HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg safely and effectively. See full prescribing information for Atazanavir Sulfate and Ritonavir Tablets.

Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg for oral use

------------------INDICATIONS AND USAGE------------------
Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg, a combination of a protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection (1)

------------DOSAGE AND ADMINISTRATION------------
Take Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg with food.
- *Adults and pediatric patients (at least 6 years of age and weighing 35 kg):* Atazanavir Sulfate and Ritonavir Tablet, 300 mg/100 mg once daily with food. (2.1)
- *Pregnancy:* Atazanavir Sulfate and Ritonavir Tablet, 300 mg/100 mg once daily with food, with dosing modifications for some concomitant medications. (2.2)

------------DOSAGE FORMS AND STRENGTHS------------
Tablet: 300 mg atazanavir and 100 mg ritonavir (3)

--------------------CONTRAINDICATIONS--------------------
Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg are contraindicated in patients with known hypersensitivity (e.g., erythema multiforme, toxic skin eruptions, or Stevens-Johnson syndrome or toxic skin eruptions to any of the components of this product). (4)
Coadministration with alfuzosin, triazolam, orally administered midazolam, ergot derivatives, rifampin, irinotecan, lovastatin, simvastatin, indinavir, cisapride, pimozide, St. John's wort, and sildenafil.(4)

-------------WARNINGS AND PRECAUTIONS-------------
Cardiac conduction abnormalities: PR interval prolongation may occur in some patients. Use with caution in patients with preexisting conduction system disease or when administered with other drugs that may prolong the PR interval (5.2, 6.4, 7.3, 12.2, 17.3)
Hepatotoxicity: Fatalities have occurred. Monitor liver function before and during therapy, especially in patients with underlying hepatic disease, including hepatitis B and hepatitis C, or marked transaminase elevations (5.3, 6.3, 6.4, 8.8)
Pancreatitis: Fatalities have occurred; suspend therapy as clinically appropriate (5.4)
Allergic Reactions/Hypersensitivity: Allergic reactions have been reported and include anaphylaxis, toxic epidermal necrolysis, Stevens-Johnson syndrome, bronchospasm and angioedema. Discontinue treatment if severe reactions develop (5.5)
Hyperbilirubinemia: Most patients experience asymptomatic increases in indirect bilirubin, which is reversible upon discontinuation. Do not reduce the dose. If a concomitant transaminase increase occurs, evaluate for alternative etiologies (5.6)
Total cholesterol and triglycerides elevations: Monitor prior to therapy and periodically thereafter. (5.7)
Nephrolithiasis and cholelithiasis has been reported. Consider temporary interruption or discontinuation (5.8)
Patients may develop new onset or exacerbations of diabetes mellitus, hyperglycemia (5.9)
Patients may develop immune reconstitution syndrome. (5.10)
Patients may develop redistribution/accumulation of body fat. (5.11)
Hemophilia: Spontaneous bleeding may occur, and additional factor VIII may be required (5.12)
Drug interaction: Concomitant use of Atazanavir/Ritonavir with other drugs may result in known or potentially significant drug interactions.

--------------------ADVERSE REACTIONS--------------------
Atazanavir: The most common adverse reactions (greater than or equal to 2%) are nausea, jaundice/scleral icterus, rash, headache, abdominal pain, vomiting, insomnia, peripheral neurologic symptoms, dizziness, myalgia, diarrhea, depression, and fever. (6.1, 6.2)
Ritonavir: The most common adverse reactions (>2%) were 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 Heritage Pharmaceuticals Inc. at 1-866-901-DRUG (3784) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

--------------------DRUG INTERACTIONS--------------------
Co-administration of Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg can alter the concentration of other drugs and other drugs may alter the concentration of atazanavir, ritonavir. The potential drug-drug interactions must be considered prior to and during therapy (4, 5.1, 7, 12.3)

--------------USE IN SPECIFIC POPULATIONS--------------
Pregnancy: Available human and animal data suggest the atazanavir does not increase the risk of major birth defects overall compared to the background rate (8.1)
Nursing mothers: Nursing mothers should be instructed not to breastfeed due to the potential for postnatal HIV transmission (8.3)
Hepatitis B or C co-infection: Monitor liver enzymes (5.3)
Hepatitis B or C co-infection: Monitor liver enzymes (5.3)
Renal impairment: Do not use in treatment-experienced patients with end stage renal disease managed with hemodialysis (2.3, 8.6)
Hepatic impairment: Not recommended for patients with severe hepatic impairment. Atazanavir Sulfate and Ritonavir is not recommended in patients with any degree of hepatic impairment. (2.4, 8.8)

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

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*** Sections or subsections omitted from the full prescribing information are not listed.**

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for oral use
Tablets, 300 mg/100 mg
Atazanavir Sulfate and Ritonavir
20603

20603
Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg for oral use
Rev. 08/17 510006671IN01

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg, a combination with other antiretroviral agents for the treatment of HIV-1 infection for patients 6 years and older weighing at least 35 kg.
Limitation of Use:
- Atazanavir is not recommended for use in pediatric patients below the age of 3 months due to the risk of kernicterus.
- Use of atazanavir/ritonavir in treatment-experienced patients should be guided by the number of baseline primary protease inhibitor resistance substitutions. [see *Clinical Pharmacology (12.4)*].

2 DOSAGE AND ADMINISTRATION
- Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg is recommended in treatment naïve and treatment experienced patients.
- Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg must be used in combination with other antiretroviral agents for the treatment of HIV-1 infection.
- Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg must be taken orally with food.
- The recommended oral dosage of Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg depends on the treatment history of the patient and the use of the other coadministered drugs. When coadministered with H2-receptor antagonists or proton pump inhibitors, dose separation may be required [see *Dosage and Administration (2.1)*]
- Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg should be swallowed whole, and not chewed, broken or crushed. Take Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg with meals.

2.1 Recommended Dosage
Adults and pediatric patients (at least 6 years of age and weighing atleast 35 kg): The recommended dosage of Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg is shown in Table 1

Table 1: Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg Dosing Regimens

Treatment-Naive Patients and treatment experienced patients.	One tablet once daily
Do not coadminister with efavirenz, -H2RA AND Tenofovir DF	

- The H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 40 mg twice daily. Administer Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg with, and/or at least 10 hours after the H_2-receptor antagonist.
- The proton-pump inhibitor dose should not exceed a dose comparable to omeprazole 20 mg daily and must be taken approximately 12 hours prior to Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg.

[For these drugs and other antiretroviral agents for which dosing modification may be appropriate, see *Drug Interactions (7)*].

2.2 Pregnancy
Dosing During Pregnancy and the Postpartum Period:
- It should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir, one component of Atazanavir Sulfate and Ritonavir Tablets.
- Not recommended for treatment-experienced pregnant women during the second or third trimester, when coadministered with either an H_2-receptor antagonist or tenofovir DF because higher doses of atazanavir are required. There are insufficient data to recommend an atazanavir dose for use with both an H_2-receptor antagonist and tenofovir DF in treatment-experienced pregnant women.
- No dose adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir, one component of Atazanavir Sulfate and Ritonavir Tablets, exposures could be higher during the first 2 months after delivery. [*See Use in Specific Populations (8.1) and Clinical Pharmacology (12.3).*]

2.3 Renal Impairment
Treatment-naïve patients:
No dose adjustment is required for patients with renal impairment, including treatment-naive patients with end stage renal disease managed with hemodialysis.

Treatment-experienced patients:
Atazanavir Sulfate and Ritonavir Tablets should not be administered to HIV-treatment- experienced patients with end stage renal disease managed with hemodialysis. [*See Use in Specific Populations (8.7)*]. No dose adjustment is required for other treatment-experienced patients with renal impairment.

2.4 Hepatic Impairment
Atazanavir Sulfate and Ritonavir Tablets are not recommended for use in patients with any degree of hepatic impairment, because atazanavir with ritonavir has not been studied in this population. [See *Warnings and Precautions (5.3) and Use in Specific Populations (8.8)*].

3 DOSAGE FORMS AND STRENGTHS
Creamish yellow colored modified capsule shaped film coated tablets containing atazanavir 300 mg and ritonavir 100 mg debossed with "EM" on one side and "149" on the other side.

4 CONTRAINDICATIONS
Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg are contraindicated:
- in patients with known hypersensitivity (e.g., erythema multiforme, toxic skin eruptions, or Stevens-Johnson syndrome) to any components of this product.
- when co-administered 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. These and other contraindicated drugs are listed in Table 2.
- when coadministered with drugs that strongly induce CYP3A and may lead to lower exposure and loss of efficacy of atazanavir.

Table 2 : Drugs That Are Contraindicated With Atazanavir Sulfate and Ritonavir Tablets

Drug Class	Drugs within class that are contraindicated with atazanavir	Clinical Comment
Alpha 1-Adrenoreceptor Antagonist	Alfuzosin	Potential for increased alfuzosin concentrations, which can result in hypotension.
Antimycobacterials	Rifampin	Rifampin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect and development of resistance.
Antineoplastics	Irinotecan	Atazanavir inhibits UGT1A1 and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.
Antianginal	Ranolazine	Potential for serious and/or lifethreatening reactions.
Antipsychotics	Lurasidone	Potential for serious and/or life-threatening reactions if Atazanavir is coadministered with ritonavir.
	Pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
	Perphenazine, risperidone, thioridazine	A dose decrease may be needed for these drugs when co-administered with Atazanavir/ritonavir.
Antiarrhythmic	Amiodarone, dronedarone, flecainide, propafenone, quinidine	Potential for cardiac arrhythmias.
Anti-gout	Colchicine	Potential for serious and/or lifethreatening reactions in patients with renal and/or hepatic impairment.
Benzodiazepines	Triazolam, orally administered midazolam[a]	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with atazanavir may cause large increases in the concentration of these benzodiazepines. Potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
Ergot Derivatives	Dihydroergotamine, ergotamine, ergonovine, methylergonovine	Potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	Cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products	St. John's wort (*Hypericum perforatum*)	Patients taking atazanavir should not use products containing St. John's wort because coadministration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for serious reactions such as myopathy including rhabdomyolysis.
PDE5 Inhibitor	Sildenafil[b] when dosed for the treatment of pulmonary arterial hypertension	A safe and effective dose in combination with atazanavir has not been established for sildenafil when used for the treatment of pulmonary hypertension. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, priapism, and syncope).
Protease Inhibitors	Indinavir	Both atazanavir and indinavir are associated with indirect (unconjugated) hyperbilirubinemia.
Sedative/hypnotics	Oral midazolam[c], triazolam	Prolonged or increased sedation or respiratory depression.

[a] See *Drug Interactions, Table 10 (7)* for parenterally administered midazolam
[b] See *Drug Interactions, Table 10 (7)* for sildenafil when dosed for erectile dysfunction.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions
Atazanavir Sulfate
Initiation of atazanavir with ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medication 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 2 for a listing of drugs that are contraindicated for use with atazanavir sulfate due to potentially life-threatening adverse events, significant drug interactions, or loss of virologic activity [See *Contraindications (4)*]. Please refer to Table 10 and Table 11 for established and other potentially significant drug interactions [see *Drug Interactions (7.3)*].
Consider the potential for drug interactions prior to and during treatment with atazanavir with ritonavir, review concomitant medications and monitor for the adverse reactions associated with the concomitant medications. *[see Contraindications (4) and Drug interactions (7)]*.

5.2 Cardiac Conduction Abnormalities/ PR interval prolongation
Atazanavir Sulfate
Atazanavir has been shown to prolong the PR interval of the electrocardiogram in some patients. In healthy volunteers and in patients, abnormalities in atrioventricular (AV) conduction were asymptomatic and generally limited to first-degree AV block. There have been reports of second-degree AV block and other conduction abnormalities [see *Adverse Reactions (6.4)* and *Overdosage (10)*]. In clinical trials that included electrocardiograms, asymptomatic first-degree AV block was observed in 5.9% of atazanavir-treated patients (n=920), 5.2% of lopinavir/ritonavir-treated patients (n=252), 10.4% of nelfinavir-treated patients (n=48), and 3.0% of efavirenz-treated patients (n=329). In Study AI424-045 asymptomatic first-degree AV block was observed in 5% (6/118) of atazanavir/ritonavir-treated patients and 5% (6/116) of lopinavir/ritonavir-treated patients who had on-study electrocardiogram measurements. Because of limited clinical experience in patients with preexisting conduction system disease (eg, marked first-degree AV block, ECG monitoring should be considered in these patients. [See *Clinical Pharmacology (12.2)*].

Ritonavir
Ritonavir prolongs the PR interval in some patients. Post marketing cases of second or third degree atrioventricular block have been reported in patients.

Ritonavir should be used with caution in patients with underlying structural heart disease, preexisting conduction system abnormalities, ischemic heart disease, cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities.

The impact on the PR interval of co-administration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers, beta-adrenergic blockers, digoxin and atazanavir) has not been evaluated. As a result, co-administration of ritonavir with these drugs should be undertaken with caution, particularly with those drugs metabolized by CYP3A. Clinical monitoring is recommended.

5.3 Hepatotoxicity/ Hepatic Reactions
Atazanavir Sulfate
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 sulfate and during treatment [See *Adverse Reactions (6.3)* and *Use in Specific Populations (8.8)*].

Ritonavir
Hepatic transaminase elevations exceeding 5 times the upper limit of normal, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir alone or in combination with other antiretroviral drugs. There may be an increased risk for transaminase elevations in patients with underlying hepatitis B or C. Therefore, caution should be exercised when administering ritonavir to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis. Increased AST/ALT monitoring should be considered in these patients, especially during the first three months of ritonavir treatment [see *Use in Specific Populations (8.8)*].

There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients taking multiple concomitant medications and/or with advanced AIDS.

5.4 Pancreatitis
Pancreatitis has been observed in patients receiving ritonavir therapy, including those who developed hypertriglyceridemia. In some cases fatalities have been observed. Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis [see *Warnings and Precautions (5.7)*]. Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and ritonavir therapy should be discontinued if a diagnosis of pancreatitis is made.

5.5 Allergic Reactions/Hypersensitivity/Severe Skin Reactions
Atazanavir Sulfate
In controlled clinical trials, rash (all grades, regardless of causality) occurred in approximately 20% of patients treated with atazanavir sulfate. The median time to onset of rash in clinical studies was 7.3 weeks and the median duration of rash was 1.4 weeks. Rashes were generally mild-to-moderate maculopapular skin eruptions. Treatment-emergent adverse reactions of moderate or severe rash (occurring at a rate of greater than or equal to 2%) are presented for the individual clinical studies [see *Adverse Reactions (6.1)*]. Dosing with atazanavir sulfate was often continued without interruption in patients who developed rash. The discontinuation rate for rash in clinical trials was less than 1%. Atazanavir sulfate should be discontinued if severe rash develops. Cases of Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions, including drug rash, eosinophilia and systemic symptoms (DRESS) syndrome, have been reported in patients receiving atazanavir sulfate [See *Contraindications (4)*].

Ritonavir
Allergic reactions including urticaria, mild skin eruptions, bronchospasm, and angioedema have been reported with ritonavir. Cases of anaphylaxis, toxic epidermal necrolysis (TEN), and Stevens-Johnson syndrome have also been reported. Discontinue treatment if severe reactions develop.

5.6 Hyperbilirubinemia
Most patients taking atazanavir sulfate experience asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT). This hyperbilirubinemia is reversible upon discontinuation of atazanavir sulfate. 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 greater than 5 times the upper limit of normal (ULN). Alternative antiretroviral therapy to atazanavir sulfate 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, 6.2)*].

5.7 Lipid Disorders
Treatment with ritonavir therapy alone or in combination with saquinavir has resulted in substantial increases in the concentration of total cholesterol and triglycerides [see *Adverse Reactions (6.1)*]. Triglyceride and cholesterol testing should be performed prior to initiating ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate, taking into account any potential drug-drug interactions with ritonavir and HMG CoA reductase inhibitors [see *Contraindications (4)* and *Drug Interactions (7)*].

5.8 Nephrolithiasis and Cholelithiasis
Cases of nephrolithiasis and/or cholelithiasis have been reported during postmarketing surveillance were reported in HIV-infected patients receiving atazanavir sulfate 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 (6.4)*].

5.9 Diabetes Mellitus/Hyperglycemia
New-onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, and/or cholelithiasis have been reported during postmarketing surveillance were reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy, including atazanavir sulfate and ritonavir. 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. Consider monitoring for hyperglycemia, new onset diabetes mellitus, or an exacerbation of diabetes mellitus in patients treated with atazanavir and ritonavir [See *Adverse Reactions (6.4)*].

5.10 Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including atazanavir and ritonavir. 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) 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, including atazanavir sulfate and ritonavir. 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, including atazanavir sulfate and ritonavir have been observed. Resistance to atazanavir may not preclude the subsequent use of other protease inhibitors [See *Clinical Pharmacology (12.4)*].

5.14 Laboratory Tests
Ritonavir has been shown to increase triglycerides, cholesterol, SGOT (AST), SGPT (ALT), GGT, CPK, and uric acid. Appropriate laboratory testing should be performed prior to initiating ritonavir therapy and at periodic intervals or if any clinical signs or symptoms occur during therapy.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling.
- Drug interactions [See *Warnings and Precautions (5.1)*]
- Cardiac conduction abnormalities/PR interval prolongation [See *Warnings and Precautions (5.2)*]
- Allergic reactions/Hypersensitivity/Severe Skin Reactions [See *Warnings and Precautions (5.5)*]
- Hepatotoxicity/Hepatic Reactions [See *Warnings and Precautions (5.3)*]
- Hyperbilirubinemia [See *Warnings and Precautions (5.6)*]
- Nephrolithiasis and cholelithiasis [See *Warnings and Precautions (5.8)*]
- Pancreatitis [See *Warnings and Precautions (5.4)*]

Because clinical trials are conducted under widely varying conditions, adverse reactions 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.

6.1 Clinical Trial Experience in Adults
Treatment-Emergent Adverse Reactions in Treatment-Naive Patients
The safety profile of atazanavir sulfate in treatment-naive adults is based on 1625 HIV-1 infected patients in clinical trials. 536 patients received atazanavir sulfate 300 mg with ritonavir 100 mg.

The most common adverse reactions are nausea, jaundice/sclera icterus, and rash.

Selected clinical adverse reactions of moderate or severe intensity reported in greater than or equal to 2% of treatment-naive patients receiving combination therapy including Atazanavir 300 mg with ritonavir 100 mg is presented in Table 3.

Table 3: Selected Treatment-Emergent Adverse Reactions[a] of Moderate or Severe Intensity Reported in greater than or equal to 2% of Adult Treatment-Naive Patients,[b] Study AI424-138

	96 weeks[c] Atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir DF with emtricitabine[d] (n=441)	96 weeks[c] lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir DF with emtricitabine[d] (n=437)
Digestive System		
Nausea	4%	8%
Jaundice/scleral icterus	5%	*
Diarrhea	2%	12%
Skin and Appendages		
Rash	3%	2%

* None reported in this treatment arm.
[a] Includes events of possible, probable, certain, or unknown relationship to treatment regimen.
[b] Based on the regimen containing atazanavir.
[c] Median time on therapy.
[d] As a fixed-dose combination: 300 mg tenofovir DF, 200 mg emtricitabine once daily.

Treatment-Emergent Adverse Reactions in Treatment-Experienced Patients
The safety profile of atazanavir in treatment-experienced adults is based on 119 HIV-1 infected patients in clinical trials.
The most common adverse reactions are jaundice/scleral icterus and myalgia.
Selected clinical adverse reactions of moderate or severe intensity reported in greater than or equal to 2% of treatment-experienced patients receiving Atazanavir sulfate/ritonavir are presented in Table 4.

Table 4: Selected Treatment-Emergent Adverse Reactions[a] of Moderate or Severe Intensity Reported in greater than or equal to 2% of Adult Treatment-Experienced Patients,[b] Study AI424-045

	48 weeks[c] atazanavir/ritonavir 300/100 mg once daily + tenofovir DF + NRTI (n=119)	48 weeks[c] lopinavir/ritonavir 400/100 mg twice daily[d] + tenofovir DF + 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.

Laboratory Abnormalities in Treatment-Naive Patients
The percentages of adult treatment-naive patients treated with combination therapy including atazanavir sulfate 300 mg with ritonavir 100 mg with Grade 3 to 4 laboratory abnormalities are presented in Table 5.

Table 5: Grade 3 to 4 Laboratory Abnormalities Reported in greater than or equal to 2% of Adult Treatment-Naive Patients,[a] Study AI424-138

Variable	Limit[c]	96 weeks[b] atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir DF with emtricitabine[d] (n=441)	96 weeks[b] lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir DF with 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/mm³	5%	2%

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

Laboratory Abnormalities in Treatment-Experienced Patients
The percentages of adult treatment-experienced patients treated with combination therapy including atazanavir sulfate/ritonavir with Grade 3 to 4 laboratory abnormalities are presented in Table 6.

Table 6: Grade 3 to 4 Laboratory Abnormalities Reported in greater than or equal to 2% of Adult Treatment-Experienced Patients, Study AI424-045[a]

Variable	Limit[c]	48 weeks[b] atazanavir/ritonavir 300/100 mg once daily + tenofovir DF + NRTI (n=119)	48 weeks[b] lopinavir/ritonavir 400/100 mg twice daily[d] + tenofovir DF + 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/mm³	2%	3%
Neutrophils	<750 cells/mm³	7%	8%

[a] Based on regimen(s) containing atazanavir sulfate.
[b] Median time on therapy.
[c] ULN = upper limit of normal.

Lipids, Change from Baseline in Treatment-Naive Patients
For Study AI424-138 and Study AI424-034, changes from baseline in LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglycerides are shown in Table 7.

Table 7: Lipid Values, Mean Change from Baseline, Study AI424-138

	Atazanavir sulfate/ritonavir[a,b] Baseline mg/dL (n=428[e])	Week 48 mg/dL (n=372[e])	Week 48 Change[d] (n=372[e])	Week 96 mg/dL (n=342[e])	Week 96 Change[d] (n=342[e])	lopinavir/ritonavir[b,c] Baseline mg/dL (n=424[e])	Week 48 mg/dL (n=335[e])	Week 48 Change[d] (n=335[e])	Week 96 mg/dL (n=291[e])	Week 96 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 sulfate 300 mg with ritonavir 100 mg once daily with the fixed-dose combination: 300 mg tenofovir DF, 200 mg emtricitabine once daily.
[b] Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 1% in the lopinavir/ritonavir treatment arm and 1% in the atazanavir sulfate/ritonavir arm. Through Week 48, serum lipid-reducing agents were used in 8% in the lopinavir/ritonavir treatment arm and 2% in the atazanavir sulfate/ritonavir arm. Through Week 96, serum lipid-reducing agents were used in 10% in the lopinavir/ritonavir treatment arm and 3% in the atazanavir sulfate/ritonavir arm.
[c] Lopinavir 400 mg with ritonavir 100 mg twice daily with the fixed-dose combination 300 mg tenofovir DF, 200 mg emtricitabine once daily.
[d] The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 or Week 96 values and is not a simple difference of the baseline and Week 48 or Week 96 mean values, respectively.
[e] Number of patients with LDL-cholesterol measured.
[f] Fasting.

The safety of Ritonavir alone and in combination with other antiretroviral agents was studied in 1,755 adult patients. Table 8 lists treatment-emergent Adverse Reactions (with possible or probable relationship to study drug) occurring in greater than or equal to 1% of adult patients receiving Ritonavir in combined Phase II/IV studies.

The most frequently reported adverse drug reactions among patients receiving Ritonavir alone or in combination with other antiretroviral drugs were gastrointestinal (including diarrhea, nausea, vomiting, abdominal pain (upper and lower), neurological disturbances (including paresthesia and oral paresthesia), rash, and fatigue/asthenia.

Table 8 Treatment-Emergent Adverse Reactions (With Possible or Probable Relationship to Study Drug) Occurring in greater than or equal to 1% of Adult Patients Receiving ritonavir in Combined Phase II/IV Studies (N = 1,755)

Adverse Reactions	n	%
Eye disorders		
Blurred vision	113	6.4
Gastrointestinal disorder		
Abdominal Pain (upper and lower)*	464	26.4
Diarrhea including severe with electrolyte imbalance*	1,192	67.9
Dyspepsia	201	11.5
Flatulence	142	8.1
Gastrointestinal hemorrhage*	41	2.3
Gastroesophageal reflux disease (GERD	19	1.1
Nausea	1,007	57.4
Vomiting*	559	31.9
General disorders and administration site conditions		
Fatigue including asthenia*	811	46.2
Hepatobiliary disorders		
Blood bilirubin increased (including jaundice)*	25	1.4
Hepatitis (including increased AST, ALT, GGT)*	153	8.7
Immune system disorder		
Hypersensitivity including urticaria and face edema*	114	8.2
Metabolism and nutrition disorder		
Edema and peripheral edema*	110	6.3
Gout*	24	1.4
Hypercholesterolemia*	52	3.0
Hypertriglyceridemia*	158	9.0
Lipodystrophy acquired*	51	2.9
Musculoskeletal and connective tissue disorders		
Arthralgia and back pain*	326	18.6
Myopathy/creatine phosphokinase increased*	66	3.8
Myalgi	156	8.9
Nervous system disorders		
Dizziness*	274	15.6
Dysgeusia*	285	16.2
Paresthesia (including oral paresthesia)*	889	50.7
Peripheral neuropathy	178	10.1
Syncope*	58	3.3
Psychiatric disorder		
Confusion*	52	3.0
Disturbance in attention	44	2.5
Renal and urinary disorder		
Increased urination*	74	4.2
Respiratory, thoracic and mediastinal disorder		
Coughing*	380	21.7
Oropharyngeal Pain*	279	15.9
Skin and subcutaneous tissue disorders		
Acne*	67	3.8
Pruritus*	214	12.2
Rash (includes erythematous and maculopapular)*	475	27.1
Vascular disorders		
Flushing, feeling hot*	232	13.2
Hypertension*	58	3.3
Hypotension including orthostatic hypotension*	30	1.7
Peripheral coldness*	21	1.2

* Represents a medical concept including several similar MedDRA PTs

Laboratory Abnormalities in Adults
Table 9. shows the percentage of adult patients who developed marked laboratory abnormalities

Table 9: Percentage of Adult Patients, by Study and Treatment Group, with Chemistry and hematology abnormalities occurring in greater than 3% of patients receiving Ritonavir

Variable	Limit	Study 245 Naive Patients: Ritonavir plus ZDV	Ritonavir	ZDV	Study 247 Advanced Patients: Ritonavir	Placebo	Study 462 PI-Naive Patients: Ritonavir plus Saquinavir
Chemistry	**High**						
Cholesterol	> 240 mg/dL	30.7	44.8	9.3	36.5	8.0	65.2
CPK	> 1000 IU/L	9.6	12.1	11.0	9.1	6.3	9.9
GGT	> 300 IU/L	1.8	5.2	1.7	19.6	11.3	9.2
SGOT (AST)	> 180 IU/L	5.3	9.5	2.5	6.4	7.0	7.8
SGPT (ALT)	> 215 IU/L	5.3	7.8	3.4	8.5	4.4	9.2
Triglycerides	> 800 mg/dL	9.6	17.2	3.4	33.6	9.4	23.4
Triglycerides	>1500 mg/dL	1.8	2.6	-	12.6	0.4	11.3
Triglycerides Fasting	> 1500mgldL	1.5	1.3	-	9.9	0.3	-
Uric Acid	> 12 mg/dL	-	-	-	3.8	0.2	1.4
Hematology	**Low**						
Hematocrit	< 30%	2.6	-	0.8	17.3	22.0	0.7
Hemoglobin	< 8.0 g/dL	0.9	-	-	3.8	3.9	-
Neutrophils	≤ 0.5 X 10⁹/L	-	-	-	6.0	8.3	-
RBC	<3.0 X 10 ¹²/L	1.8	-	5.9	18.6	24.4	-
WBC	< 2.5 x 10⁹/L	-	0.9	6.8	36.9	59.4	3.5

- Indicates no events reported.

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

The safety profile of atazanavir sulfate in pediatric patients (6 to less than 18 years of age) was generally similar to that observed in clinical studies of atazanavir sulfate in adults. The most common Grade 2 to 4 adverse events (greater than or equal to 5%, regardless of causality) reported in pediatric patients 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 less than 2% of patients. The most common Grade 3 to 4 laboratory abnormalities occurring in pediatric patients were elevation of total bilirubin (greater than or equal to 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%.

Ritonavir, one component of Atazanavir Sulfate and Ritonavir Tablets, has been studied in 265 pediatric patients greater than 1 month to 21 years of age. The adverse event profile observed during pediatric clinical trials was similar to that for adult patients.

Vomiting, diarrhea, and skin rash/allergy were the only drug-related clinical adverse events of moderate to severe intensity observed in greater than or equal to 2% of pediatric patients enrolled in ritonavir clinical trials.

Laboratory Abnormalities
The following Grade 3 to 4 laboratory abnormalities occurred in greater than 3% of pediatric patients who received treatment with ritonavir either alone or in combination with reverse transcriptase inhibitors: neutropenia (9%), hyperamylasemia (7%), thrombocytopenia (5%), anemia (4%), and elevated AST (3%).

6.3 Patients Co-infected With Hepatitis B and/or Hepatitis C Virus
Liver function tests should be monitored in patients with a history of hepatitis B or C.

In study AI424-138, 60 patients treated with atazanavir sulfate/ritonavir 300 mg/100 mg once daily, and 51 patients treated with lopinavir/ritonavir 400 mg/100 mg twice daily, each with fixed dose tenofovir DF-emtricitabine, were seropositive for hepatitis B and/or C at study entry. ALT levels greater than 5 times ULN developed in 10% (6/60) of the atazanavir/ritonavir-treated patients and 8% (4/50) of the lopinavir/ritonavir-treated patients. AST levels greater than 5 times ULN developed in 10% (6/60) of the atazanavir sulfate/ritonavir-treated patients and none (0/50) of the lopinavir/ritonavir treated patients.

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

6.4 Clinical Experience
Atazanavir, one component of Atazanavir Sulfate and Ritonavir Tablets
The following events have been identified during postmarketing use of atazanavir sulfate. 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 (5.2)*].

Gastrointestinal System: pancreatitis

Hepatic System: hepatic function abnormalities

Hepatobiliary Disorders: cholelithiasis, 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 (5.8)*], interstitial nephritis

Skin and Appendages: alopecia, maculopapular rash [see *Contraindications (4)* and *Warnings and Precautions (5.5)]*, pruritus, angioedema

Ritonavir, one component of Atazanavir Sulfate and Ritonavir Tablets
The following adverse events (not previously mentioned in the labeling) have been reported during post-marketing use of ritonavir. Because these reactions are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to ritonavir exposure.

Body as a Whole
Dehydration, usually associated with gastrointestinal symptoms, and sometimes resulting in hypotension, or renal insufficiency has been reported. Syncope, orthostatic hypotension, and renal insufficiency have also been reported without known dehydration.
Coadministration of ritonavir with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system.

Cardiovascular System
First-degree AV block, second-degree AV block, third-degree AV block, right bundle branch block have been reported [*see Warnings and Precautions (5.2)*].

Cardiac and neurologic events have been reported when ritonavir has been coadministered with disopyramide, mexiletine, nefazodone, fluoxetine, and beta blockers. The possibility of drug interaction cannot be excluded.

Endocrine System
Cushing's syndrome and adrenal suppression have been reported when ritonavir has been coadministered with fluticasone propionate or budesonide.

Nervous System
There have been postmarketing reports of seizure. Also, see Cardiovascular System.

Skin and subcutaneous tissue disorders
Toxic epidermal necrolysis (TEN) has been reported.

7 DRUG INTERACTIONS
See also *Contraindications (4)* and *Clinical Pharmacology (12.3).*

7.1 Potential to Affect Other Drugs
Atazanavir
Atazanavir is an inhibitor of CYP3A and UGT1A1. Coadministration of atazanavir sulfate 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 10 and Table 11 (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.

Ritonavir
Ritonavir is an inhibitor of cytochrome P450 3A (CYP3A) and may increase plasma concentrations of agents that are primarily metabolized by CYP3A. Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (greater than 3-fold) when co-administered with ritonavir. Thus, co-administration of ritonavir with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring.

Ritonavir also inhibits CYP2D6 to a lesser extent. Co-administration of substrates of CYP2D6 with ritonavir could result in increases (up to 2-fold) in the AUC of the other agent, possibly requiring a proportional dosage reduction. Ritonavir also appears to induce CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2B6 as well as other enzymes, including glucuronosyl transferase.

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 sulfate'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.

7.3 Established and Other Potentially Significant Drug Interactions
Table 10 provides dosing recommendation in adults as a result of drug interactions with one or both components of Atazanavir Sulfate and Ritonavir Tablets. 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 10: 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/ritonavir 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 DF	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 reactions. For pregnant women taking atazanavir with ritonavir *and* tenofovir DF, see *Dosage and Administration (2.3).*
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.
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 1200 mg coadministered with atazanavir 400 mg and tenofovir DF 300 mg (all given once daily) plus nucleoside analogue reverse transcriptase inhibitors did not provide adequate efficacy [see *Clinical Studies (14.2)*].
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/ritonavir and an additional protease inhibitors would be expected to increase exposure to the other protease inhibitor. Such coadministration is not recommended.
HCV Antiviral Agents		
Protease Inhibitors: boceprevir	↓ atazanavir ↓ ritonavir	Concomitant administration of boceprevir and atazanavir/ritonavir resulted in reduced steady-state exposures to atazanavir and ritonavir. Coadministration of atazanavir/ritonavir and boceprevir is not recommended.
Other Agents		
Antacids and buffered medications	↓ atazanavir	Reduced plasma concentrations of atazanavir are expected if antacids, including buffered medications, are administered with atazanavir. Atazanavir should be administered 2 hours before or 1 hour after these medications.
Antiarrhythmics: amiodarone, bepridil, lidocaine (systemic), quinidine	↑ amiodarone, bepridil, lidocaine (systemic), quinidine	Coadministration with atazanavir has the potential to produce serious and/or life-threatening adverse events and has not been studied. Caution is warranted and therapeutic concentration monitoring of these drugs is recommended if they are used concomitantly with atazanavir sulfate and ritonavir.
Anticoagulants: warfarin	↑↓warfarin	Coadministration with atazanavir has the potential to produce serious and/or life-threatening bleeding and has not been studied. Initial and frequent monitoring of the International Normalized Ratio (INR) is recommended.
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 and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as atazanavir, the combination should be used with caution and a lower dose of trazodone should be considered.
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 treatment with atazanavir / ritonavir have been titrated to a stable dose of carbamazepine, a dose reduction for carbamazepine may be necessary.
phenytoin, phenobarbital	↓ atazanavir ↓ phenytoin ↓ phenobarbital	Plasma concentrations of atazanavir may be decreased when phenytoin or phenobarbital is administered with atazanavir without ritonavir. Coadministration of phenytoin or phenobarbital and atazanavir without ritonavir is not recommended. Ritonavir may decrease the plasma level 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. Dose adjustment of lamotrigine may be required when coadministered with atazanavir and ritonavir.
Antifungals: ketoconazole, itraconazole	***atazanavir/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 with atazanavir/ritonavir.
Voriconazole	**Atazanavir/ ritonavir in subjects with a functional CYP2C19 allele:** ↓voriconazole ↓atazanavir **Atazanavir/ ritonavir in subjects without a functional CYP2C19 allele:** ↑voriconazole ↓atazanavir	The use of voriconazole in patients receiving atazanavir/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/ritonavir. Coadministration of voriconazole with atazanavir (without ritonavir) may affect atazanavir concentrations; however, no data are available.
Antigout: colchicine	↑ colchicine	Atazanavir co-administered with colchicine in patients with renal or hepatic impairment is not recommended. ***Recommended adult dosage of colchicine when administered with atazanavir and ritonavir:*** ***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: 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.
Antipsychotics: quetiapine and lurasidone	↑ quetiapine ***atazanavir*** ↑lurasidone ***atazanavir/ritonavir*** ↑lurasidone	***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. ***Atazanavir without ritonavir*** If coadministration is necessary, reduce the lurasidone dose. Refer to the lurasidone prescribing information for concomitant use with moderate. CYP3A4 inhibitors. ***Atazanavir/ritonavir*** Use of lurasidone is contraindicated.
Benzodiazepines: 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. Coadministration of oral midazolam with atazanavir is CONTRAINDICATED.
Calcium channel blockers: diltiazem Nifedipine Verapamil	↑ diltiazem and desacetyl-diltiazem	Caution is warranted and clinical monitoring of patients is recommended. A dose reduction of diltiazem by 50% should be considered. ECG monitoring is recommended. Coadministration of atazanavir/ritonavir with diltiazem has not been studied. A dose decrease may be needed for these drugs when co-administered with Atazanair/ ritonavir.
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/ritonavir:*** For patients who have been receiving atazanavir/ ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based on individual tolerability. ***Coadministration of atazanavir/ritonavir in adult patients on bosentan:*** Discontinue bosentan at least 36 hours before starting atazanavir/ritonavir. At least 10 days after starting atazanavir/ritonavir, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.
HMG-CoA reductase inhibitors: 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/ritonavir, are used in combination with these drugs.
H_2-Receptor antagonists	↓ atazanavir	***In treatment-naive 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) H_2-receptor antagonist 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. ***In treatment-experienced patients:*** Whenever an H2RA is given to a patient receiving atazanavir with ritonavir, the H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 20 mg twice daily, and the atazanavir and ritonavir doses should be administered simultaneously with, and/or at least 10 hours after, the dose of the H_2-receptor antagonist. • Atazanavir 300 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with an H_2-receptor antagonist. For pregnant women taking atazanavir with ritonavir and an H_2-receptor antagonist. • Atazanavir and ritonavir tablets should not be taken with both tenofovir DF and an H_2-receptor antagonist because higher doses of atazanavir are required. see *Use in special populations (8.1).*
Hormonal contraceptives: ethinyl estradiol and norgestimate or norethindrone	↓ ethinyl estradiol ↑ norgestimate[c] ↑ ethinyl estradiol	Use with caution if coadministration of atazanavir or atazanavir/ritonavir with oral contraceptives is considered. If an oral contraceptive is administered with atazanavir plus ritonavir, 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/ritonavir with 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: cyclosporin, sirolimus, tacrolimus, rapamycin	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for these immunosuppressants when coadministered with atazanavir sulfate/ritonavir.
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	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.
betamethasone budesonide ciclesonide dexamethasone fluticasone methylprednisolone mometasone prednisone triamcinolone	***atazanavir/ritonavir***	Concomitant use of fluticasone propionate and atazanavir/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression, have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Coadministration of fluticasone propionate and atazanavir/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)*]. Alternative corticosteroids including beclomethasone and prednisolone (whose PK and/ or PD are less affected by strong CYP3A inhibitors relative to other studied steroids) should be considered, particularly for long-term use.
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 and ritonavir when CrCL is 30-60mL/min. • For patients with CLCR less than 30 mL per min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary. 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/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 plus ritonavir with buprenorphine warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered. Coadministration of buprenorphine and atazanavir with ritonavir is not expected to decrease atazanavir plasma concentrations. Coadministration of buprenorphine and atazanavir without ritonavir may decrease atazanavir plasma concentrations.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):*** Use of sildenafil for the treatment of pulmonary hypertension (PAH) is contraindicated with atazanavir [see *Contraindications (4)*]. The following dose adjustments are recommended for the use of tadalafil with atazanavir: Coadministration of tadalafil in patients on atazanavir (with or without ritonavir): • For patients receiving atazanavir (with or without ritonavir) for at least one week, start tadalafil 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 tadalafil: • Avoid the use of tadalafil when starting atazanavir (with or without ritonavir). Stop tadalafil at least 24 hours before starting atazanavir (with or without ritonavir). At least one week after starting atazanavir (with or without ritonavir), resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability. ***Use of PDE5 inhibitors for erectile dysfunction:*** Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Use tadalafil with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. ***atazanavir/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/ritonavir 100 mg once daily was administered with omeprazole 40 mg once daily, which may result in loss of therapeutic effect and development of resistance. ***In treatment-naive patients:*** The proton-pump inhibitor dose should not exceed a dose comparable to omeprazole 20 mg and must be taken approximately 12 hours prior to the atazanavir 300 mg with ritonavir 100 mg dose. ***In treatment-experienced patients:*** The use of Proton-pump inhibitors in treatment-experienced patients receiving atazanavir is not recommended.

[a] For magnitude of interactions see *Clinical Pharmacology, Table 14.*
[b] See *Contraindications (4), Table 2* for orally administered midazolam.
[c] In combination with atazanavir 300 mg and ritonavir 100 mg once daily.

Table 11: Established and other potentially Significant Drug Interactions

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Ritonavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
Non-Nucleoside Reverse Transcriptase Inhibitor: delavirdine	ritonavir	Appropriate doses of this combination with respect to safety and efficacy have not been established.
HIV-1 CCR5 – antagonist: maraviroc	↑ maraviroc	See the complete prescribing information for maraviroc for details on co-administration of maraviroc and ritonavir-containing protease inhibitors.
Integrase Inhibitor: raltegravir	↓ raltegravir	The effects of ritonavir on raltegravir with ritonavir dosage regimens greater than 100 mg twice daily have not been evaluated, however raltegravir concentrations may be decreased with ritonavir coadministration.
Other Agents		
Analgesics, Narcotic: tramadol, propoxyphene, methadone, fentanyl	↑ analgesic ↓ methadone ↑ fentanyl	A dose decrease may be needed for these drugs when co-administered with ritonavir. Dosage increase of methadone may be considered Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantl administered with ritonavir.
Anesthetic: meperidine	↓ meperidine/ ↑ normeperidine (metabolite	Dosage increase and long-term use of meperidine with ritonavir are not recommended due to the increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (e.g., seizures).
Antialcoholics: disulfiram/ metronidazole		Ritonavir formulations contain ethanol, which can produce disulfiram-like reactions when coadministered with disulfiram or other drugs that produce this reaction (e.g., metronidazole).
Anticancer Agents: dasatinib, nilotinib, venetoclax, vincristine, vinblastin	↑ anticancer agent	For vincristine and vinblastine, consideration should be given to temporarily withholding the ritonavirn containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when ritonavir is administered concurrently with vincristine or vinblastine.Clinicians should be aware that if the ritonavir containing regimen is withheld for a prolonged period, consideration should be given to altering the regimen to not include a CYP3A or P-gp inhibitor in order to control HIV-1 viral load. A decrease in the dosage or an adjustment of the dosing interval of nilotinib and dasatinib may be necessary for patients requiring co-administration with strong CYP3A inhibitors such as ritonavir. Please refer to the nilotinib and dasatinib prescribing information for dosing instructions. Coadministration of venetoclax and ritonavir. may increase the risk of tumor lysis syndrome Refer to the venetoclax prescribing information for dosing instructions.
Anticoagulant: rivaroxaban	↑ rivaroxaban	Avoid concomitant use of rivaroxaban and ritonavir. Co-administration of ritonavir and rivaroxaban may lead to risk of increased bleeding.
Anticonvulsants: carbamazepine, clonazepam, ethosuximide	↑ anticonvulsant	A dose decrease may be needed for these drugs when co-administered with ritonavir and therapeutic concentration monitoring is recommended for these anticonvulsants, if available.
Anticonvulsants: Divalproex, lamotrigine, phenytoin	↓ anticonvulsants	A dose increase may be needed for these drugs when co-administered with ritonavir and therapeutic concentration monitoring is recommended for these anticonvulsants, if available.
Antidepressants: nefazodone, selective serotonin reuptake inhibitors (SSRIs): e.g. fluoxetine, paroxetine, tricyclics: e.g. amitriptyline, nortriptyline	↑ antidepressant	A dose decrease may be needed for these drugs when co-administered with ritonavir.
Antidepressant: bupropion	↓ bupropion ↓ active metabolite, hydroxybupropion	Patients receiving ritonavir and bupropion concurrently should be monitored for an adequate clinical response to bupropion.
Antidepressant: desipramine	↑ desipramine	Dosage reduction and concentration monitoring of desipramine is recommended.
Antidepressant: trazodone	↑ trazodone	Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir.. A lower dose of trazodone should be considered.
Antiemetic: dronabinol	↑ dronabinol	A dose decrease of dronabinol may be needed when co-administered with ritonavir.
Antifungals: Ketoconazole itraconazol voriconazol	↑ ketoconazole ↑ itraconazole ↓ voriconazole	High doses of ketoconazole or itraconazole (greater than 200 mg per day) are not recommended. Coadministration of voriconazole and ritonavir 100 mg should be avoided, unless an assessment of the benefit/ risk to the patient justifies the use of voriconazole.
Antimycobacterial: bedaquiline	↑ bedaquiline	Bedaquiline should only be used with ritonavir if the benefit of co-administration outweighs the risk.
Antimycobacterial: rifampin	↓ ritonavir	May lead to loss of virologic response. Alternate antimycobacterial agents such as rifabutin should be considered.
Antiparasitic: atovaquone	↓ atovaquone	Clinical significance is unknown; however, increase in atovaquone dose may be needed.
Antipsychotics: Perphenazine, risperidone, thioridazine	↑ antipsychotics	
β-Blockers: metoprolol, timolol	↑ beta-blockers	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with ritonavir.
Bronchodilator: theophylline	↓ theophylline	Increased dosage of theophylline may be required; therapeutic monitoring should be considered.
Digoxin	↑ digoxin	Concomitant administration of ritonavir with digoxin may increase digoxin levels. Caution should be exercised when co-administering ritonavir with digoxin, with appropriate monitoring of serum digoxin levels.
Hepatitis C direct acting antiviral: simeprevir	↑simeprevir	It is not recommended to co-administer ritonavir with simeprevir.
Systemic/Inhaled/ Nasal/Ophthalmic Corticosteroids: e.g., betamethasone budesonide ciclesonide dexamethasone fluticasone methylprednisolone mometasone prednisone triamcinolone	↑ glucocorticoids	Coadministration with corticosteroids whose exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone and prednisolone (whose PK and/or PD are less affected by strong CYP3A inhibitors relative to other studied steroids) should be considered, particularly for long-term use.
Long-acting beta-adrenoceptor agonist: salmeterol	↑ salmeterol	Concurrent administration of salmeterol and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Sedative/hypnotics: buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem	↑ sedative/hypnotic	A dose decrease may be needed for these drugs when co-administered with ritonavir.
Stimulant: methamphetamine	↑ methamphetamine	Use with caution. A dose decrease of methamphetamine may be needed when coadministered with ritonavir.

7.4 Drugs with No Observed or Predicted Interactions with atazanavir
No clinically significant drug interactions were observed when atazanavir sulfate was coadministered with methadone,

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fluconazole, acetaminophen, or atenolol or or nucleoside reverse transcriptase inhibitors lamivudine or zidovudine. *[See Clinical Pharmacology, Table 14 and Table 15 (12.3)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg: No data available.

***Atazanavir:* Pregnancy Category B**

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 2-4% and 15-20%, repectively. No treatment-related malformations were observed in rats and rabbits, for which the atazanavir exposures were 0.7-1.2 times of those at the human clinical dose (300 mg/day ritonavir). When atazanavir was administered to rats during preganacy and throughout lactation, reversible neonatal growth retardation was observed. [see data]

Clinical Considerations
Dosing During Pregnancy and the Postpartum Period:
- Atazanavir sulfate should only be administered to pregnant women.
- No dose adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir exposures could be higher during the first 2 months after delivery [See *Clinical Pharmacology (12.3)*].

Human data: In clinical trial AI424-182, atazanavir sulfate/ritonavir (300/100 mg) in combination with zidovudine/ lamivudine was administered to 41 HIV-infected pregnant women during the second or third trimester. Among the 39 women who completed the study, 38 women achieved an HIV RNA less than 50 copies/mL at time of delivery. Six of 20 (30%) women on atazanavir sulfate /ritonavir 300/100 mg experienced hyperbilirubinemia (total bilirubin greater than or equal to 2.6 times the upper limit of normal). There were no cases of lactic acidosis observed in this clinical trail AI424-182.

Atazanavir drug concentrations in fetal umbilical cord blood were approximately 12–19% of maternal concentrations. Among the 40 infants born to 40 HIV-infected pregnant women, 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 <40 mg/dL that could not be attributed to maternal glucose intolerance, difficult delivery, or sepsis.

Antiretroviral Pregnancy Registry Data: Based on prospective reports from the APR of approximately 1600 live births following exposure to atazanavir-containing regimens (including 1037 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 pregnacies is 2-4%.

Pharmacokinetics of Atazanavir in Pregnancy
[See *Clinical Pharmacology (12.3)*.]

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 post-natal 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.

***Ritonavir:* Pregnancy Category B**
Risk Summary: Prospective pregnancy data from the Antiretroviral Pregnancy Registry (APR) are not sufficient to adequately assess the risk of birth defects or miscarriage. Available data from the APR show no difference in the rate of overall birth defects for ritonavir compared to the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) [see Data]. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with oral administration of ritonavir to pregnant rats and rabbits. During organogenesis in the rat and rabbit, systemic exposure (AUC) was approximately 1/3 lower than human exposure at the recommended daily dose. In the rat pre- and post-natal developmental study, maternal systemic exposure to ritonavir was approximately 1/2 of the exposure in humans at the recommended daily dose, based on a body surface area conversion factor [see Data].
The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.
Human data: Based on prospective reports to the APR of approximately 6100 live births following exposure to ritonavir-containing regimens (including over 2800 live births exposed in the first trimester and over 3200 live births exposed in the second and third trimesters), there was no difference in the rate of overall birth defects for ritonavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.3% (95% CI: 1.7%-2.9%) following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.3%-3.5%) following second and third trimester exposure to ritonavir-containing regimens.

While placental transfer of ritonavir and fetal ritonavir concentrations are generally low, detectable levels have been observed in cord blood samples and neonate hair.

Animal data: Ritonavir was administered orally to pregnant rats (at 0, 15, 35, and 75 mg/kg/day) and rabbits (at 0, 25, 50, and 110 mg/kg/day) during organogenesis (on gestation days 6 through 17 and 6 through 19, respectively). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at doses producing systemic exposures (AUC) equivalent to approximately 1/3 lower than human exposure at the recommended daily dose. Developmental toxicity observed in rats (early resorptions, decreased fetal body weight and ossification delays and developmental variations) occurred at a maternally toxic dose, at an exposure equivalent to approximately 1/3 lower than human exposure at the recommended daily dose. A slight increase in the incidence of cryptorchidism was also noted in rats (at a maternally toxic dose) at an exposure approximately 1/5 lower than human exposure at the recommended daily dose. Developmental toxicity was observed in rabbits (resorptions, decreased litter size and decreased fetal weights) at maternally toxic doses approximately 1.8 times higher than the recommended daily dose, based on a body surface area conversion factor. In pre-and postnatal development study in rats, ritonavir was administered at doses of 0, 15, 35, and 60 mg/kg/day from gestation day 6 through postnatal day 20. At doses of 60 mg/kg/day, no developmental toxicity was noted with ritonavir dosage equivalent to 1/2 of the recommended daily dose, based on a body surface area conversion factor.

8.3 Nursing Mothers/Lactation

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. 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.Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the both drugs on milk production.Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are taking Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg.**

8.4 Pediatric Use

Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg should only be administered to pediatric patients at least 6 years of age and weighing 35 kg.

Atazanavir: Atazanavir is not recommended for use in pediatric patients below the age of 3 months due to the risk of kernicterus.

Ritonavir: In HIV-infected patients age greater than 1 month to 21 years, the antiviral activity and adverse event profile seen during clinical trials and through clinical experience were similar to that for adult patients.

8.5 Geriatric Use

Clinical studies of atazanavir and ritonavir 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 Sulfate and Ritonavir Tablets, 300 mg/100 mg 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, one component of Atazanavir Sulfate and Ritonavir Tablets, was performed in young (n=29; 18 to 40 years) and elderly (n=30; greater than or equal to 65 years) healthy subjects. There were no clinically important pharmacokinetic differences observed due to age or gender.

8.7 Impaired Renal Function

Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg should not be administered to HIV-treatment-experienced patients with end stage renal disease managed with hemodialysis. [See Dosage and Administration (2.1).

Atazanavir
In healthy subjects, the renal elimination of unchanged atazanavir, one component of Atazanavir Sulfate and Ritonavir Tablets was approximately 7% of the administered dose. Atazanavir sulfate has been studied in adult subjects with severe renal impairment (n=20), including those on hemodialysis, at multiple doses of 400 mg once daily. The mean atazanavir C_{max} was 9% lower, AUC was 19% higher, and C_{min} was 96% higher in subjects with severe renal impairment not undergoing hemodialysis (n=10), than in age, weight, and gender matched subjects with normal renal function. Atazanavir was not appreciably cleared during hemodialysis. In a 4-hour dialysis session, 2.1% of the administered dose was removed. 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.

8.8 Impaired Hepatic Function

The Atazanavir with ritonavir is neither recommended for use in in subjects with severe hepatic impairment nor in patients with any degree of hepatic impairment. [See Dosage and Administration (2.4) and Warnings and Precautions (5.5).]

10 OVERDOSAGE

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

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.

Ritonavir
Acute Overdosage - Human Overdose Experience
Human experience of acute overdose with ritonavir, a component of Atazanavir Sulfate and Ritonavir Tablets, is limited. One patient in clinical trials took ritonavir 1500 mg/day for two days. The patient reported paresthesias which resolved after the dose was decreased. A post-marketing case of renal failure with eosinophilia has been reported with ritonavir overdose.

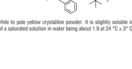
The approximate lethal dose of ritonavir was found to be greater than 20 times the related human dose in rats and 10 times the related human dose in mice.

Management of Overdosage
Treatment of overdose with ritonavir, one component of Atazanavir Sulfate and Ritonavir Tablets, consists of general supportive measures including monitoring of vital signs and ECG, and observation of the clinical status of the patient. There is no specific antidote for overdose with atazanavir and ritonavir. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since atazanavir and ritonavir is extensively metabolized by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug. A Certified Poison Control Center should be consulted for up-to-date information on the management of overdose with this drug.

11 DESCRIPTION

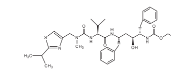
Atazanavir and ritonavir are inhibitors of HIV-1 protease with activity against the Human Immunodeficiency Virus (HIV). Each film coated tablet contains equivalent of 300 mg of Atazanavir as Atazanavir Sulfate and Ritonavir USP.

Atazanavir
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 $C_{38}H_{52}N_6O_7 \cdot H_2SO_4$, which corresponds to a molecular weight of 802.9 (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 slightly soluble in water (4 to 5 mg/mL, free base equivalent) with the pH of a saturated solution in water being about 1.9 at 24 °C ± 3° C.

Ritonavir
Ritonavir is chemically designated as [5S-(5R*,8R*,10R*,11R*)]-10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1 methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12- tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Ritonavir is a white-to-light-tan powder. Ritonavir has a bitter metallic taste. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg are available for oral administration in strength of 300 mg of atazanavir and 100 mg of ritonavir with the following inactive ingredients: lactose monohydrate, crospovidone, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate, copovidone, sorbitan monolaurate, polysorbate 80 and sodium stearyl fumarate. Atazanavir Sulfate and Ritonavir Tablets are coated with hypromellose 2910, titanium dioxide, macrogol, talc, iron oxide yellow and polysorbate 80.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atazanavir sulfate and ritonavir are antiviral drugs [see *Clinical Pharmacology (12.4)*].

12.2 Pharmacodynamics

Cardiac Electrophysiology
Atazanavir
Concentration- and dose-dependent prolongation of the PR interval in the electrocardiogram has been observed in healthy volunteers receiving atazanavir. In a placebo-controlled study (AI424-076), the mean (±SD) maximum change in PR interval from the 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 (5.2)*].

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 1793 HIV-infected patients receiving antiretroviral regimens, QTc prolongation was comparable in the atazanavir and comparator regimens. No atazanavir-treated healthy subject or HIV-infected patient in clinical trials had a QTc interval greater than 500 msec [See *Warnings and Precautions (5.2)*].

In a pharmacokinetic study between atazanavir 400 mg once daily and diltiazem 180 mg once daily, a CYP3A substrate, there was a 2-fold increase in the diltiazem plasma concentration and an additive effect on the PR interval. In a pharmacokinetic study between atazanavir 400 mg once daily and atenolol 50 mg once daily, there was no substantial additive effect of atazanavir and atenolol on the PR interval [See *Warnings and Precautions (5.2)*].

Ritonavir: QTcF interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg once- daily) controlled crossover study in 45 healthy adults, with 10 measurements over 12 hours on Day 3. The maximum mean (95% upper confidence bound) time-matched difference in QTcF from placebo after baseline correction was 5.5 (7.6) milliseconds (msec) for 400 mg twice-daily ritonavir. Ritonavir 400 mg twice daily resulted in day 3 ritonavir exposure that was approximately 1.5 fold higher than observed with ritonavir 600 mg twice-daily dose at steady state.

PR interval prolongation was also noted in subjects receiving ritonavir in the same study on day 3. The maximum mean (95% confidence interval) difference from placebo in the PR interval after baseline correction was 22 (25) msec for 400 mg twice-daily ritonavir *[see Warnings and Precautions (5.2)]*.

12.3 Pharmacokinetics

Pharmacokinetics in Adults
Atazanavir Sulfate and Ritonavir Tablets: Atazanavir exposure following administration of atazanavir sulfate and ritonavir combination tablets (300 mg/100 mg) was comparable to exposure following administration of (atazanavir sulfate) Capsules and (ritonavir) Tablets, when administered to healthy volunteers under fasted and fed conditions.

Atazanavir
The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV- infected patients after administration of atazanavir 300 mg and ritonavir 100 mg once daily (see Table 12).

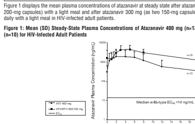
Table 12: Steady-State Pharmacokinetics of Atazanavir in Healthy Subjects or HIV-Infected Patients in the Fed State

	atazanavir 300 mg and ritonavir 100 mg once daily	
Parameter	**Healthy Subjects (n=28)**	**HIV-Infected Patients (n=10)**
C_{max} (ng/mL)		
Geometric mean (CV%)	6129 (31)	4422 (58)
Mean (SD)	6450 (2031)	5233 (3033)
T_{max} (h)		
Median	2.7	3.0
AUC (ng•h/mL)		
Geometric mean (CV%)	57039 (37)	46073 (66)
Mean (SD)	61435 (22911)	53761 (35294)
T-half (h)		
Mean (SD)	18.1 (6.2)[a]	8.6 (2.3)
C_{min} (ng/mL)		
Geometric mean (CV %)	1227 (53)	636 (97)
Mean (SD)	1441 (757)	862 (838)

[a] n=26.

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

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



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

Food Effect
Atazanavir: Administration of atazanavir with food enhances bioavailability and reduces pharmacokinetic variability. 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 Cmax 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 Cmax 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 Tmax 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 Cmax 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).

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 volunteers (n=214) and HIV-infected adult patients (n=13) was approximately 7 hours at steady state following a dose of 400 mg daily with a light meal.

Special Populations
Pediatrics
Atazanavir Sulfate and Ritonavir Tablets should not be administered to HIV-1 infected pediatric patients less than 6 years of age and weighing less than 35 kg.

Pregnancy
Atazanavir Sulfate and Ritonavir: The pharmacokinetic data from HIV-infected pregnant women receiving atazanavir capsules with ritonavir are presented in Table 13.

Table 13: Steady-State Pharmacokinetics of Atazanavir with ritonavir in HIV-Infected Pregnant Women in the Fed State

	Atazanavir 300 mg with ritonavir 100 mg		
Pharmacokinetic Parameter	**2nd Trimester (n=5[a])**	**3rd Trimester (n=20)**	**Postpartum[b] (n=34)**
C_{max} ng/mL	3078.85	3291.46	5721.21
Geometric mean (CV%)	(50)	(48)	(31)
AUC ng·h/mL	27657.1	34251.5	61990.4
Geometric mean (CV%)	(43)	(43)	(32)
C_{min} ng/mL[c]	538.70	668.48	1462.59
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 HIV-infected, non-pregnant patients. Atazanavir plasma trough concentrations were approximately 2.2-fold higher during the postpartum period when compared to those observed historically in HIV-infected, non-pregnant patients.
[c] C_{min} is concentration 24 hours post-dose.

Renal Impairment [*See Impaired Renal Function (8.7)*]

Hepatic Impairment [*See Impaired Hepatic Function (8.8)*]

Drug Interaction Data

Atazanavir
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 µM. Atazanavir is also a direct inhibitor for UGT1A1 (K_i=1.9 µM) and CYP2C8 (K_i=2.1 µM).

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 6_{β}-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, CYP2A2, or CYP2E1. Clinically significant interactions are not expected between atazanavir when administered with ritonavir for information on other potential drug interactions with ritonavir.

Based on known metabolic profiles, cinically significant drug interactions are not expected betwenn 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 sulfate on the AUC, Cmax, and Cmin are summarized in Tables 14 and 15. Neither didanosine EC nor diltiazem had a significant effect on atazanavir exposures. (see Table 16 for effect of atazanavir on didanosine EC or diltiazem exposures.)

Atazanavir did not have a significant effect on the exposures of didanasoine (when administered as the buffered tablet), stavudine, or fluconazole. For information regarding clinical recommendations, *see Drug Interactions (7)*.

Table 14: 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 7–11 (n=19) and d 19–23	400 mg QD, d 1–11 (n=19)	1.00 (0.89, 1.12)	0.93 (0.85, 1.01)	0.74 (0.65, 0.86)
boceprevir	800 mg TID, d 1-6, 25-31	300 mg QD/ritonavir 100 mg QD, d 10-31	atazanavir: 0.75 (0.64-0.88) ritonavir: 0.73 (0.64-0.83)	atazanavir: 0.65 (0.55-0.78) ritonavir: 0.64 (0.58-0.72)	atazanavir: 0.51 (0.44-0.61) ritonavir: 0.55 (0.45-0.67)
clarithromycin	500 mg BID, d 7–10 (n=29) and d 18–21	400 mg QD, d 1–10 (n=29)	1.06 (0.93, 1.20)	1.28 (1.16, 1.43)	1.91 (1.66, 2.21)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)[b]	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose (n=31)	400 mg x 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 x 1 dose, d4T: 40 mg x 1 dose (n=32)	400 mg x 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 7–20 (n=27)	400 mg QD, d 1–20 (n=27)	0.41 (0.33, 0.51)	0.26 (0.22, 0.32)	0.07 (0.05, 0.10)
	600 mg QD, d 7–20 (n=13)	400 mg QD, d 1–6 (n=23) then 300 mg/ritonavir 100 mg QD, 2 h before efavirenz, d 7–20 (n=13)	1.14 (0.83, 1.58)	1.39 (1.02, 1.88)	1.48 (1.24, 1.76)
	600 mg QD, d 11–24 (pm) (n=14)	300 mg QD/ritonavir 100 mg QD, d 1–10 (pm) (n=22), then 400 mg QD/ritonavir 100 mg QD, d 11–24 (pm), (simultaneous 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 7–12 (n=15)	400 mg QD, d 1–6 (n=45), d 7–12 (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 7–12 (n=14)	400 mg QD (pm), d 1–6 (n=14), d 7–12 (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 11–20 (n=14)[d]	300 mg QD/ritonavir 100 mg QD, d 1–10 (n=46), d 11–20[c] (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 11–17 (n=18)	300 mg QD/ritonavir 100 mg QD/tenofovir DF 300 mg QD, d 1–10 (am) (n=39), d 11–17 (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 18–24 (n=20)	300 mg QD/ritonavir 100 mg QD/tenofovir DF 300 mg QD, d 1–10 (am) (n=39), d 18–24 (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 18–24 (n=18)	300 mg QD/ritonavir 100 mg QD/tenofovir DF 300 mg QD, d 1–10 (am) (n=39), d 18–24 (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 11–20 (n=15)	300 mg QD/ritonavir 100 mg QD, d 1–10 (am) (n=46), then 400 mg QD/ritonavir 100 mg QD, d 11–20 (am) (n=15)	1.02 (0.87, 1.18)	1.03 (0.86, 1.22)	0.86 (0.68, 1.08)
ketoconazole	200 mg QD, d 7–13 (n=14)	400 mg QD, d 1–13 (n=14)	0.99 (0.77, 1.28)	1.10 (0.89, 1.37)	1.03 (0.53, 2.01)
nevirapine[g,h]	200 mg BID, d 1–23 (n=23)	300 mg QD/ritonavir 100 mg QD, d 4–13, then 400 mg QD/ritonavir 100 mg QD, d 14–23 (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 7–12 (n=16)[i]	400 mg QD, d 1–6 (n=48), d 7–12 (n=16)	0.04 (0.04, 0.05)	0.06 (0.05, 0.07)	0.05 (0.03, 0.07)
	40 mg QD, d 11–20 (n=15)[i]	300 mg QD/ritonavir 100 mg QD, d 1–20 (n=15)	0.28 (0.24, 0.32)	0.24 (0.21, 0.27)	0.22 (0.19, 0.26)
	20 mg QD, d 17–23 (am) (n=13)	300 mg QD/ritonavir 100 mg QD, d 7–16 (pm) (n=27), d 17–23 (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 17–23 (am) (n=14)	300 mg QD/ritonavir 100 mg QD, d 7–16 (am) (n=27), then 400 mg QD/ritonavir 100 mg QD, d 17–23 (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 15–28 (n=7)	400 mg QD, d 1–28 (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 17–26 (n=16)	300 mg QD/ritonavir 100 mg QD, d 7–16 (n=48), d 17–26 (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 11–20 (n=28)	300 mg QD, d 1–20 (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 9–16 (n=34)	400 mg QD, d 2–16 (n=34)	0.79 (0.73, 0.86)	0.75 (0.70, 0.81)	0.60 (0.52, 0.68)
	300 mg QD, d 15–42 (n=10)	300 mg/ritonavir 100 mg QD, d 1–42 (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 2-3, 22-30; 400 mg BID, d 1, 21 (n=20)	300 mg/ritonavir 100 mg QD, d 11-30 (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 2-3, 22-30; 100 mg BID, d 1, 21 (n=8)	300 mg/ritonavir 100 mg QD, d 11-30 (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 plus ritonavir 100 mg once daily coadministered with famotidine 40 mg twice daily resulted in atazanavir geometric mean C_{max} that was similar and AUC and C_{min} values that were 1.79- and 4.46-fold higher relative to atazanavir 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 and ritonavir 100 mg plus tenofovir DF 300 mg.
[e] Atazanavir/ritonavir/tenofovir DF was administered after a light meal.
[f] Study was conducted in HIV-infected individuals.
[g] Compared with atazanavir 400 mg historical data without nevirapine (n=13), the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 1.42 (0.98, 2.05), 1.64 (1.11, 2.42), and 1.25 (0.66, 2.36), respectively, for atazanavir/ritonavir 300/100 mg; and 2.02 (1.42, 2.87), 2.28 (1.54, 3.38), and 1.80 (0.94, 3.45), respectively, for atazanavir/ritonavir 400/100 mg.
[h] Parallel group design; n=23 for atazanavir/ritonavir plus 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 plus ritonavir 100 mg in the evening after a light meal, separated by 12 hours from omeprazole.
[k] atazanavir 300 mg plus ritonavir 100 mg once daily separated by 12 hours from omeprazole 20 mg daily resulted in increases in atazanavir geometric mean AUC (10%) and C_{min} (2.4-fold), with a decrease in C_{max} (29%) relative to atazanavir 400 mg once daily in the absence of omeprazole (study days 1–6).
[l] Omeprazole 20 mg was given 30 minutes prior to a light meal in the morning and atazanavir 400 mg plus ritonavir 100 mg once daily after a light meal, 1 hour 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 plus ritonavir 100 mg once daily administered with omeprazole 20 mg once daily resulted in increases in atazanavir geometric mean AUC (32%) and C_{min} (3.3-fold), with a decrease in C_{max} (26%) relative to atazanavir 400 mg once daily in the absence of omeprazole (study days 1–6).
[n] Compared with atazanavir 400 mg QD historical data, administration of atazanavir/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 plus ritonavir plus tenofovir to atazanavir plus ritonavir. Atazanavir 300 mg plus 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} = 3190 ng/mL, AUC = 34459 ng•h/mL, and C_{min} = 491 ng/mL. Study was conducted in HIV-infected individuals.
NA = not available.

Table 15: 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 1–20 (n=10)	300 mg QD/ ritonavir 100 mg QD, d 11–20 (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 7–11 (n=19) and d 19–23	400 mg QD, d 1–11 (n=19)	1.34 (1.26, 1.42)	1.25 (1.16, 1.34)	1.02 (0.88, 1.19)
boceprevir	800 mg TID, d 1-6, 25-31	300 mg QD/ ritonavir 100 mg QD, d 10-31	0.93 (0.80, 1.08)	0.95 (0.87, 1.05)	0.82 (0.68, 0.98)
clarithromycin	500 mg BID, d 7–10 (n=21) and d 18–21	400 mg QD, d 1–10 (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 2–8 (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/ ritonavir 100 mg QD, d 9–19 (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 7–11 (n=28) and d 19–23	400 mg QD, d 1–11 (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 & norgestimate[c]	Norethindrone (0.5 mg + ethinyl estradiol 0.035 mg) QD, d 1–29 (n=19)	400 mg QD, d 16–29 (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]	Norgestimate (0.180 mg) + ethinyl estradiol (0.035 mg) QD, d 1–28 (n=18), then Norgestimate (0.180 mg) + ethinyl estradiol (0.025 mg) QD, d 29–42[e] (n=14)	300 mg QD/ ritonavir 100 mg QD, d 29–42 (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)
methadone	Stable maintenance dose, d 1–15 (n=16)	400 mg QD, d 2–15 (n=16)	(R)-methadone[g] 0.91 (0.84, 1.0) total: 0.85 (0.78, 0.93)	(R)-methadone[g] 1.03 (0.95, 1.10) total: 0.94 (0.87, 1.02)	(R)-methadone[g] 1.11 (1.02, 1.20) total: 1.02 (0.93, 1.12)
nevirapine[h,i]	200 mg BID, d 1–23 (n=23)	300 mg QD/ ritonavir 100 mg QD, d 4–13, then 400 mg QD/ ritonavir 100 mg QD, d 14–23 (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[j]	40 mg single dose, d 7 and d 20 (n=16)	400 mg QD, d 1–12 (n=16)	1.24 (1.04, 1.47)	1.45 (1.20, 1.76)	NA
rifabutin	300 mg QD, d 1–10 then 150 mg QD, d 11–20 (n=3)	600 mg QD,[k] d 11–20 (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 1–15 (n=7)	300 mg QD/ ritonavir 100 mg QD, d 1–17 (n=7)	2.49[l] (2.03, 3.06) 25-O-desacetyl-rifabutin: 7.77 (6.13, 9.83)	1.48[l] (1.19, 1.84) 25-O-desacetyl-rifabutin: 10.90 (8.14, 14.61)	1.40[l] (1.05, 1.87) 25-O-desacetyl-rifabutin: 11.45 (8.15, 16.10)
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[m]	4 mg single dose, d 1, 7, 17 (n=14)	400 mg QD, d 2–7, then 300 mg QD/ ritonavir 100 mg QD, d 8–17 (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/ ritonavir 100 mg QD for 7 days	↑7-fold[n]	↑3-fold[n]	NA
saquinavir[o] (soft gelatin capsules)	1200 mg QD, d 1–13 (n=7)	400 mg QD, d 7–13 (n=7)	4.39 (3.24, 5.95)	5.49 (4.04, 7.47)	6.86 (5.29, 8.91)
tenofovir DF[q]	300 mg QD, d 9–16 (n=33) and d 24–30 (n=33)	400 mg QD, d 2–16 (n=33)	1.14 (1.08, 1.20)	1.24 (1.21, 1.28)	1.22 (1.15, 1.30)
	300 mg QD, d 1–7 (pm) (n=14) d 25–34 (pm) (n=12)	300 mg QD/ ritonavir 100 mg QD, d 25–34 (am) (n=12)[f]	1.34 (1.20, 1.51)	1.37 (1.30, 1.45)	1.29 (1.21, 1.36)
voriconazole (Subjects with at least one functional CYP2C19 allele)	200 mg BID, d 2-3, 22-30; 400 mg BID, d 1, 21 (n=20)	300 mg/ritonavir 100 mg QD, d 11-30 (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 2-3, 22-30; 100 mg BID, d 1, 21 (n=8)	300 mg/ritonavir 100 mg QD, d 11-30 (n=8)	4.38 (3.55, 5.39)	5.61 (4.51, 6.99)	7.65 (5.71, 10.2)
lamivudine + zidovudine	150 mg lamivudine + 300 mg zidovudine BID, d 1–12 (n=19)	400 mg QD, d 7–12 (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/ritonavir relative to ethinyl estradiol 25 mcg without atazanavir/ritonavir, the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 1.17 (1.03, 1.34), 1.13 (1.05, 1.22), and 0.88 (0.77, 1.00), respectively.
[e] All subjects were on a 28 day lead-in period.
[f] 17-deacetyl norgestimate is the active component of norgestimate.
[g] (R)-methadone is the active isomer of methadone.
[h] Study was conducted in HIV-infected individuals.
[i] Subjects were treated with nevirapine prior to study entry.
[j] 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.
[k] Not the recommended therapeutic dose of atazanavir.
[l] When compared to rifabutin 150 mg QD alone d1–10 (n=14). Total of Rifabutin + 25-O-desacetyl-rifabutin: AUC 2.19 (1.78, 2.69).
[m] Rosiglitazone used as a probe substrate for CYP2C8.
[n] Mean ratio (with/without coadministered drug). ↑indicates an increase in rosuvastatin exposure.
[o] The combination of atazanavir and saquinavir 1200 mg QD produced daily saquinavir exposures similar to the values produced by the standard therapeutic dosing of saquinavir at 1200 mg TID. However, the C_{max} is about 79% higher than that for the standard dosing of saquinavir (soft gelatin capsules) alone at 1200 mg TID.
[p] Note that similar results were observed in a study where administration of tenofovir DF and atazanavir was separated by 12 hours.
[q] Administration of tenofovir DF and atazanavir was temporally separated by 12 hours.
NA = not available.

12.4 Microbiology

Mechanism of Action
Atazanavir: 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.

Ritonavir: Ritonavir is a peptidomimetic inhibitor of the HIV-1 protease. Inhibition of HIV protease renders the enzyme incapable of processing the *Gag-Pol* polyprotein precursor which leads to production of non-infectious immature HIV particles.

Antiviral Activity in Cell Culture
Atazanavir: Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC_{50}) in the absence of human serum of 2 to 5 nM against a variety of laboratory and clinical HIV-1 isolates grown in peripheral blood mononuclear cells, macrophages, CEM-SS cells, and MT-2 cells. ATV has activity against HIV-1 Group M subtype viruses A, B, C, D, AE, AG, F, G, and J isolates in cell culture. ATV has variable activity against HIV-2 isolates (1.9 to 32 nM), with EC_{50} values above the EC_{50} values of failure isolates. Two-drug combination antiviral activity studies with ATV showed no antagonism in cell culture with NNRTIs (delavirdine, efavirenz, and nevirapine), PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir), 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.

Ritonavir: The activity of ritonavir was assessed in acutely infected lymphoblastoid cell lines and in peripheral blood lymphocytes. The concentration of drug that inhibits 50% (EC_{50}) value of viral replication ranged from 3.8 to 153 nM depending upon the HIV-1 isolate and the cells employed. The average EC_{50} value for low passage clinical isolates was 22 nM (n = 13). In MT_4 cells, ritonavir demonstrated additive effects against HIV-1 in combination with either didanosine (ddI) or zidovudine (ZDV). Studies which measured cytotoxicity of ritonavir on several cell lines showed that greater than 20 µM was required to inhibit cellular growth by 50% resulting in a cell culture therapeutic index of at least 1000.

Resistance

In Cell Culture:
Atazanavir: HIV-1 isolates with a decreased susceptibility to ATV have been selected in cell culture and obtained from patients treated with ATV or atazanavir/ritonavir (ATV/RTV). HIV-1 isolates with 93- to 183-fold reduced susceptibility to ATV from three different viral strains were selected in cell culture by 5 months. The substitutions in these HIV-1 viruses that contributed to ATV 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 ATV and amprenavir, respectively, and did not appear to be cross-resistant.

Ritonavir: HIV-1 isolates with reduced susceptibility to ritonavir have been selected in cell culture. Genotypic analysis of these isolates showed mutations in the HIV-1 protease gene leading to amino acid substitutions 184V, V82F, A71V, and M461. Phenotypic (n=18) and genotypic (n=48) changes in HIV-1 isolates from selected patients treated with ritonavir were monitored in phase I/II trials over a period of 3 to 32 weeks. Substitutions associated with the HIV-1 viral protease in isolates obtained from 43 patients appeared to occur in a stepwise and ordered fashion at positions V82A/F/T/S, 154V, A71V/T, and 136L, followed by combinations of substitutions at an additional 5 specific amino acid positions (M461/L, K20R, 184V, L33F and L90M). Of 18 patients for whom both phenotypic and genotypic analysis were performed on free virus isolated from plasma, 12 showed reduced susceptibility to ritonavir in cell culture. AlliS patients possessed one or more substitutions in the viral protease gene. The V82A/F substitution appeared to be necessary but not sufficient to confer phenotypic resistance. Phenotypic resistance was defined as a greater than or equal to 5-fold decrease in viral sensitivity in cell culture from baseline.

Clinical Studies of Treatment-Naive Patients: 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 HIV-infected treatment-naive patients. A summary of the number of virologic failures and virologic failure isolates with ATV resistance in each arm is shown in Table 16.

Table 16: Summary of Virologic Failures[a] at Week 96 in Study AI424-089: Comparison of Ritonavir Boosted atazanavir vs. Unboosted atazanavir: Randomized Patients

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

[a] Virologic failure includes patients who were never suppressed through Week 96 and on study at Week 96, had virologic rebound or discontinued due to insufficient viral load response.
[b] Percentage of Virologic Failure Isolates with genotypic and phenotypic data.
[c] Mixture of I50I/L emerged in 2 other ATV 400 mg-treated patients. Neither isolate was phenotypically resistant to ATV.

Clinical Studies of Treatment-Naive Patients Receiving atazanavir 300 mg With Ritonavir 100 mg: In Phase III study AI424-138, an as-treated genotypic and phenotypic analysis was conducted on samples from patients who experienced virologic failure (HIV-1 RNA greater than or equal to 400 copies/mL) or discontinued before achieving suppression on ATV/RTV (n=39; 9%) and LPV/RTV (n=39; 9%) through 96 weeks of treatment. In the ATV/RTV arm, one of the virologic failure isolates had a 56-fold decrease in ATV 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 ATV/RTV-virologic failure isolates had baseline phenotypic ATV 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 ATV susceptibility from baseline and the other failure isolate with baseline ATV resistance and PI substitutions (M46M/I and I84I/V) had additional IAS-defined major PI substitutions (V32I, M46I, and I84V) emerge on ATV treatment associated with a 3-fold decrease in ATV susceptibility from baseline. Five of the treatment failure isolates in the ATV/RTV 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 LPV/RTV arm, one of the virologic failure patient isolates had a 69-fold decrease in LPV 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 LPV/RTV virologic failure isolates developed the M184V substitution and phenotypic emtricitabine resistance and two developed phenotypic tenofovir disoproxil resistance.

Clinical Studies of Treatment-Experienced Patients: In studies of treatment-experienced patients treated with ATV or ATV/RTV, most ATV-resistant isolates from patients 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 patients who failed treatment with ATV 300 mg once daily and RTV 100 mg once daily (together with tenofovir DF and an NRTI) included V32I, L33F/V/I, E35D/G, M46I/L, I50L, F53L/V, I54V, A71V/T/I, G73S/T/C, V82A/T/L, I85V, and L89V/Q/M/T. Other substitutions that developed on ATV/RTV treatment including E34K/A/Q, G48V, I84V, N88S/D/T, and L90M occurred in less than 10% of patient isolates. Generally, if multiple PI resistance substitutions were present in the HIV-1 virus of the patient at baseline, ATV 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 patients experiencing virologic failure after long-term treatment. Protease cleavage site changes also emerged on ATV treatment but their presence did not correlate with the level of ATV resistance.

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

Ritonavir: Among protease inhibitors variable cross-resistance has been recognized. Serial HIV-1 isolates obtained from six patients during ritonavir therapy showed a decrease in ritonavir susceptibility in cell culture but did not demonstrate a concordant decrease in susceptibility to saquinavir in cell culture when compared to matched baseline isolates. However, isolates from two of these patients demonstrated decreased susceptibility to indinavir in cell culture (8-fold). Isolates from 5 patients were also tested for cross-resistance to amprenavir and nelfinavir; isolates from 3 patients had a decrease in susceptibility to nelfinavir (6- to 14-fold), and none to amprenavir. Cross-resistance between ritonavir and reverse transcriptase inhibitors is unlikely because of the different enzyme targets involved. One ZDV-resistant HIV-1 isolate tested in cell culture retained full susceptibility to ritonavir.

Baseline Genotype/Phenotype and Virologic Outcome Analyses
Atazanavir
Genotypic and/or phenotypic analysis of baseline virus may aid in determining ATV susceptibility before initiation of ATV/ RTV 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 patients receiving ATV/RTV once daily or lopinavir (LPV)/RTV twice daily in a Study AI424-045 is shown in Table 17.

Overall, both the number and type of baseline PI substitutions affected response rates in treatment-experienced patients. In the ATV/RTV group, patients 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 patients with 1 to 2 PI substitutions, including one of these substitutions.

Table 17. HIV RNA Response by Number and Type of Baseline PI Substitution, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

Number and Type of Baseline PI Substitutions[a]	Virologic Response = HIV RNA <400 copies/mL[b] ATV/RTV (n=110)	LPV/RTV (n=113)
3 or more primary PI substitutions including:[c]		
D30N	75% (6/8)	50% (3/6)
M36I/V	19% (3/16)	33% (6/18)
M46I/L/T	24% (4/17)	23% (5/22)
I54V/L/T/M/A	31% (5/16)	31% (5/16)
A71V/T/I/G	34% (10/29)	39% (12/31)
G73S/A/C/T	14% (1/7)	38% (3/8)
V77I	47% (7/15)	44% (7/16)
V82A/F/T/S/I	29% (6/21)	27% (7/26)
I84V/A	11% (1/9)	33% (2/6)
N88D	63% (5/8)	67% (4/6)
L90M	10% (2/21)	44% (11/25)
Number of baseline primary PI substitutions[a]		
All patients, as-treated	58% (64/110)	59% (67/113)
0–2 PI substitutions	75% (50/67)	75% (50/67)
3–4 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] There were insufficient data (n less than 3) for PI substitutions V32I, I47V, G48V, I50V, and F53L.

The response rates of antiretroviral-experienced patients in Study AI424-045 were analyzed by baseline phenotype (shift in susceptibility in cell culture relative to reference, Table 18). The analyses are based on a select patient population with 62% of patients receiving an NNRTI-based regimen before study entry compared to 35% receiving a PI-based regimen. Additional data are needed to determine clinically relevant break points for atazanavir.

Table 18: Baseline Phenotype by Outcome, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

Baseline Phenotype[a]	Virologic Response = HIV RNA <400 copies/mL[b] ATV/RTV (n=111)	LPV/RTV (n=111)
0–2	71% (55/78)	70% (56/80)
>2–5	53% (8/15)	44% (4/9)
>5–10	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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Atazanavir: 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 1200 mg/kg/day, for which AUCs were 1.1 (males) or 3.9 (females) times those measured in humans at the clinical dose.

Ritonavir: Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100 or 200 mg per kg per day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 0.3-fold for males that of the exposure in humans with the recommended therapeutic dose (600 mg twice-daily). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 0.6-fold for the females that of the exposure in humans. In rats dosed at levels of 7, 15 or 30 mg per kg per day there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 6% that of the exposure in humans with the recommended therapeutic dose. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known.

Mutagenesis
Atazanavir: 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).

Ritonavir: However, ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of in *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Impairment of Fertility
Atazanavir: 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.

Ritonavir: Ritonavir produced no effects on fertility in rats at drug exposures approximately 40% (male) and 60% (female) of that achieved with the proposed therapeutic dose. Higher dosages were not feasible due to hepatic toxicity.

14 CLINICAL STUDIES

14.1 Adult Patients Without Prior Antiretroviral Therapy

Study AI424-138: A 96-week study comparing the antiviral efficacy and safety of atazanavir/ritonavir with lopinavir/ ritonavir, each in combination with fixed-dose tenofovir DF - emtricitabine in HIV-1 infected treatment-naive subjects. This study is a 96-week, open- label, randomized, multicenter study, comparing atazanavir (300 mg once daily) with ritonavir DF (100 mg once daily) to lopinavir with ritonavir (400/100 mg twice daily), each in combination with fixed-dose tenofovir DF with emtricitabine (300/200 mg once daily), in 878 antiretroviral treatment-naive treated patients. Patients 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/mm^3 (range: 2 to 810 cells/mm^3) 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 19.

Table 19: Outcomes of Treatment Through Week 96 (Study AI424-138)

Outcome	atazanavir 300 mg + ritonavir 100 mg (once daily) with tenofovir DF/emtricitabine (once daily)[a] (n=441)	lopinavir 400 mg + ritonavir 100 mg (twice daily) with tenofovir DF/emtricitabine (once daily)[a] (n=437)
	96 Weeks	**96 Weeks**
Responder[b,c,d]	75%	68%
Virologic failure[e]	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[f]	4%	7%

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

Through 96 weeks of therapy, the proportion of responders among patients with high viral loads (ie, baseline HIV RNA greater than or equal to 100,000 copies/mL) was comparable for the atazanavir/ritonavir (165 of 223 patients, 74%) and lopinavir/ritonavir (148 of 222 patients, 67%) arms. At 96 weeks, the median increase from baseline in CD4+ cell count was 261 cells/mm^3 for the atazanavir/ritonavir arm and 273 cells/mm^3 for the lopinavir/ritonavir arm.

14.2 Adult Patients With Prior Antiretroviral Therapy

Study AI424-045: Atazanavir once daily + ritonavir once daily compared to atazanavir once daily + saquinavir (soft gelatin capsules) once daily, and compared to lopinavir + ritonavir twice daily, each in combination with tenofovir DF + one NRTI. Study AI424-045 is an ongoing, randomized, 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 (1200 mg once daily), and to lopinavir + ritonavir (400/100 mg twice daily), each in combination with tenofovir DF and one NRTI, in 347 (of 358 randomized) patients who experienced virologic failure on HAART regimens containing PIs, NRTIs, and NNRTIs. The mean time of prior exposure to antiretrovirals was 139 weeks for PIs, 283 weeks for NRTIs, and 85 weeks for NNRTIs. The mean age was 41 years (range: 24 to 74); 60% were Caucasian, and 78% were male. The mean baseline CD4+ cell count was 338 cells/mm^3 (range: 14 to 1543 cells/mm^3) 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/ritonavir and lopinavir/ritonavir treatment arms are presented in Table 20. Atazanavir/ritonavir and lopinavir/ritonavir were similar for the primary efficacy outcome measure of time-averaged difference in change from baseline in HIV RNA level. Study AI424-045 was not large enough to reach a definitive conclusion that atazanavir/ritonavir and lopinavir/ritonavir are equivalent on the secondary efficacy outcome measure of proportions below the HIV RNA lower limit of detection.

Table 20: Outcomes of Treatment Through Week 48 in Study AI424-045 (Patients with Prior Antiretroviral Experience)

Outcome	atazanavir 300 mg + ritonavir 100 mg once daily + tenofovir DF + 1 NRTI (n=119)	lopinavir/ritonavir (400/100 mg) twice daily + tenofovir DF + 1 NRTI (n=118)	Difference[a] (atazanavir-lopinavir/ ritonavir) (CI)
HIV RNA Change from Baseline (log10 copies/mL)[b]	–1.58	–1.70	+0.12[c] (–0.17, 0.41)
CD4+ Change from Baseline (cells/mm^3)[d]	116	123	–7 (–67, 52)
Percent of Patients Responding[e]			
HIV RNA <400 copies/mL[b]	55%	57%	-2.2% (–14.8%, 10.5%)
HIV RNA <50 copies/mL[b]	38%	45%	–7.1% (–19.6%, 5.4%)

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

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

14.3 Pediatric Patients

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

One-hundred five patients (6 to less than 18 years of age) treated with the atazanavir capsule formulation, with or without ritonavir, were evaluated. Using an ITT analysis, the overall proportions of antiretroviral-naive and -experienced patients with HIV RNA less than 400 copies/mL at Week 96 were 51% (22/43) and 34% (21/62), respectively. The overall proportions of antiretroviral-naive and -experienced patients with HIV RNA less than 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/mm^3 in antiretroviral-naive patients and 220 cells/mm^3 in antiretroviral-experienced patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg are available in HDPE bottle of 30 tablets with child resistant closure.
Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg should be stored at room temperature below 30°C (86°F).
Exposure of this product to high humidity outside the original or USP equivalent tight container (150 ml or less) is not recommended.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Atazanavir Sulfate and Ritonavir Tablets are not a cure for HIV infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections.

17.1 Dosing Instructions
Patients should remain under the care of a physician while using Atazanavir Sulfate and Ritonavir Tablets. Patients should be advised to take Atazanavir Sulfate and Ritonavir Tablets with food every day and take other concomitant antiretroviral therapy as prescribed. Atazanavir sufate and Ritonavir Tablets must always be used in combination with other antiretroviral drugs. If the dose of Atazanavir sulfate and Ritonavir Tablet is missed, advise patients that they should not alter the dose or discontinue therapy without consulting with their healthcare provider. However, if a dose is skipped the patient should not double the next dose.

17.2 Drug Interactions
Atazanavir Sulfate and Ritonavir Tablets 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.

17.3 Cardiac Conduction Abnormalities
Patients should be informed that Atazanavir and Ritonavir tablets 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.

17.4 Rash
Inform patients that there have been reports of severe skin reactions (eg, Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions) with Atazanavir and Ritonavir Tablets. Advise patients that if signs or symptoms of severe skin reactions or hypersensitivity reactions develop, they must discontinue Atazanavir and Ritonavir tablets and seek medical evaluation immediately.

17.5 Hyperbilirubinemia
Inform patients that asymptomatic elevations in indirect bilirubin have occurred in patients receiving Atazanavir Sulfate and Ritonavir Tablets. 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.

17.6 Fat Redistribution
Patients should be informed 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.

17.7 Hepatotoxicity
Pre-existing liver disease including Hepatitis B or C can worsen with use of Atazanavir Sulfate and Ritonavir Tablets. This can be seen as worsening of transaminase elevations or hepatic decompensation. Advise patients that their liver function tests will need to be monitored closely especially during the first several months of treatment and that they should notify their healthcare provider if they develop the signs and symptoms of worsening liver disease including loss of appetite, abdominal pain, jaundice, and itchy skin.

17.8 Pancreatitis
Pancreatitis, including some fatalities, has been observed in patients receiving Atazanavir sulfate and ritonavir. Advise patients to notify their healthcare provider of signs and symptoms (nausea, vomiting, and abdominal pain) that might be suggestive of pancreatitis.

17.9 Lipid Disorders
Treatment with Atazanavir Sulfate and Ritonavir Tablets therapy can result in increases in the concentration of total cholesterol and triglycerides.

17.10 Diabetes Mellitus/Hyperglycemia
Advise patients that new onset of diabetes or exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported and to notify their healthcare provider if they develop the signs and symptoms of diabetes mellitus including frequent urination, excessive thirst, extreme hunger or unusual weight loss and/or an increased blood sugar while on Atazanavir and Ritonavir Tablet as they may require a change in their diabetes treatment or new treatment.

17.11 Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including atazanavir sulfate and ritonavir.

17.12 Nephrolithiasis and Choletithiasis
Inform patients that kidney stones and/or gallstones have been reported with Atazanavir Sulfate and Ritonavir Tablets use. Some patients with kidney stones and/or gallstones required hospitalization for additional management and some had complications. Discontinuation of Atazanavir Sulfate and Ritonavir Tablets may be necessary as part of the medical management of these adverse events.

17.13 Pregnancy
Inform pregnant patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women 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)].

17.14 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)].

Patient Information

Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg

Read the Patient Information that comes with Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg before you start using it and each time you get a refill. There may be new information. This leaflet provides a summary about Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg and does not include everything there is to know about your medicine. This information does not substitute talking with your healthcare provider about your medical condition or treatment.

What is Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg?
Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg is a prescription medicine used with other antiretroviral medicines to treat HIV infection in patients aged at least 6 years and at least 35 kg body weight.HIV is the virus that causes acquired immune deficiency syndrome (AIDS).

Atazanavir and ritonavir should not be used in children younger than 6 years of age and whose body weight is less than 35 kg.

Atazanavir and ritonavir Tablets when used with other antiretroviral medicines to treat HIV-1 infection, it may help
- reduce the amount of HIV-1 in your blood. This is called "viral load".
- increase the number of CD4+ (T) cells in your blood that help fight off other infections.

Reducing the amount of HIV-1 and increasing the CD4+ (T) cells in your blood may help improve your immune system. This may reduce your risk of death or getting infections that can happen when your immune system is weak (opportunistic infections).

Does Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg cure HIV or AIDS?
Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg do not cure HIV-1 infection or AIDS .You must keep taking HIV-1 medicines to control HIV-1 infection and decrease HIV-related illness.

Who should not take Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg?

Do not take Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg if you:
- **are taking certain medicines** (See "What important information should I know about taking Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg with other medicines?") Serious life-threatening side effects or death may happen. Before you take Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg, tell your healthcare provider about all medicines you are taking or planning to take. These include other prescription and nonprescription medicines, vitamins, and herbal supplements.
- **are allergic to atazanavir, ritonavir or any of the tablet ingredients.** The active ingredients are atazanavir sulfate and ritonavir. See the end of this leaflet for a complete list of ingredients in Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg. Tell your healthcare provider, if you think you have had an allergic reaction to any of these ingredients.

What should I tell my healthcare provider before I take Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg?

Tell your healthcare provider:
- **If you are pregnant or plan to become pregnant.** Talk to your healthcare provider about taking Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg during pregnancy or if you are planning to become pregnant.
- 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/Ritonavir. Talk to your healthcare provider about forms of birth control that may be used during treatment with Atazanavir/Ritonavir.
- **After your baby is born,** tell your healthcare provider if your baby's skin or the white part of his/her eyes turns yellow.
- **If you are breastfeeding. Do not breastfeed.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - atazanavir and ritonavir can be passed to the baby into your breastmilk.
  - Talk to your healthcare provider about the best way to feed your baby.
- **If you have liver problems or are infected with the hepatitis B or C virus.** See "What are the possible side effects of Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg?"
- **If you have end stage kidney disease** managed with hemodialysis.
- **If you have high blood sugar level (diabetes).** See "What are the possible side effects of Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg?"
- **If you have hemophilia or bleeding problems.** See "What are the possible side effects of Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg?"
- **If you have heart problem.**
- **About all the medicines you take** including prescription and nonprescription medicines, vitamins, and herbal supplements. Keep a list of your medicines with you to show your healthcare provider. For more information, see "What important information should I know about taking Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg with other medicines?" and "Who should not take Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg?" Some medicines can cause serious side effects if taken with Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg.
- **If you have any other medical condition.**

How should I take Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg?
- **Take atazanavir and ritonavir tablets once every day exactly as instructed by your healthcare provider.**
- **Always take atazanavir and ritonavir tablets with food** (a meal or snack) to help it work better. Take atazanavir and ritonavir tablets at the same time each day.
- Tablets should be swallowed whole and not chewed, broken or crushed.
- **If you are taking antacids or didanosine**, take Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg tablet 2 hours before or 1 hour after these medicines.
- **If you are taking medicines for indigestion, heartburn, or ulcers such as nizatidine, famotidine, cimetidine, ranitidine, rabeprazole, esomeprazole, lansoprazole, omeprazole, or pantoprazole**, talk to your healthcare provider.
- **Do not change your dose or stop taking Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg without first talking with your healthcare provider.** It is important to stay under a healthcare provider's care while taking atazanavir and ritonavir tablets.
- **When your supply of Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg starts to run low**, get more from your healthcare provider or pharmacy. It is important not to run out of atazanavir and ritonavir tablets. The amount of HIV in your blood may increase if the medicine is stopped for even a short time. The virus may become resistant to Atazanavir/ritonavir and harder to treat.
- **If you miss a dose of Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg**, take it as soon as possible and then take your next scheduled dose at its regular time. If, however, it is within 6 hours of your next dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not double the next dose. **It is important that you do not miss any doses of atazanavir ritonavir tablet or your other anti- HIV medicines.**
- **If you take more than the prescribed dose of Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg**, call your healthcare provider or poison control center right away or go to the nearest hospital emergency room right away.

What are the possible side effects of Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg?
The following list of side effects is **not** complete. Report any new or continuing symptoms to your healthcare provider. If you have questions about side effects, ask your healthcare provider. Your healthcare provider may be able to help you manage these side effects.

See "What is the most important information I should know about Atazanavir Sulfate and Ritonavir Tablets, 300 mg/ 100 mg".

The following side effects have been reported :
- 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/Allergic reaction.** Sometimes these allergic reactions can become severe and require treatment ina hospital. Call your healthcare provider right away if you develop a rash. Stop taking **Atazanavir Sulfate and Ritonavir Tablets** and get medical help right away if you have any of the following symptoms of a severe allergic reaction:
- General feeling of discomfort or 'flu-like' symptoms
- Fever
- Muscle or joint aches
- Red or inflamed eyes, like 'pink eye' (conjuntivitis)
- Blisters or skin lesions
- Mouth sores or ulcers
- Swelling of your face, lips or tongue
- Painful, warm or red lump under your skin
- Trouble breathing
- Sweating
- Wheezing
- Throat tightness or hoarseness
- Faster heartbeat or pounding in your chest
- **yellowing of the skin or the white part of your eyes.** These effects may be due to increases in bilirubin levels in the blood (bilirubin is made by the liver). Although these effects may not be damaging to your liver, skin, or eyes, call your healthcare provider promptly if your skin or the white part of your eyes turn yellow.
- **a change in the way your heart beats (heart rhythm change).** Tell your healthcare provider right away if you get dizziness, lightheadedness, feel faint or pass out and abnormal heart beat. These could be symptoms of a heart problem.
- **diabetes and high blood sugar (hyperglycemia)** some patients taking protease inhibitor medicines like atazanavir and ritonavir can get high blood sugar, develop diabetes, or your diabetes can get worse. Some patients had diabetes before taking protease inhibitors while others did not. Some patients may need changes in their diabetes medicine.
- **Liver Problems**
- If you have liver problems, including hepatitis B or C infection, your liver problems may get worse when you take Atazanavir sulfate and Ritonavir tablets.. Your healthcare provider will do blood tests to check your liver before you start Atazanavir sulfate and Ritonavir treatment. Tell your healthcare provider right away if you get any of the following symptoms:
  - yellowing of your skin or whites of your eyes
  - itching
  - stomach area pain
  - eyes turns yellow
  - light coloured stools
  - nausea
  - dark "tea-colored" urine
  - loss of appetite
  - pain or tenderness on your right side below your ribs.
- **kidney stones** have happened in some people taking atazanavir. 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 disorders have happened in some people who take atazanavir. Tell your healthcare provider right away if you get symptoms of gallbladder problems 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
- **swelling of your pancreas (pancreatitis).** atazanavir sulfate and ritonavir tablets can cause serious pancreas problems, which may lead to death. Tell your doctor right away if you have signs or symptoms of pancreatitis such as:
  - Nausea
  - Vomiting
  - stomach (abdominal) pain
  - **Some patients with hemophilia** have increased bleeding problems with protease inhibitors like atazanavir and ritonavir.The most comman side effect include
    - nausea
    - headache
    - stomach area pain
    - vomiting
    - trouble sleeping
    - numbness, tingling, or burning of hands or feet
    - dizziness
    - muscle pain
    - diarrhea
    - depression
    - fever
- **changes in body fat** can happen in people taking HIV-1 medicines. These changes may include increased amount of fat in the upper back 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.
- **Changes in 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 and Ritonavir treatment.
- **Increase in cholesterol and triglyceride levels.** Treatment with atazanavir sulfate and ritonavir tablets may increase your blood levels of cholesterol and triglycerides. Your doctor should do blood tests before you start your treatment with atazanavir sulfate and ritonavir tablets and regularly to check for an increase in your cholesterol and triglycerides levels.

Other common side effects of atazanavir and ritonavir tablets taken with other anti-HIV medicines include nausea; headache; stomach pain; vomiting; diarrhea; depression; fever; dizziness; trouble sleeping; numbness, tingling, or burning of hands or feet or around the lips; muscle pain; feeling weak or tired; rash; and upper and lower stomach (abdomen) pain.

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/ritonavir. For more information, ask your healthcare provider or pharmacist.

What important information should I know about taking Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg with other medicines?

Do not take Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg if you take the following medicines (tell your healthcare provider about all the medicines you take). Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg may cause serious, life-threatening side effects or death when used with these medicines.
- Alfluzosin
- Ergot medicines: dihydroergotamine, ergonovine, ergotamine, and methylergonovine such as, ergotrate maleate, and others (used for migraine headaches).
- Pimozide (used for Tourette's disorder).
- Cisapride (used for certain stomach problems).
- Triazolam (used for insomnia).
- Midazolam (used for sedation), when taken by mouth.
- Lovastatin, simvastatin
- Nevirapine
- Rifampin
- Indinavir
- Irinotecan
- Lurasidone
- Sildenafil
- St.John's wort
- Amiodarone
- Colchicine
- Dronaderone
- Flecainide
- Propafenone
- Quinidine
- Ranolazine
- Voriconazole

Remember:
1. **Know all the medicines you take.**
2. **Tell your healthcare provider about all the medicines you take.**
3. **Do not start a new medicine without talking to your healthcare provider.**

How should I store Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg?
- Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg should be stored at room temperature below 30 ºC (86 ºF). Do **not** store this medicine in a damp place such as a bathroom medicine cabinet or near the kitchen sink.
- Keep your medicine in a tightly closed container.
- Exposure of this product to high humidity outside the original or USP equivalent tight container (150 ml or less) for longer than 2 weeks is not recommended.
- Keep all medicines out of the reach of children and pets at all times. Do not keep medicine that is out of date or that you no longer need. Dispose of unused medicines through community take-back disposal programs when available or place Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg in an unrecognizable, closed container in the household trash.

General information about Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg
Do not accept if seal over bottle opening is broken or missing. This medicine was prescribed for your particular condition. Do not use Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg for another condition. Do not give Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg to other people, even if they have the same symptoms you have. It may harm them. **Keep Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg and all medicines out of the reach of children and pets.**

This summary does not include everything there is to know about Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg. Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Remember no written summary can replace careful discussion with your healthcare provider. If you would like more information, talk with your healthcare provider or you can call Heritage Pharmaceuticals Inc. at 1-866-901-DRUG (3784).

What are the ingredients in Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg?

Active Ingredient: atazanavir sulfate, ritonavir

Inactive Ingredients: Lactose monohydrate, crospovidone, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate, copovidone, sorbitan monolaurate, polysorbate 80 and sodium stearyl fumarate. Atazanavir Sulfate and Ritonavir Tablets, 300 mg/100 mg are coated hypromellose 2910, titanium dioxide, macrogol, talc, iron oxide yellow and polysorbate 80.

Manufactured by:
Emcure Pharmaceuticals Ltd.,
Hinjawadi, Pune, India.

Manufactured for:
Heritage Pharmaceuticals Inc.
Eatontown, NJ 07724
1-866-901-DRUG (3784)

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