsules must be taken with ritonavir during pregnancy.**
  - **Hormonal forms of birth control, such as injections, vaginal rings or implants, contraceptive patch, and some birth control pills may not work during treatment with atazanavir capsules.** Talk to your healthcare provider about forms of birth control that may be used during treatment with atazanavir capsules.
  - **Pregnancy Exposure Registry.** There is a pregnancy exposure registry for people who take atazanavir capsules during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
  - **After your baby is born,** tell your healthcare provider if your baby's skin or the white part of their eyes turns yellow.
- are breastfeeding or plan to breastfeed. **Do not breastfeed if you are taking atazanavir capsules.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby. Atazanavir can pass into your breast milk.
  - Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines interact with atazanavir capsules. **Keep a list of your medicines to show your healthcare provider and pharmacist.**

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with atazanavir capsules.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take atazanavir capsules with other medicines.

How should I take atazanavir capsules?

- **Take atazanavir capsules exactly as your healthcare provider tells you to.**
- Do not change your dose or stop taking atazanavir capsules unless your healthcare provider tells you to.
- Stay under the care of your healthcare provider during treatment with atazanavir capsules.
- Atazanavir capsules must be used with other HIV-1 medicines.
- Take atazanavir capsule 1 time each day.
- Atazanavir comes as capsules.
- Take atazanavir capsules with food.
- Swallow the capsules whole. Do not open the capsules.
- Your child's healthcare provider will prescribe the right dose of atazanavir capsules based on your child's weight.
- If you miss a dose of atazanavir capsules, take it as soon as you remember. Then take the next dose at your regular time. Do not take 2 doses at the same time.
- If you take too much atazanavir capsules, call your healthcare provider or go to the nearest hospital emergency room right away.

When your supply of atazanavir capsules starts to run low, get more from your healthcare provider or pharmacy. It is important not to run out of atazanavir capsules. The amount of HIV-1 in your blood may increase if the medicine is stopped for even a short time. The virus may become resistant to atazanavir capsules and harder to treat.

What are the possible side effects of atazanavir capsules?

Atazanavir capsules can cause serious side effects, including:

- **A change in the way your heart beats (heart rhythm change).** Tell your healthcare provider right away if you get dizzy or lightheaded. These could be symptoms of a heart problem.
- **Skin rash.** Skin rash is common with atazanavir capsules but can sometimes be severe. Severe rash may develop with other symptoms which could be serious. If you develop a severe rash or a rash with any of the following symptoms, stop taking atazanavir capsules and call your healthcare provider or go to the nearest hospital emergency room right away:
  - general feeling of discomfort or "flu- like" symptoms
  - fever
  - muscle or joint aches
  - red or inflamed eyes, like "pink eye" (conjunctivitis)
  - blisters
  - mouth sores
  - swelling of your face
  - painful, warm, or red lump under your skin
- **Liver problems.** If you have liver problems, including hepatitis B or C infection, your liver problems may get worse when you take atazanavir capsules. Your healthcare provider will do blood tests to check your liver before you start atazanavir capsules and during treatment. Tell your healthcare provider right away if you get any of the following symptoms:
  - dark "tea-colored" urine
  - your skin or the white part of your eyes turns yellow
  - light colored stools
  - nausea
  - itching
  - stomach-area pain
- **Chronic kidney disease.** Atazanavir capsules may affect how well your kidneys work. Your healthcare provider will do blood and urine tests to check your kidneys before you start atazanavir capsules and during treatment. Drink plenty of fluids during treatment with atazanavir capsules.
- **Kidney stones** have happened in some people who take atazanavir capsules, and sometimes may lead to hospitalization. Tell your healthcare provider right away if you get symptoms of kidney stones which may include pain in your low back or low stomach area, blood in your urine, or pain when you urinate.
- **Gallbladder stones** have happened in some people who take atazanavir capsules, and sometimes may lead to hospitalization. Tell your healthcare provider right away if you get symptoms of a gallbladder problem which may include:
  - pain in the right or middle upper stomach area
  - fever
  - nausea and vomiting
  - your skin or the white part of your eyes turns yellow
- **Yellowing of your skin or the white part of your eyes** is common with atazanavir capsules but may be a symptom of a serious problem. These symptoms may be due to increases in bilirubin levels in your blood (bilirubin is made by the liver). Tell your healthcare provider right away if your skin or the white part of your eyes turns yellow.
- **New or worsening diabetes and high blood sugar (hyperglycemia)** have happened in some people who take protease inhibitor medicines like atazanavir capsules. Some people have had to start taking medicine to treat diabetes or have changes to their dose of their diabetes medicine. Tell your healthcare provider if you notice an increase in thirst or if you start urinating more often while taking atazanavir capsules.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider if you start having new symptoms after starting atazanavir capsules.
- **Changes in body fat** can happen in people taking HIV-1 medicines. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- **Increased bleeding problems in people with hemophilia** have happened when taking protease inhibitors like atazanavir capsules.

The most common side effects of atazanavir capsules include:

- nausea
- headache
- stomach-area pain
- vomiting
- trouble sleeping
- numbness, tingling, or burning of hands or feet
- dizziness
- muscle pain
- diarrhea
- depression
- fever

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of atazanavir capsules. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store atazanavir capsules?

- Store atazanavir capsules at room temperature, between 68°F to 77°F (20°C to 25°C).
- Keep capsules in a tightly closed container.
- The atazanavir capsules bottle comes with a child-resistant closure.

Keep atazanavir capsules and all medicines out of the reach of children.

General information about the safe and effective use of atazanavir capsules

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use atazanavir capsules for a condition for which they were not prescribed. Do not give atazanavir capsules to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about atazanavir capsules that is written for health professionals.

For more information call Laurus Generics Inc. at 1-833-3-LAURUS (1-833-352-8787).

What are the ingredients in atazanavir capsules?

Active ingredient: atazanavir sulfate

Inactive ingredients: crospovidone, lactose monohydrate, and magnesium stearate. The capsule shells contain the following inactive ingredients: gelatin, FD&C Blue No. 2, FD & C Yellow 6, iron oxide yellow, and titanium dioxide. The capsules are printed with ink containing butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, shellac, strong ammonia solution, and titanium dioxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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○ muscle or joint aches
○ red or inflamed eyes, like "pink eye" (conjunctivitis)
○ swelling of your face
○ painful, warm, or red lump under your skin

• **Liver problems.** If you have liver problems, including hepatitis B or C infection, your liver problems may get worse when you take atazanavir capsules. Your healthcare provider will do blood tests to check your liver before you start atazanavir capsules and during treatment. Tell your healthcare provider right away if you get any of the following symptoms:
○ dark "tea-colored" urine
○ your skin or the white part of your eyes turns yellow
○ light colored stools
○ nausea
○ itching
○ stomach-area pain

• **Chronic kidney disease.** Atazanavir capsules may affect how well your kidneys work. Your healthcare provider will do blood and urine tests to check your kidneys before you start atazanavir capsules and during treatment. Drink plenty of fluids during treatment with atazanavir capsules.

• **Kidney stones** have happened in some people who take atazanavir capsules, and sometimes may lead to hospitalization. Tell your healthcare provider right away if you get symptoms of kidney stones which may include pain in your low back or low stomach area, blood in your urine, or pain when you urinate.

• **Gallbladder stones** have happened in some people who take atazanavir capsules, and sometimes may lead to hospitalization. Tell your healthcare provider right away if you get symptoms of a gallbladder problem which may include:
○ pain in the right or middle upper stomach area
○ fever
○ nausea and vomiting
○ your skin or the white part of your eyes turns yellow

• **Yellowing of your skin or the white part of your eyes** is common with atazanavir capsules but may be a symptom of a serious problem. These symptoms may be due to increases in bilirubin levels in your blood (bilirubin is made by the liver). Tell your healthcare provider right away if your skin or the white part of your eyes turns yellow.

• **New or worsening diabetes and high blood sugar (hyperglycemia)** have happened in some people who take protease inhibitor medicines like atazanavir capsules. Some people have had to start taking medicine to treat diabetes or have changes to their dose of their diabetes medicine. Tell your healthcare provider if you notice an increase in thirst or if you start urinating more often while taking atazanavir capsules.

• **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider if you start having new symptoms after starting atazanavir capsules.

• **Changes in body fat** can happen in people taking HIV-1 medicines. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.

• **Increased bleeding problems in people with hemophilia** have happened when taking protease inhibitors like atazanavir capsules.

The most common side effects of atazanavir capsules include:
○ nausea
○ headache
○ stomach-area pain
○ vomiting
○ trouble sleeping
○ numbness, tingling, or burning of hands or feet
○ dizziness
○ muscle pain
○ diarrhea
○ depression
○ fever

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of atazanavir capsules. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store atazanavir capsules?
• Store atazanavir capsules at room temperature, between 68°F to 77°F (20°C to 25°C).
• Keep capsules in a tightly closed container.
• The atazanavir capsules bottle comes with a child-resistant closure.

Keep atazanavir capsules and all medicines out of the reach of children.

General information about the safe and effective use of atazanavir capsules
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use atazanavir capsules for a condition for which they were not prescribed. Do not give atazanavir capsules to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about atazanavir capsules that is written for health professionals.

For more information call Laurus Generics Inc. at 1-833-3-LAURUS (1-833-352-8787).

What are the ingredients in atazanavir capsules?
Active ingredient: atazanavir sulfate
Inactive ingredients: crospovidone, lactose monohydrate, and magnesium stearate. The capsule shells contain the following inactive ingredients: gelatin, FD&C Blue No. 2, FD & C Yellow 6, iron oxide yellow, and titanium dioxide. The capsules are printed with ink containing butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, shellac, strong ammonia solution, and titanium dioxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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Manufactured by:
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500(L) x 980(W) mm

LAURUS Labs	Product Name: Atazanavir Capsules		Component: Leaflet
	Market: US		No. of Colours: 01
	Pharma Code: 288		List. of Colours:
Date: 21/06/2021	SAP Code: 2000897		Black
	Font: Helvetica		
Functional areas	Prepared by	Reviewed by	Approved by
	MFG-PKD	MFG-PKD / RA	QA
Signature & Date			