

## 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

#### INDICATIONS AND USAGE

Atazanavir Sulfate and Ritonavir Tablets, a combination of a protease inhibitor and a protease inhibitor used as a pharmacokinetic enhancer, is indicated for use 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 40 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

- Tablets: Atazanavir sulfate 300 mg in combination with ritonavir 100 mg. (3, 16)

#### CONTRAINDICATIONS

- Atazanavir Sulfate and Ritonavir Tablets are contraindicated in patients with previously demonstrated hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product. (4)
- Coadministration with alfuzosin, triazolam, orally administered midazolam, ergot derivatives, rifampin, irinotecan, lovastatin, simvastatin, indinavir, cisapride, pimozone, St. John's wort, and sildenafil when dosed as REVATIO<sup>®</sup>. (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, ischemic heart disease, cardiomyopathy, underlying structural heart disease or when administered with other drugs that may prolong the PR interval. Cases of second and third degree heart block have been reported. (5.2, 6.3, 7.3, 12.2, 17.3)
- *Allergic Reactions/Hypersensitivity:* Allergic reactions have been reported and include anaphylaxis, Stevens-Johnson Syndrome, bronchospasm and angioedema. Discontinue treatment if severe reactions or rash develops. (5.3, 6.3, 17.4)
- *Hyperbilirubinemia:* Most patients experience asymptomatic increases in indirect bilirubin, which is reversible upon discontinuation. Do not dose reduce. If a concomitant transaminase increase occurs, evaluate for alternative etiologies. (5.4, 6.2)

- *Hepatotoxicity:* Patients with hepatitis B or C are at risk of increased transaminases or hepatic decompensation. Monitor liver function tests prior to therapy and during treatment. (2.4, 5.5, 6.3, 6.4, 8.8)
- *Nephrolithiasis* has been reported. Consider temporary interruption or discontinuation. (5.6, 6.4)
- Patients may develop new onset or exacerbations of diabetes mellitus/hyperglycemia (5.7, 6.3), immune reconstitution syndrome (5.8), and redistribution/accumulation of body fat. (5.9)
- *Hemophilia:* Spontaneous bleeding may occur and additional factor VIII may be required. (5.10)
- *Drug Interactions:* Consider drug-drug interaction potential to reduce risk of serious or life-threatening adverse reactions. (5.1)
- *Pancreatitis:* Fatalities have occurred; suspend therapy as clinically appropriate. (5.13)
- *Total cholesterol and triglycerides elevations:* Monitor prior to therapy and periodically thereafter. (5.14)

#### ADVERSE REACTIONS

The most common adverse reactions (> 5%) were asthenia, malaise, anorexia, nausea, paresthesia, circumoral paresthesia, peripheral paresthesia, jaundice/scleral icterus, rash, headache, abdominal pain, vomiting, insomnia, peripheral neurologic symptoms, dizziness, myalgia, diarrhea, depression, fever, and taste perversion. (6.1, 6.2)

To report SUSPECTED ADVERSE REACTIONS, call Matrix Laboratories Limited, at 1-877-4-INFO-RX (1-877-446-3679), or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

#### DRUG INTERACTIONS

Coadministration of Atazanavir Sulfate and Ritonavir Tablets can alter the concentration of other drugs and other drugs may alter the concentration of Atazanavir Sulfate and Ritonavir Tablets. The potential drug-drug interactions must be considered prior to and during therapy. (4, 5.1, 7, 12.3)

#### USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Use only if the potential benefit justifies the potential risk. (8.1)
- *Nursing mothers* should be instructed not to breast-feed due to the potential for postnatal HIV transmission and the potential for serious adverse reactions in nursing infants. (8.3)
- *Hepatitis B or C co-infection:* Monitor liver enzymes. (5.5, 6.4)
- *Renal impairment:* Do not use in treatment-experienced patients with end stage renal disease managed with hemodialysis. (2.3, 8.7)
- *Hepatic impairment:* Atazanavir Sulfate and Ritonavir Tablets is not recommended. (2.4, 8.8)

See 17 for PATIENT COUNSELING INFORMATION and FDA-proposed patient labeling

Revised 11/2011

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1. INDICATIONS AND USAGE

### 2. DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage
- 2.2 Pregnancy
- 2.3 Renal Impairment
- 2.4 Hepatic Impairment

### 3. DOSAGE FORMS AND STRENGTHS

### 4. CONTRAINDICATIONS

### 5. WARNINGS AND PRECAUTIONS

- 5.1 Drug Interactions
- 5.2 Cardiac Conduction Abnormalities
- 5.3 Rash
- 5.4 Hyperbilirubinemia
- 5.5 Hepatotoxicity

### 5.6 Nephrolithiasis

### 5.7 Diabetes Mellitus/Hyperglycemia

### 5.8 Immune Reconstitution Syndrome

### 5.9 Fat Redistribution

### 5.10 Hemophilia

### 5.11 Resistance/Cross-Resistance

### 5.12 Laboratory tests

### 5.13 Pancreatitis

### 5.14 Lipid disorders

### 6. ADVERSE REACTIONS

#### 6.1 Clinical Trial Experience in Adults

#### 6.2 Clinical Trial Experience in Pediatric Patients

#### 6.3 Postmarketing Experience

#### 6.4 Patients Co-infected With Hepatitis B and/or Hepatitis C Virus

## 7. DRUG INTERACTIONS

- 7.1 Potential to Affect Other Drugs
- 7.2 Potential for Other Drugs to Affect Atazanavir
- 7.3 Established and Other Potentially Significant Drug Interactions
- 7.4 Drugs with No Observed or Predicted Interactions with atazanavir sulfate

## 8. USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Age/Gender
- 8.7 Impaired Renal Function
- 8.8 Impaired Hepatic Function

## 10. OVERDOSAGE

## 11. DESCRIPTION

## 12. CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology

## 13. NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

## 14. CLINICAL STUDIES

- 14.1 Adult Patients Without Prior Antiretroviral Therapy
- 14.2 Adult Patients With Prior Antiretroviral Therapy
- 14.3 Pediatric Patients

## 16. HOW SUPPLIED/STORAGE AND HANDLING

## 17. PATIENT COUNSELING INFORMATION

- 17.1 Dosing Instructions
- 17.2 Drug Interactions
- 17.3 Cardiac Conduction Abnormalities
- 17.4 Rash
- 17.5 Hyperbilirubinemia
- 17.6 Fat Redistribution
- 17.7 Hepatic Reactions
- 17.8 Pancreatitis
- 17.9 Lipid Elevations
- 17.10 Diabetes Mellitus/Hyperglycemia
- 17.11 Immune Reconstitution Syndrome

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

---

# FULL PRESCRIBING INFORMATION

## 1. INDICATIONS AND USAGE

Atazanavir Sulfate and Ritonavir Tablets are indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

## 2. DOSAGE AND ADMINISTRATION

General Dosing Recommendations:

- Atazanavir Sulfate and Ritonavir Tablets must be taken with food.
- When coadministered with H<sub>2</sub>-receptor antagonists or proton-pump inhibitors, dose separation may be required [see *Dosage and Administration (2.1)*].
- When coadministered with didanosine buffered or enteric-coated formulations, Atazanavir Sulfate and Ritonavir Tablets should be given (with food) 2 hours before or 1 hour after didanosine.

### 2.1 Recommended Dosage

*Adults and pediatric patients (at least 6 years of age and 40 kg):* Atazanavir sulfate and Ritonavir Tablet, 300 mg/100 mg once daily with food.

For Treatment-Naive Patients:

- Do not coadminister with efavirenz in treatment naïve patients,
- When combined with an H<sub>2</sub>-receptor antagonist or Proton-Pump Inhibitor:
  - Atazanavir and ritonavir tablets should not be taken with both tenofovir and an H-2 receptor blocker because higher doses of atazanavir are required.
  - The H<sub>2</sub>-receptor antagonist dose should not exceed a dose comparable to famotidine 40 mg twice daily. Administer Atazanavir sulfate and Ritonavir Tablet simultaneously with, and/or at least 10 hours after the H<sub>2</sub>-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 Tablet.

For Treatment-Experienced Patients:

- Do not coadminister with proton-pump inhibitors or efavirenz in treatment-experienced patients.
- Atazanavir and ritoanvir tablets should not be taken with both tenofovir and an H-2 receptor blocker because higher doses of atazanavir are required.
- The H<sub>2</sub>-receptor antagonist dose should not exceed a dose comparable to famotidine 20 mg twice daily. Administer Atazanavir sulfate and Ritonavir Tablet simultaneously with, and/or at least 10 hours after the H<sub>2</sub>-receptor antagonist.

[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: Atazanavir sulfate and Ritonavir Tablet, 300 mg/100 mg once daily with food.

- Atazanavir Sulfate and Ritonavir Tablets should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir and ritonavir(?).
- Not recommended for treatment-experienced pregnant women during the second or third trimester, when coadministered with either an H<sub>2</sub>-receptor antagonist or Proton-Pump Inhibitor.
- No dose adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir sulfate, a 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-naïve 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 hepatic impairment, because atazanavir with ritonavir has not been studied in that population. [See *Warnings and Precautions (5.5)* and *Use in Specific Populations (8.8)*].

## **3. DOSAGE FORMS AND STRENGTHS**

Atazanavir Sulfate and Ritonavir Tablets 300 mg/100 mg Bilayer, film coated, capsule shaped, biconvex tablet, having one layer plain with pale yellow to yellow color and, a white to off-white layer debossed with “M777”.

#### 4. CONTRAINDICATIONS

Atazanavir Sulfate and Ritonavir Tablets are contraindicated:

- in patients with previously demonstrated clinically significant hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product.
- when coadministered with drugs that are highly dependent on CYP3A or UGT1A1 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These and other contraindicated drugs are listed in Table 1.

**Table 1: Drugs That Are Contraindicated with Atazanavir Sulfate and Ritonavir Tablets**

<b>Drug Class</b>	<b>Drugs within class that are contraindicated with Atazanavir Sulfate and Ritonavir Tablets</b>	<b>Clinical Comment</b>
Alpha 1 Adrenoreceptor Antagonist	Alfuzosin	Potential for increased alfuzosin concentrations, which can result in hypotension.
Antiarrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine	Potential for cardiac arrhythmias when administered with ritonavir, a component of Atazanavir Sulfate and Ritonavir Tablets.
Antimycobacterials	Rifampin	Rifampin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect and development of resistance.
Antineoplastics	Irinotecan	Atazanavir inhibits UGT1A1 and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.
Benzodiazepines	Triazolam, orally administered midazolam <sup>a</sup>	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with Atazanavir Sulfate and Ritonavir Tablets, 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 ( <i>Hypericum perforatum</i> )	Patients taking Atazanavir Sulfate and Ritonavir Tablets, 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 Inhibitors	Reductase	Lovastatin, simvastatin	Potential for serious reactions such as myopathy including rhabdomyolysis.
Neuroleptic		Pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
PDE5 Inhibitor		Sildenafil <sup>b</sup> when dosed as REVATIO <sup>®</sup> for the treatment of pulmonary arterial hypertension	A safe and effective dose in combination with Atazanavir Sulfate and Ritonavir Tablets, has not been established for sildenafil (REVATIO <sup>®</sup> ) 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.

---

<sup>a</sup> See *Drug Interactions, Table 8 (7)* for parenterally administered midazolam.

<sup>b</sup> See *Drug Interactions, Table 8 (7)* for sildenafil when dosed as VIAGRA<sup>®</sup> for erectile dysfunction.

---

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Drug Interactions

See Table 1 for a listing of drugs that are contraindicated for use with atazanavir sulfate and ritonavir due to potentially life-threatening adverse events, significant drug interactions, or loss of virologic activity. [See *Contraindications (4)*.] Please refer to Tables 9 and 12 for established and other potentially significant drug interactions [see *Drug Interactions (7.3)*].

### 5.2 Cardiac Conduction Abnormalities

Atazanavir sulfate, a component of Atazanavir Sulfate and Ritonavir Tablets, 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 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 or second- or third-degree AV block), atazanavir should be used with caution in these patients. [See *Clinical Pharmacology (12.2)*.]

Atazanavir in combination with diltiazem increased diltiazem plasma concentration by 2-fold with an additive effect on the PR interval. When used in combination with atazanavir, a dose reduction of diltiazem by one-half should be considered and ECG monitoring is recommended. In a pharmacokinetic study between atazanavir 400 mg once daily and atenolol 50 mg once daily, no clinically significant additive effect of atazanavir and atenolol on the PR interval was observed. Dose adjustment of atenolol is not required when used in combination with atazanavir. [See *Drug Interactions (7)* and *Clinical Pharmacology (12.2)*.] Pharmacokinetic studies between atazanavir and other drugs that prolong the PR interval including beta blockers [other than atenolol, see *Drug Interactions (7)*], calcium channel blockers like verapamil and digoxin have not been performed. An additive effect of atazanavir and these drugs cannot be excluded; therefore, caution should be exercised when atazanavir and ritonavir is given concurrently with these drugs, especially those that are metabolized by CYP3A (eg, verapamil).

Clinical monitoring is recommended. [see *Clinical Pharmacology (12.3)*].

### **5.3 Rash/Hypersensitivity**

In controlled clinical trials, rash (all grades, regardless of causality) occurred in approximately 20% of patients treated with atazanavir sulfate, a component of Atazanavir Sulfate and Ritonavir Tablets. 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  $\geq 2\%$ ) 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  $< 1\%$ . Atazanavir Sulfate and Ritonavir Tablets should be discontinued if severe rash develops. Cases of anaphylaxis, Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions have been reported in patients receiving atazanavir sulfate and ritonavir . [See *Contraindications (4)*.]

#### **5.4 Hyperbilirubinemia**

Most patients taking atazanavir, a component of Atazanavir Sulfate and Ritonavir Tablets, experience asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT). This hyperbilirubinemia is reversible upon discontinuation of atazanavir. Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies. No long-term safety data are available for patients experiencing persistent elevations in total bilirubin  $> 5$  times ULN. Alternative antiretroviral therapy to atazanavir, a component of Atazanavir Sulfate and Ritonavir Tablets, may be considered if jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for patients. Dose reduction of Atazanavir Sulfate and Ritonavir Tablets is not recommended since long-term efficacy of reduced doses has not been established. [See *Adverse Reactions (6.1, 6.2)*.]

#### **5.5 Hepatic Reactions**

There may be an increased risk for transaminase elevations in patients with underlying hepatitis B or C. Therefore, caution should be exercised when administering Atazanavir Sulfate and Ritonavir Tablets to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.

In patients, hepatic laboratory testing should be conducted prior to initiating therapy with Atazanavir Sulfate and Ritonavir Tablets and during treatment. [See *Adverse Reactions (6.4)* and *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.

### **5.6 Nephrolithiasis**

Cases of nephrolithiasis were reported during postmarketing surveillance in HIV-infected patients receiving atazanavir, a component of Atazanavir Sulfate and Ritonavir Tablets. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made. If signs or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of therapy may be considered. [See *Adverse Reactions* (6.3).]

### **5.7 Diabetes Mellitus/Hyperglycemia**

New-onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established. [See *Adverse Reactions* (6.3).]

### **5.8 Immune Reconstitution Syndrome**

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including atazanavir sulfate 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.

### **5.9 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.

### **5.10 Hemophilia**

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

### **5.11 Resistance/Cross-Resistance**

Various degrees of cross-resistance among protease inhibitors have been observed. Resistance to atazanavir sulfate and ritonavir may not preclude the subsequent use of other protease inhibitors. [See *Clinical Pharmacology* (12.4).]

### **5.12 Laboratory Tests**

Ritonavir, a component of Atazanavir Sulfate and Ritonavir Tablets, 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 therapy and at periodic intervals or if any clinical signs or symptoms occur during therapy. For comprehensive information concerning laboratory test alterations associated with reverse transcriptase inhibitors, physicians should refer to the complete product information for each of these drugs.

### **5.13 Pancreatitis**

Pancreatitis has been observed in patients receiving ritonavir, a component of Atazanavir Sulfate and Ritonavir Tablets, 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 (5.8)*]. 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.

#### **5.14 Lipid Disorders**

Triglyceride and cholesterol testing should be performed prior to initiating therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate, taking into account any potential drug-drug interactions with HMG CoA reductase inhibitors [see *Contraindications (4) and Drug Interactions (7)*].

### **6 ADVERSE REACTIONS**

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

- cardiac conduction abnormalities [see *Warnings and Precautions (5.2)*]
- rash/hypersensitivity [see *Warnings and Precautions (5.3)*]
- hyperbilirubinemia [see *Warnings and Precautions (5.4)*]
- nephrolithiasis [see *Warnings and Precautions (5.6)*]
- Drug Interactions [see *Warnings and Precautions (5.1)*]
- Hepatotoxicity [see *Warnings and Precautions (5.5)*]
- Pancreatitis [see *Warnings and Precautions (5.13)*]

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

## 6.1 Clinical Trial Experience in Adults

### Atazanavir component of Atazanavir Sulfate and Ritonavir Tablets - Treatment-Emergent Adverse Reactions in Treatment-Naive Patients

The safety profile of atazanavir, a component of Atazanavir Sulfate and Ritonavir Tablets, in treatment-naive adults is based on 1625 HIV-1 infected patients in clinical trials. 536 patients received atazanavir 300 mg with ritonavir 100 mg and 1089 patients received atazanavir 400 mg or higher (without ritonavir).

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

Selected clinical adverse reactions of moderate or severe intensity reported in  $\geq 2\%$  of treatment-naive patients receiving combination therapy including atazanavir 300 mg with ritonavir 100 mg is presented in Table 2.

**Table 2: Selected Treatment-Emergent Adverse Reactions<sup>a</sup> of Moderate or Severe Intensity Reported in  $\geq 2\%$  of Adult Treatment-Naive Patients,<sup>b</sup> Study AI424-138**

	96 weeks <sup>c</sup> Atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine <sup>d</sup> (n=441)	96 weeks <sup>c</sup> lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir with emtricitabine <sup>d</sup> (n=437)
<b>Digestive System</b>		
Nausea	4%	8%
Jaundice/scleral icterus	5%	*
Diarrhea	2%	12%
<b>Skin and Appendages</b>		
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, 200 mg emtricitabine once daily.

### Treatment-Emergent Adverse Reactions in Treatment-Experienced Patients

The safety profile of atazanavir, a component of Atazanavir Sulfate and Ritonavir Tablets, 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  $\geq 2\%$  of treatment-experienced patients receiving atazanavir/ritonavir are presented in Table 3.

**Table 3: Selected Treatment-Emergent Adverse Reactions<sup>a</sup> of Moderate or Severe Intensity Reported in  $\geq 2\%$  of Adult Treatment-Experienced Patients, <sup>b</sup> Study AI424-045**

	48 week <sup>c</sup> Atazanavir/ritonavir 300/100 mg once daily + tenofovir + NRTI (n=119)	48 week <sup>c</sup> lopinavir/ritonavir 400/100 mg once daily + tenofovir + NRTI (n=118)
<b>Body as a Whole</b>		
Fever	2%	*
<b>Digestive System</b>		
Jaundice/scleral icterus	9%	*
Diarrhea	3%	11%
Nausea	3%	2%
<b>Nervous System</b>		
Depression	2%	<1%
<b>Musculoskeletal System</b>		
Myalgia	4%	*

\* None reported in this treatment arm.

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

b. Based on the regimen containing atazanavir.

c. Median time on therapy.

d. As a fixed-dose combination.

### Laboratory Abnormalities in Treatment-Naive Patients

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

**Table 4: Grade 3–4 Laboratory Abnormalities Reported in  $\geq 2\%$  of Adult Treatment-Naive Patients, <sup>a</sup> Study AI424-138**

Variable	Limit <sup>c</sup>	96 week <sup>b</sup> ATAZANAVIR 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine <sup>d</sup> (n=441)	96 week <sup>b</sup> lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir with emtricitabine <sup>d</sup> (n=437)
		Chemistry	High
SGOT/AST	$\geq 5.1 \times \text{ULN}$	3%	1%
SGPT/ALT	$\geq 5.1 \times \text{ULN}$	3%	2%
Total Bilirubin	$\geq 2.6 \times \text{ULN}$	44%	<1%
Lipase	$\geq 2.1 \times \text{ULN}$	2%	2%
Creatine Kinase	$\geq 5.1 \times \text{ULN}$	8%	7%
Total Cholesterol	$\geq 240 \text{ mg/dL}$	11%	25%

Hematology	<u>Low</u>		
Neutrophils	<750 cells/mm <sup>3</sup>	5%	2%

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

### Laboratory Abnormalities in Treatment-Experienced Patients

The percentages of adult treatment-experienced patients treated with combination therapy including atazanavir and ritonavir with Grade 3–4 laboratory abnormalities are presented in Table 5.

**Table 5: Grade 3–4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Experienced Patients, Study AI424-045<sup>a</sup>**

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

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

### Lipids, Change from Baseline in Treatment-Naive Patients

For Study AI424-138, changes from baseline in LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglycerides are shown in Table 6.

**Table 6: Lipid Values, Mean Change from Baseline, Study AI424-138**

	Atazanavir/ritonavir <sup>a,b</sup>			lopinavir/ritonavir <sup>b,c</sup>		
	Baseline mg/dL	Week 48 mg/dL	Week 48 Change <sup>d</sup>	Baseline mg/dL	Week 48 mg/dL	Week 48 Change <sup>d</sup>

	(n=428 <sup>e</sup> )	(n=372 <sup>e</sup> )	(n=372 <sup>e</sup> )	(n=424 <sup>e</sup> )	(n=335 <sup>e</sup> )	(n=335 <sup>e</sup> )
LDL-Cholesterol <sup>f</sup>	92	105	+14%	93	111	+19%
HDL-Cholesterol <sup>f</sup>	37	46	+29%	36	48 +	37%
Total Cholesterol <sup>f</sup>	149	169	+13%	150	187 +	25%
Triglycerides <sup>f</sup>	126	145	+15%	129	194 +	52%

<sup>a.</sup> Atazanavir 300 mg with ritonavir 100 mg once daily with the fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

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

<sup>c.</sup> Lopinavir 400 mg with ritonavir 100 mg twice daily with the fixed-dose combination 300 mg tenofovir, 200 mg emtricitabine once daily.

<sup>d.</sup> The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values and is not a simple difference of the baseline and Week 48 mean values.

<sup>e.</sup> Number of patients with LDL-cholesterol measured.

<sup>f.</sup> Fasting.

### Lipids, Change from Baseline in Treatment-Experienced Patients

For Study AI424-045, changes from baseline in LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglycerides are shown in Table 7. The observed magnitude of dyslipidemia was less with atazanavir/ritonavir than with lopinavir/ritonavir. However, the clinical impact of such findings has not been demonstrated.

**Table 7: Lipid Values, Mean Change from Baseline, Study AI424-045**

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

<sup>a.</sup> Atazanavir 300 mg once daily + ritonavir + tenofovir + 1 NRTI.

<sup>b.</sup> Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 4% in the lopinavir/ritonavir treatment arm and 4% in the atazanavir/ritonavir arm. Through Week 48 serum lipid-reducing agents were used in 19% in the lopinavir/ritonavir treatment arm and 8% in the atazanavir/ritonavir arm.

<sup>c.</sup> Lopinavir/ritonavir (400/100 mg) BID + tenofovir + 1 NRTI.

<sup>d.</sup> The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values and is not a simple difference of the baseline and Week 48 mean values.

---

<sup>e.</sup> Number of patients with LDL-cholesterol measured.  
<sup>f.</sup> Fasting.

---

## 6.2 Clinical Trial Experience in Pediatric Patients

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

The safety profile of atazanavir, a component of Atazanavir Sulfate and Ritonavir Tablets, in pediatric patients (6 to less than 18 years of age) was generally similar to that observed in clinical studies of atazanavir in adults. The most common Grade 2–4 adverse events ( $\geq 5\%$ , 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 2% of patients. The most common Grade 3–4 laboratory abnormalities occurring in pediatric patients were elevation of total bilirubin ( $\geq 3.2$  mg/dL, 58%), neutropenia (9%), and hypoglycemia (4%). All other Grade 3–4 laboratory abnormalities occurred with a frequency of less than 3%.

Ritonavir, a component of Atazanavir Sulfate and Ritonavir Tablets, has been studied in 265 pediatric patients > 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  $\geq 2\%$  of pediatric patients enrolled in ritonavir clinical trials.

### *Laboratory Abnormalities*

The following Grade 3-4 laboratory abnormalities occurred in > 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 Postmarketing Experience**

#### **Atazanavir, component of Atazanavir Sulfate and Ritonavir Tablets**

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

*Body as a Whole:* edema

*Cardiovascular System:* second-degree AV block, third-degree AV block, left bundle branch block, QTc prolongation [see *Warnings and Precautions (5.2)*]. These effects are common with those observed by administration of ritonavir.

*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 (5.7)*]

*Musculoskeletal System:* arthralgia

*Renal System:* nephrolithiasis [see *Warnings and Precautions (5.6)*]

*Skin and Appendages:* alopecia, maculopapular rash [see *Contraindications (4)* and *Warnings and Precautions (5.3)*], pruritus.

#### **Ritonavir, 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.

Co-administration 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.

Cardiac and neurologic events have been reported when ritonavir has been co-administered 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.

### *Nervous System*

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

## **6.4 Patients Co-infected With Hepatitis B and/or Hepatitis C Virus**

Liver function tests should be monitored in patients with a history of hepatitis B or C.

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

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

[See *Warnings and Precautions (5.5)*.]

## **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. When atazanavir sulfate with ritonavir is coadministered with substrates of CYP2C8, clinically significant interactions are not expected. [See *Clinical Pharmacology, Table 13 (12.3)*.]

**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 (> 3-fold) when co-administered with ritonavir. Thus, coadministration 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 as shown in Table 12.

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’s therapeutic effect.

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

## 7.3 Established and Other Potentially Significant Drug Interactions

Table 8 provides dosing and clinical recommendations 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 8: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies<sup>a</sup> or Predicted Interactions (Information in the table applies to atazanavir with or without ritonavir, unless otherwise indicated)**

<i>Concomitant Drug Class: Specific Drugs</i>	<b>Effect on Concentration of Atazanavir or Concomitant Drug</b>	<b>Clinical Comment</b>
<i><b>HIV Antiviral Agents</b></i>		
<i>HIV CCR5-antagonist: maraviroc</i>	↑ maraviroc	Maraviroc dose should be reduced to 150 mg twice daily when administered with atazanavir and ritonavir tablets.
<i>Nucleoside Reverse Transcriptase Inhibitors (NRTIs): didanosine buffered formulations enteric- coated (EC) capsules</i>	↓ 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

<i>Nucleotide Reverse Transcriptase Inhibitors:</i> tenofovir disoproxil fumarate	↓ atazanavir ↑ tenofovir	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. Atazanavir increases tenofovir concentrations. The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving atazanavir and tenofovir should be monitored for tenofovir associated adverse events.
<i>Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs):</i> efavirenz	↓ atazanavir	Efavirenz decreases atazanavir exposure. Do not coadminister atazanavir and ritonavir tablets with efavirenz due to decreased exposures of atazanavir
<i>Non-nucleoside Reverse Transcriptase Inhibitors:</i> nevirapine	↓ atazanavir ↑ nevirapine	Do not coadminister atazanavir with nevirapine because: <ul style="list-style-type: none"> <li>• Nevirapine substantially decreases atazanavir exposure.</li> <li>• Potential risk for nevirapine associated toxicity due to increased nevirapine exposures.</li> </ul>
<i>Protease Inhibitors:</i> saquinavir (soft gelatin capsules)	↑ saquinavir	Appropriate dosing recommendations for this combination with respect to efficacy and safety have not been established. In a clinical study, saquinavir 1200 mg coadministered with atazanavir 400 mg and tenofovir 300 mg (all given once daily) plus nucleoside analogue reverse transcriptase inhibitors did not provide adequate efficacy [see <i>Clinical Studies (14.2)</i> ].
<i>Protease Inhibitors:</i> others	↑ other protease inhibitor	<b>Atazanavir/ritonavir:</b> Although not studied, the coadministration of atazanavir/ritonavir and other protease inhibitors would be expected to increase exposure to the other protease inhibitor. Such coadministration is not recommended.
<b><i>Other Agents</i></b>		
<i>Analgesics, Narcotic:</i> tramadol, propoxyphene	↑ tramadol, propoxyphene	A dose decrease may be needed for these drugs when co-administered with ritonavir, a component of atazanavir and ritonavir tablets..
<i>Anesthetic:</i> meperidine	↑ meperidine ↓ normeperidine (metabolite)	Dosage increase and long-term use of meperidine with ritonavir, a component of atazanavir and ritonavir tablets, is not recommended due to

		the increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (e.g., seizures). The effect of atazanavir plus ritonavir on meperidine metabolism is not known.
<i>Antacids and buffered medications</i>	↓ 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.
<i>Antiarrhythmics:</i> amiodarone, bepridil, lidocaine (systemic), quinidine, disopyramide, mexilitine	↑ amiodarone, bepridil, lidocaine (systemic), quinidine, disopyramide, mexilitine	Coadministration with atazanavir and ritonavir 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 and ritonavir tablets.
<i>Anticancer agents:</i> vincristine, vinblastine	↑ anticancer agents	Concentrations of vincristine or vinblastine may be increased when co-administered with ritonavir, a component of atazanavir and ritonavir tablets, resulting in the potential for increased adverse events usually associated with these anticancer agents. Consideration should be given to temporarily withholding the ritonavir 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.
<i>Anticoagulants:</i> warfarin	Potential effect of atazanavir: ↑ warfarin  Potential effect of ritonavir: ↓ R-warfarin ↓↑ S-warfarin	Coadministration with atazanavir has the potential to produce serious and/or life-threatening bleeding and has not been studied. Coadministration with ritonavir may alter warfarin concentrations. It is recommended that INR (International Normalized Ratio) be monitored.
<i>Anticonvulsants:</i> carbamazepine, clonazepam, ethosuximide	↑ anticonvulsants	Use with caution. A dose decrease may be needed for these drugs when co-administered with ritonavir, a

<i>Anticonvulsants:</i> divalproex, lamotrigine, phenytoin	↓ anticonvulsants	<p>component of atazanavir and ritonavir tablets, and therapeutic concentration monitoring is recommended for these anticonvulsants, if available.</p> <p>Use with caution. A dose increase may be needed for these drugs when co-administered with ritonavir, a component of atazanavir and ritonavir tablets. The effect of atazanavir plus ritonavir on these drugs is not known. Therapeutic concentration monitoring is recommended for these anticonvulsants, if available.</p>
<i>Antidepressants:</i> tricyclic antidepressants, bupropion, nefazodone, selective serotonin reuptake inhibitors (SSRIs)	↑ antidepressants	<p>Coadministration with atazanavir plus ritonavir has the potential to produce serious and/or life-threatening adverse events and has not been studied. Consider a dose reduction of the antidepressants. Concentration monitoring of these drugs is recommended.</p>
trazodone	↑ trazodone	<p>Concomitant use of trazodone and atazanavir with ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following coadministration of trazodone and ritonavir. The combination should be used with caution and a lower dose of trazodone should be considered.</p>
<i>Antifungals:</i> ketoconazole, itraconazole	<b>Atazanavir/ ritonavir:</b> ↑ ketoconazole ↑ itraconazole	<p>Coadministration of ketoconazole has only been studied with atazanavir without ritonavir (negligible increase in atazanavir AUC and C<sub>max</sub>). Due to the effect of ritonavir on ketoconazole, high doses of ketoconazole and itraconazole (&gt;200 mg/day) should be used cautiously with atazanavir/ritonavir.</p>
<i>Antifungals:</i> voriconazole	Effect is unknown	<p>Coadministration of voriconazole with atazanavir, with or without ritonavir, has not been studied. Administration of voriconazole with ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%. Voriconazole should not be administered to patients receiving atazanavir/ritonavir, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Coadministration of voriconazole with atazanavir (without ritonavir) may increase atazanavir concentrations; however, no data are</p>

<i>Antigout:</i> colchicine	↑ colchicine	<p>available.</p> <p>Atazanavir and ritonavir tablets should not be Coadministered with colchicine to patients with renal or hepatic impairment.</p> <p><b>Recommended dosage of colchicine when administered with atazanavir plus ritonavir tablets:</b></p> <p><b>Treatment of gout flares:</b> 0.6 mg (1 tablet) for 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Not to be repeated before 3 days.</p> <p><b>Prophylaxis of gout flares:</b> If the original regimen was 0.6 mg <i>twice</i> a day, the regimen should be adjusted to 0.3 mg <i>once a day</i>. If the original regimen was 0.6 mg <i>once</i> a day, the regimen should be adjusted to 0.3 mg <i>once every other day</i>.</p> <p><b>Treatment of familial Mediterranean fever (FMF):</b></p>
<i>Antimycobacterials:</i> rifabutin	↑ rifabutin	<p>Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day). A rifabutin dose reduction of up to 75% (eg, 150 mg every other day or 3 times per week) is recommended.</p>
<i>Calcium channel blockers:</i> diltiazem	↑ diltiazem and desacetyl-diltiazem	<p>Caution is warranted. A dose reduction of diltiazem by 50% should be considered. ECG monitoring is recommended. Coadministration of atazanavir/ritonavir with diltiazem has not been studied.</p>
eg, felodipine, nifedipine, nicardipine, and verapamil	↑ calcium channel blocker	<p>Caution is warranted. Dose titration of the calcium channel blocker should be considered. ECG monitoring is recommended.</p>
Digoxin	↑ digoxin	<p>Concomitant administration of ritonavir, a component of atazanavir and ritonavir tablets, with digoxin may increase digoxin levels. Caution should be exercised when coadministering ritonavir with digoxin, with appropriate monitoring of serum digoxin levels.</p>
<i>Endothelin receptor antagonists:</i> bosentan	↓ atazanavir ↑ bosentan	<p><b>Coadministration of bosentan in patients on atazanavir/ritonavir:</b> For patients who have been receiving atazanavir/ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based on individual tolerability.</p> <p><b>Coadministration of atazanavir/ritonavir in patients on bosentan:</b></p>

*HMG-CoA reductase inhibitors:*  
atorvastatin, rosuvastatin

↑ atorvastatin  
↑ rosuvastatin

*H2-Receptor antagonists*

↓ atazanavir

*Hormonal contraceptives:* ethinyl  
estradiol and norgestimate or  
norethindrone

↓ ethinyl estradiol ↑  
norgestimate<sup>c</sup>

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.

Use the lowest possible dose of atorvastatin or rosuvastatin with careful monitoring. The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including atazanavir, are used in combination with these drugs.

***In treatment-naïve patients:***

Atazanavir and ritonavir Tablets once daily with food should be administered simultaneously with, and or at least 10 hours after, a dose of the H2-receptor antagonist. An H2-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-naïve patients.

***In treatment-experienced patients:***

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

- Atazanavir and ritonavir tablets once daily with food if taken with an H2-receptor antagonist.
- Atazanavir and ritonavir tablets should not be take with both tenofovir and an H2-receptor antagonist because higher doses of tenofovir are required.

Use with caution if coadministration of atazanavir/ritonavir with oral contraceptives is considered. If an oral contraceptive is administered with atazanavir plus ritonavir, it is recommended that the oral

	↑ ethinyl estradiol ↑ norethindrone <sup>d</sup>	<p>contraceptive contain at least 35 mcg of ethinyl estradiol.</p> <p>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.</p> <p>Coadministration of atazanavir or atazanavir/ritonavir with other hormonal contraceptives (eg, contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestagens other than norethindrone or norgestimate, or less than 25 mcg of ethinyl estradiol, has not been studied; therefore, alternative methods of contraception are recommended.</p>
<i>Immunosuppressants:</i> cyclosporin, sirolimus, tacrolimus	↑ immunosuppressants	<p>Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with atazanavir (atazanavir sulfate).</p>
<i>Inhaled beta agonist:</i> salmeterol	↑ salmeterol	<p>Coadministration of salmeterol with atazanavir and ritonavir tablets is not recommended. Concomitant use of salmeterol and atazanavir and ritonavir tablets may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.</p>
<i>Inhaled/nasal steroid:</i> fluticasone	<b>Atazanavir/ritonavir</b> ↑ fluticasone	<p>Concomitant use of fluticasone propionate and atazanavir/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression, have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. 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 <i>Warnings and</i></p>

*Macrolide antibiotics:*  
clarithromycin

↑ clarithromycin  
↓ 14-OH clarithromycin  
↑ atazanavir

*Narcotic Analgesic:* methadone

↓ methadone

*Neuroleptics:* perphenazine,  
risperidone, thioridazine

↑ neuroleptics

*PDE5 inhibitors:* sildenafil,  
tadalafil, vardenafil

↑ sildenafil  
↑ tadalafil  
↑ vardenafil

*Precautions (5.1)].*

Increased concentrations of clarithromycin may cause QTc prolongations; therefore, a dose reduction of clarithromycin by 50% should be considered when it is coadministered with atazanavir. In addition, concentrations of the active metabolite 14-OH clarithromycin are significantly reduced; consider alternative therapy for indications other than infections due to *Mycobacterium avium* complex. Coadministration of atazanavir/ritonavir with clarithromycin has not been studied. Dosage increase of methadone may be considered, based on monitoring for methadone withdrawal symptoms..

Ritonavir, a component of atazanavir and ritonavir tablets, may increase the concentrations of these drugs.

A dose decrease may be needed for these drugs when co-administered with atazanavir and ritonavir tablets.

Coadministration with atazanavir has not been studied but may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances, and priapism.

***Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH):***

Use of REVATIO® (sildenafil) for the treatment of pulmonary hypertension (PAH) :

Use of REVATIO® (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 ADCIRCA® (tadalafil) with atazanavir:

Coadministration of ADCIRCA® in patients on atazanavir (with or without ritonavir):

- For patients receiving atazanavir (with or without ritonavir) for at least one

® at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability.

Coadministration of atazanavir (with or without ritonavir) in patients on ADCIRCA® :

- Avoid the use of ADCIRCA® when starting atazanavir (with or without ritonavir). Stop ADCIRCA® at least 24 hours before starting atazanavir (with or without ritonavir). At least one week after starting atazanavir (with or without ritonavir), resume ADCIRCA® at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability.

***Use of PDE5 inhibitors for erectile dysfunction:***

Use VIAGRA® (sildenafil) with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events.

Use CIALIS® (tadalafil) with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events.

***Atazanavir/ritonavir:*** Use LEVITRA® (vardenafil) with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events.

***Atazanavir:*** Use LEVITRA® (vardenafil) with caution at reduced doses of no more than 2.5 mg every 24 hours with increased monitoring for adverse events.

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

*Proton-pump inhibitors:*  
omeprazole

↓ atazanavir

*Sedative/hypnotics:*  
 Buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem      ↑ sedative/hypnotics

*Sedative/hypnotics:*  
 Parenteral midazolam      ↑ midazolam

*Stimulant:* methamphetamine      ↑ methamphetamine

of resistance.

***In treatment-naïve 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:***

Proton-pump inhibitors should not be used in treatment-experienced patients receiving atazanavir.

A dose decrease may be needed for these drugs when co-administered with ritonavir, a component of Atazanavir Sulfate and Ritonavir Tablets.

Concomitant use of parenteral midazolam with Atazanavir Sulfate and Ritonavir Tablets 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 Sulfate and Ritonavir Tablets is CONTRAINDICATED.

Ritonavir, a component of atazanavir and rionavir tablets, may increase methamphetamine concentrations.

Use with caution. A dose decrease of methamphetamine may be needed when co-administered with atazanavir and ritonavir tablets.

- a. For magnitude of interactions see *Clinical Pharmacology, Tables 10 and 11 (12.3)*.
- b. See *Contraindications (4), Table 1* for orally administered midazolam.
- c. In combination with atazanavir 300 mg and ritonavir 100 mg once daily.
- d. In combination with atazanavir 400 mg once daily.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Atazanavir, component of Atazanavir Sulfate and Ritonavir Tablets

#### Pregnancy Category B

## **Risk Summary**

Atazanavir, a component of Atazanavir Sulfate and Ritonavir Tablets, has been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate. However, because the studies in humans cannot rule out the possibility of harm, Atazanavir Sulfate and Ritonavir Tablets should be used during pregnancy only if clearly needed.

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

Hyperbilirubinemia occurs frequently in patients who take atazanavir, including pregnant women. All infants, including neonates exposed to atazanavir in-utero, should be monitored for the development of severe hyperbilirubinemia during the first few days of life.

## **Clinical Considerations**

### *Dosing During Pregnancy and the Postpartum Period:*

- Atazanavir Sulfate and Ritonavir Tablets should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir and ritonavir(?).
- 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 *Dosage and Administration* (2, 2.2) and *Clinical Pharmacology* (12.3).]

### ***Human Data***

***Clinical Trials:*** In clinical trial AI424-182, atazanavir/ritonavir (300/100 mg or 400/100 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 <50 copies/mL at time of

delivery. Six of 20 (30%) women on atazanavir/ritonavir 300 mg/100 mg and 13 of 21 (62%) women on atazanavir/ritonavir 400/100 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 clinical trial 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:** As of January 2010, the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 635 exposures to atazanavir-containing regimens (425 exposed in the first trimester and 160 and 50 exposed in second and third trimester, respectively). Birth defects occurred in 9 of 393 (2.3%) live births (first trimester exposure) and 5 of 212 (2.4%) live births (second/third trimester exposure). Among pregnant women in the U.S. reference population, the

background rate of birth defects is 2.7%. There was no association between atazanavir and overall birth defects observed in the APR.

### ***Pharmacokinetics of Atazanavir in Pregnancy***

[See *Clinical Pharmacology (12.3)*.]

### ***Animal Data***

In animal reproduction studies, there was no evidence of 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 body weight loss or weight gain suppression in the animal offspring with maternal drug exposure (AUC) 1.3 times the human exposure at this clinical dose. However, maternal toxicity also occurred at this exposure level.

## **8.3 Nursing Mothers**

**The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.** It is not known whether atazanavir or ritonavir is present in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are taking Atazanavir Sulfate and Ritonavir Tablets.**

## **8.4 Pediatric Use**

The safety, activity, and pharmacokinetic profiles of atazanavir sulfate, a component of Atazanavir Sulfate and Ritonavir Tablets, in pediatric patients ages 3 months to less than 6 years have not been established.

The safety, pharmacokinetic profile, and virologic response of atazanavir sulfate were evaluated in pediatric patients in an open-label, multicenter clinical trial PACTG 1020A [see *Clinical Pharmacology (12.3)* and *Clinical Studies (14.3)*]. The safety profile in pediatric patients was generally similar to that observed in adults [see *Adverse Reactions*

(6.2)]. Please see *Dosage and Administration (2.1)* for dosing recommendations for pediatric patients 6 years of age and older.

In HIV-infected patients age greater than 1 month to 21 years, the antiviral activity and adverse event profile of ritonavir, a component of Atazanavir Sulfate and Ritonavir Tablets, seen during clinical trials and through postmarketing 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<sub>max</sub> and AUC, a dose adjustment based upon age is not recommended. In addition, Atazanavir Sulfate and Ritonavir Tablets is a fixed-dose combination that cannot be adjusted. In general, appropriate caution should be exercised in the administration and monitoring of Atazanavir Sulfate and Ritonavir Tablets, 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, a component of Atazanavir Sulfate and Ritonavir Tablets, was performed in young (n=29; 18–40 years) and elderly (n=30; ≥65 years) healthy subjects. There were no clinically important pharmacokinetic differences observed due to age or gender.

### **8.7 Impaired Renal Function**

In healthy subjects, the renal elimination of unchanged atazanavir, a component of Atazanavir Sulfate and Ritonavir Tablets, was approximately 7% of the administered dose. Atazanavir has been studied in adult subjects with severe renal impairment (n=20), including those on hemodialysis, at multiple doses of 400 mg once daily. The mean atazanavir C<sub>max</sub> was 9% lower, AUC was 19% higher, and C<sub>min</sub> 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<sub>max</sub>, AUC, and C<sub>min</sub> were approximately 25 to 43% lower compared to subjects with normal renal function. The mechanism of this decrease is unknown. Atazanavir Sulfate and Ritonavir Tablets, should not be administered to HIV-treatment-experienced patients with end stage renal disease managed with hemodialysis. [See *Dosage and Administration (2.3)*.]

### **8.8 Impaired Hepatic Function**

Atazanavir, a component of Atazanavir Sulfate and Ritonavir Tablets, is metabolized and eliminated primarily by the liver. Atazanavir has been studied in adult subjects with moderate to severe hepatic impairment (14 Child-Pugh B and 2 Child-Pugh C subjects) after a single 400-mg dose. The mean AUC(0-∞) was 42% greater in subjects with impaired hepatic function than in healthy volunteers. The mean half-life of atazanavir in hepatically impaired subjects was 12.1 hours compared to 6.4 hours in healthy volunteers. Increased concentrations of atazanavir are expected in patients with moderately or severely impaired hepatic function. The pharmacokinetics or safety of atazanavir in combination with ritonavir has not been studied in subjects with severe hepatic impairment. Atazanavir Sulfate and Ritonavir Tablets should not be administered to patients with hepatic impairment. [See *Dosage and Administration (2.4)* and *Warnings and Precautions (5.5)*.]

## **10 OVERDOSAGE**

Atazanavir sulfate:

Human experience of acute overdose with atazanavir, a component of Atazanavir Sulfate and Ritonavir Tablets, is limited. Single doses up to 1200 mg have been taken by healthy volunteers without symptomatic untoward effects. A single self-administered overdose of 29.2 g of atazanavir in an HIV-infected patient (73 times the 400-mg recommended dose) was associated with asymptomatic bifascicular block and PR interval prolongation. These

events resolved spontaneously. At high doses that lead to high drug exposures, jaundice due to indirect (unconjugated) hyperbilirubinemia (without associated liver function test changes) or PR interval prolongation may be observed. [See *Warnings and Precautions* (5.2, 5.4) and *Clinical Pharmacology* (12.2).]

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

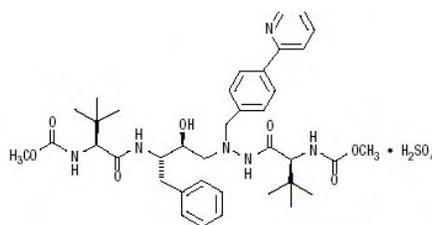
Treatment of overdose with Atazanavir Sulfate and Ritonavir Tablets consists of general supportive measures including monitoring of vital signs and ECG, and observation of the clinical status of the patient. There is no specific antidote for overdose with atazanavir and ritonavir. If indicated, elimination 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 Sulfate and Ritonavir Tablets, 300 mg/100 mg

Atazanavir sulfate is an azapeptide inhibitor of HIV-1 protease.

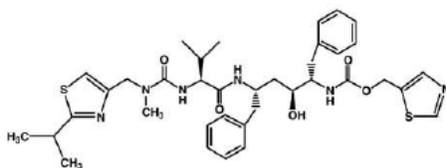
The chemical name for atazanavir sulfate is (3*S*,8*S*,9*S*,12*S*)-3,12-Bis(1,1-dimethylethyl)-8hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13pentaazatetradecanedioic acid dimethyl ester, sulfate (1:1). Its molecular formula is C<sub>38</sub>H<sub>52</sub>N<sub>6</sub>O<sub>7</sub>•H<sub>2</sub>SO<sub>4</sub>, 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 (4–5 mg/mL, free base equivalent) with the pH of a saturated solution in water being about 1.9 at 24 ± 3° C.

Ritonavir is an inhibitor of HIV protease with activity against the Human Immunodeficiency Virus (HIV).

Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5*S*-(5*R*\*,8*R*\*,10*R*\*,11*R*\*)]. Its molecular formula is C<sub>37</sub>H<sub>48</sub>N<sub>6</sub>O<sub>5</sub>S<sub>2</sub>, 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 a bilayer capsule-shaped biconvex tablet. The tablet has one plain layer with a pale yellow to yellow color and one debossed layer with white to off-white color and "M777" markings. Each tablet contains 300 mg of atazanavir, in the form of atazanavir sulfate, and 100 mg of ritonavir. In addition to the active ingredients, each tablet contains: lactose monohydrate, crospovidone, microcrystalline cellulose, magnesium stearate, copovidone, sorbitan monolaurate, methylene chloride, colloidal silicon dioxide, sodium chloride, sodium stearyl fumarate, corn starch, and sorbitol. The tablets are film coated with a clear coat containing hypromellose and polyethylene glycol.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

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

### **12.2 Pharmacodynamics**

#### **Atazanavir:**

#### **Effects on Electrocardiogram**

Concentration- and dose-dependent prolongation of the PR interval in the electrocardiogram has been observed in healthy volunteers receiving atazanavir, a component of Atazanavir Sulfate and Ritonavir Tablets. In a placebo-controlled study (AI424-076), the mean ( $\pm$ SD) maximum change in PR interval from the predose value was 24 ( $\pm$ 15) msec following oral dosing with 400 mg of atazanavir (n=65) compared to 13 ( $\pm$ 11) msec following dosing with placebo (n=67). The PR interval prolongations in this study were asymptomatic. There is limited information on the potential for a pharmacodynamic interaction in humans between atazanavir and other drugs that prolong the PR interval of the 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 and 800 mg were compared with placebo; there was no concentration-dependent effect of atazanavir on the QTc interval (using Fridericia's correction). In 1793 HIV-infected patients receiving antiretroviral

regimens, QTc prolongation was comparable in the atazanavir and comparator regimens. No atazanavir-treated healthy subject or HIV-infected patient in clinical trials had a QTc interval >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).]

### 12.3 Pharmacokinetics

Atazanavir: The pharmacokinetics of atazanavir, a component of Atazanavir Sulfate and Ritonavir Tablets, were evaluated in healthy adult volunteers and in HIV-infected patients after administration of atazanavir 400 mg once daily and after administration of atazanavir 300 mg with ritonavir 100 mg once daily (see Table 9).

**Table 9: Steady-State Pharmacokinetics of Atazanavir in Healthy Subjects or HIV-Infected Patients in the Fed State**

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

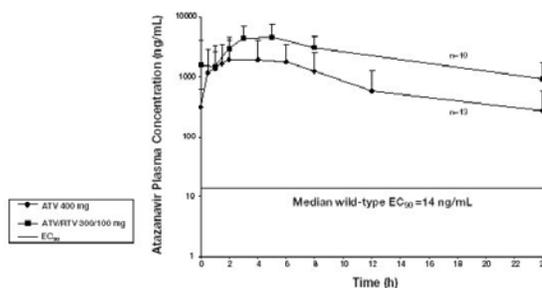
a n=26.

b n=12.

Figure 1 displays the mean plasma concentrations of atazanavir at steady state after atazanavir 400 mg once daily (as two 200-mg capsules) with a light meal and after atazanavir

300 mg (as two 150-mg capsules) with ritonavir 100 mg once daily with a light meal in HIV-infected adult patients.

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



### Absorption

Atazanavir: 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 increases bioavailability and reduces pharmacokinetic variability.

### Distribution

Atazanavir: Atazanavir is 86% bound to human serum proteins and protein binding is independent of concentration. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively). In a multiple-dose study in HIV-infected patients dosed with atazanavir 400 mg once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid and semen. The cerebrospinal fluid/plasma ratio for atazanavir (n=4) ranged between 0.0021 and 0.0226 and seminal fluid/plasma ratio (n=5) ranged between 0.11 and 4.42.

### Metabolism

Atazanavir: 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**

Atazanavir: Following a single 400-mg dose of <sup>14</sup>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.

### **Effects on Electrocardiogram**

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 (5.6)*].

### **Special Populations**

#### **Pediatrics**

The pharmacokinetic parameters for atazanavir, a component of Atazanavir Sulfate and Ritonavir Tablets, at steady state in pediatric patients were predicted by a population pharmacokinetic model and are summarized in Table 10 by weight ranges that correspond to the recommended doses. [See *Dosage and Administration (2.2)*.]

**Table 10: Predicted Steady-State Pharmacokinetics of Atazanavir (capsule formulation) with ritonavir in HIV-Infected Pediatric Patients**

Body Weight (range in kg)	atazanavir/ritonavir Dose (mg)	C <sub>max</sub> ng/mL Geometric Mean (CV%)	AUC ng•h/mL Geometric Mean (CV%)	C <sub>min</sub> ng/mL Geometric Mean (CV%)
15 – <20	150/100	5213 (78.7%)	42902 (77.0%)	504 (99.5%)
20 – <40	200/100	4954 (81.7%)	42999 (78.5%)	562 (98.9%)
≥40	300/100	5040 (84.6%)	46777 (80.6%)	691 (98.5%)

### Pregnancy

Atazanavir and ritonavir: The pharmacokinetic data from HIV-infected pregnant women receiving Atazanavir Capsules with ritonavir are presented in Table 11.

**Table 11: Steady-State Pharmacokinetics of Atazanavir with ritonavir in HIV-Infected Pregnant Women in the Fed State**

Pharmacokinetic Parameter	Atazanavir 300 mg with ritonavir 100 mg		
	2nd Trimester (n=5 <sup>a</sup> )	3rd Trimester (n=20)	Postpartum <sup>b</sup> (n=34)
C <sub>max</sub> 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 <sub>min</sub> ng/mL <sup>c</sup>	538.70	668.48	1462.59
Geometric mean (CV%)	(46)	(50)	(45)

<sup>a.</sup> Available data during the 2nd trimester are limited

<sup>b.</sup> Atazanavir peak concentrations and AUCs were found to be approximately 28–43% higher during the postpartum period (4–12 weeks) than those observed historically in HIV-infected, non-pregnant patients. Atazanavir plasma trough concentrations were approximately 2.2-fold higher during the postpartum period when compared to those observed historically in HIV-infected, non-pregnant patients.

<sup>c.</sup> C<sub>min</sub> 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 for Atazanavir

Atazanavir is a metabolism-dependent CYP3A inhibitor, with a K<sub>inact</sub> value of 0.05 to 0.06 min<sup>-1</sup> and K<sub>i</sub> value of 0.84 to 1.0 μM. Atazanavir is also a direct inhibitor for UGT1A1 (K<sub>i</sub>=1.9 μM) and CYP2C8 (K<sub>i</sub>=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 $\beta$ -OH cortisol to cortisol versus baseline, indicating that CYP3A production was not induced.

Drug interaction studies were performed with atazanavir and other drugs likely to be coadministered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of atazanavir on the AUC, C<sub>max</sub>, and C<sub>min</sub> are summarized in Tables 12 and 13. For information regarding clinical recommendations, see *Drug Interactions* (7).

**Table 12: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs<sup>a</sup>**

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 <sub>max</sub>	AUC	C <sub>min</sub>
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)
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) <sup>b</sup>	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)
ddI (enteric-coated capsules) <sup>c</sup> [EC]	400 mg d 8 (fed) (n=34) 400 mg d 19 (fed) (n=31)	400 mg QD, d 2–8 (n=34) 300 mg/ritonavir 100 mg QD, d 9–19 (n=31)	1.03 (0.93, 1.14)	0.99 (0.91, 1.08)	0.98 (0.89, 1.08)
diltiazem	180 mg QD, d 7–11 (n=30) and d 19–23	400 mg QD, d 1–11 (n=30)	1.04 (1.01, 1.07)	1.00 (0.96, 1.03)	0.98 (0.82, 0.92)
efavirenz	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)	1.17 (1.08, 1.27)	1.00 (0.91, 1.10)	0.58 (0.49, 0.69)

famotidine	40 mg BID, d 11–20 (n=14) <sup>d</sup>	(n=14) 300 mg QD/ritonavir 100 mg QD, d 1–10 (n=46), d 11–20d (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 300 mg QD, d 1–10 (am) (n=39), d 11–17 (am) (simultaneous administration with am famotidine) (n=18) <sup>e,f</sup>	0.91 (0.84, 0.99)	0.90 (0.82, 0.98)
	40 mg QD (pm), d 18–24 (n=20)	300 mg QD/ritonavir 100 mg QD/tenofovir 300 mg QD, d 1–10 (am) (n=39), d 18–24 (am) (12 h after pm famotidine) (n=20) <sup>f</sup>	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 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) <sup>f</sup>	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)
fluconazole	200 mg QD, d 11–20 (n=29)	300 mg QD/ritonavir 100 mg QD, d 1–10 (n=19), d 11–20 (n=29)	1.03 (0.95, 1.11)	1.04 (0.95, 1.13)	0.98 (0.85, 1.13)
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 <sup>g,h</sup>	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) <sup>i</sup>	0.72 (0.60, 0.86)	0.58 (0.48, 0.71)	0.28 (0.20, 0.40)
		300 mg QD/ritonavir 100 mg QD, d 14–23 (n=23) <sup>i</sup>	1.02 (0.85, 1.24)	0.81 (0.65, 1.02)	0.41 (0.27, 0.60)
omeprazole	40 mg QD, d 11–20 (n=15) <sup>j</sup>	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)	300 mg QD/ritonavir 100	0.61 (0.46, 0.81)	0.58 (0.44, 0.75)	0.54 (0.41, 0.71)

	(n=13)	mg QD, d 7–16 (pm) (n=27), d 17– 23 (pm) (n=13) <sup>k,l</sup>			
	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) <sup>m,n</sup>	0.69 (0.58, 0.83)	0.70 (0.57, 0.86)	0.69 (0.54, 0.88)
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)
tenofovir <sup>o</sup>	300 mg QD, d 9–16 (n=34) 300 mg QD, d 15–42 (n=10)	400 mg QD, d 2–16 (n=34) 300 mg/ritonavir 100 mg QD, d 1–42 (n=10)	0.79 (0.73, 0.86) 0.72 <sup>p</sup> (0.50, 1.05)	0.75 (0.70, 0.81) 0.75 <sup>p</sup> (0.58, 0.97)	0.60 (0.52, 0.68) 0.77 <sup>p</sup> (0.54, 1.10)

a. Data provided are under fed conditions unless otherwise noted.

b. All drugs were given under fasted conditions.

c. 400 mg ddI EC and atazanavir were administered together with food on Days 8 and 19.

d. 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.

e. 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 300 mg.

f. Atazanavir/ritonavir/tenofovir was administered after a light meal.

g. Study was conducted in HIV-infected individuals.

h. 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.

i. 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.

j. Omeprazole 40 mg was administered on an empty stomach 2 hours before atazanavir.

k. 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.

l. 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).

m. 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.

n. 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).

o. Note that similar results were observed in studies where administration of tenofovir 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<sup>o</sup>). The geometric mean values of atazanavir pharmacokinetic parameters when coadministered with ritonavir and tenofovir were:  $C_{max}$  = 3190 ng/mL, AUC = 34459 ng•h/mL, and  $C_{min}$  = 491 ng/mL. Study was conducted in HIV-infected individuals.

**Table 13: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Atazanavir<sup>a</sup>**

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 <sub>max</sub>	AUC	C <sub>min</sub>
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)
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)
didanosine (ddI) (buffered tablets) plus stavudine (d4T) <sup>b</sup>	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose (n=31)	400 mg x 1 dose simultaneous with ddI and d4T (n=31)	ddI: 0.92 (0.84, 1.02) d4T: 1.08 (0.96, 1.22)	ddI: 0.98 (0.92, 1.05) d4T: 1.00 (0.97, 1.03)	NA d4T: 1.04 (0.94, 1.16)
ddI (entericcoated [EC] capsules) <sup>c</sup>	400 mg d 1 (fasted), d 8 (fed) (n=34) 400 mg d 1 (fasted), d 19 (fed) (n=31)	400 mg QD, d 2–8 (n=34) 300 mg QD/ritonavir 100 mg QD, d 9–19 (n=31)	0.64 (0.55, 0.74) 0.62 (0.52, 0.74)	0.66 (0.60, 0.74) 0.66 (0.59, 0.73)	1.13 (0.91, 1.41) 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 <sup>d</sup>	Ortho Tri-Cyclen® QD, d 1–28 (n=18), then Ortho Tri-Cyclen® LO QD, d 29–42 <sup>e</sup> (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 <sup>f</sup> : 1.68 (1.51, 1.88)	ethinyl estradiol: 0.81 (0.75, 0.87) 17-deacetyl norgestimate <sup>f</sup> : 1.85 (1.67, 2.05)	ethinyl estradiol: 0.63 (0.55, 0.71) 17-deacetyl norgestimate <sup>f</sup> : 2.02 (1.77, 2.31)
fluconazole	200 mg QD, d 1–10 (n=11) and 200 mg QD, d 11–20 (n=29)	300 mg QD/ritonavir 100 mg QD, d 11–20 (n=29)	1.05 (0.99, 1.10)	1.08 (1.02, 1.15)	1.07 (1.00, 1.15)
methadone	Stable maintenance dose, d 1–15 (n=16)	400 mg QD, d 2–15 (n=16)	(R)-methadone <sup>g</sup> 0.91 (0.84, 1.0) total: 0.85 (0.78, 0.93)	(R)-methadone <sup>g</sup> 1.03 (0.95, 1.10) total: 0.94 (0.87, 1.02)	(R)-methadone <sup>g</sup> 1.11 (1.02, 1.20) total: 1.02 (0.93, 1.12)
nevirapine <sup>h,i</sup>	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 <sup>j</sup>	40 mg single dose, d	400 mg QD, d 1–12	1.24	1.45	NA

rifabutin	7 and d 20 (n=16) 300 mg QD, d 1–10 then 150 mg QD, d 11–20 (n=3)	(n=16) 600 mg QD, d 11– 20 (n=3)	(1.04, 1.47) 1.18 (0.94, 1.48) 25-O- desacetylrifab utin: 8.20 (5.90, 11.40)	(1.20, 1.76) 2.10 (1.57, 2.79) 25-O- desacetylrifabuti n: 22.01 (15.97, 30.34)	3.43 (1.98, 5.96) 25-O- desacetylrifab utin: 75.6 (30.1, 190.0)
Rosiglitazone <sup>k</sup>	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
tenofovir	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) <sup>l</sup>	1.34 (1.20, 1.51)	1.37 (1.30, 1.45)	1.29 (1.21, 1.36)
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)	amivudine: 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. All drugs were given under fasted conditions.

c. 400 mg ddI EC and atazanavir were administered together with food on Days 8 and 19.

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<sub>max</sub>, AUC, and C<sub>min</sub> were 1.17 (1.03, 1.34), 1.13 (1.05, 1.22), and 0.88 (0.77, 1.00), respectively.

e. All subjects were on a 28 day lead-in period; one full cycle of Ortho Tri-Cyclen®. Ortho Tri-Cyclen® contains 35 mcg of ethinyl estradiol. Ortho Tri-Cyclen® LO contains 25 mcg of ethinyl estradiol. Results were dose normalized to an ethinyl estradiol dose of 35 mcg.

f. 17-deacetyl norgestimate is the active component of norgestimate.

g. (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. Rosiglitazone used as a probe substrate for CYP2C8.

l. Administration of tenofovir 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 an inhibitor of the metabolism of many CYP3A-metabolized drugs and also a peptidomimetic inhibitor of the HIV-1 protease..

### **Antiviral Activity in Cell Culture**

Atazanavir: Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC50) 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 EC50 values above the EC50 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, zalcitabine, and zidovudine), the HIV-1 fusion inhibitor enfuvirtide, and two compounds used in the treatment of viral hepatitis, adefovir and ribavirin, without enhanced cytotoxicity.

### **Resistance**

Atazanavir:

*In Cell Culture:* 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.

*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 14.

**Table 14: Summary of Virologic Failures<sup>a</sup> at Week 96 in Study AI424-089: Comparison of Ritonavir Boosted atazanavir vs. Unboosted atazanavir: Randomized Patients**

	Atazanavir 300 mg + ritonavir 100 mg (n=95)	Atazanavir 400 mg (n=105)
Virologic Failure ( $\geq 50$ 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%) <sup>b</sup>	4/17 (24%) <sup>b</sup>
Virologic Failure Isolates with I50L Emergence at Week 96 <sup>c</sup>	0/5 (0%) <sup>b</sup>	2/17 (12%) <sup>b</sup>
Virologic Failure Isolates with Lamivudine Resistance at Week 96	2/5 (40%) <sup>b</sup>	11/17 (65%) <sup>b</sup>

<sup>a.</sup> 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.

<sup>b.</sup> Percentage of Virologic Failure Isolates with genotypic and phenotypic data.

<sup>c.</sup> 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  $\geq 400$  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 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**

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 >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.

### Baseline Genotype/Phenotype and Virologic Outcome Analyses

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 Study AI424-045 is shown in Table 15.

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 1–2 PI substitutions, including one of these substitutions.

**Table 15: 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 <sup>a</sup>	Virologic Response = HIV ATV/RTV (n=110)	RNA <400 copies/mL <sup>b</sup> LPV/RTV (n=113)
<b>3 or more primary PI substitutions including:<sup>c</sup></b>		
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)
<b>Number of baseline primary PI substitutions<sup>a</sup></b>		
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)
<sup>a.</sup> Primary substitutions include any change at D30, V32, M36, M46, I47, G48, I50, I54, A71, G73, V77, V82, I84, N88, and L90. <sup>b.</sup> Results should be interpreted with caution because the subgroups were small. <sup>c.</sup> There were insufficient data (n<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 16). 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 16: Baseline Phenotype by Outcome, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis**

Baseline Phenotype <sup>a</sup>	Virologic Response = HIV	RNA <400 copies/mLb
	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)
<sup>a.</sup> Fold change susceptibility in cell culture relative to the wild-type reference. <sup>b.</sup> Results should be interpreted with caution because the subgroups were small.		

## 13 NONCLINICAL TOXICOLOGY

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### 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.

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).

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:

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100 or 200 mg/kg/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/kg/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. However, ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of *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.

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/emtricitabine in HIV-1 infected treatment naive subjects.* Study AI424-138 is a 96-week open-label, randomized, multicenter study, comparing atazanavir (300 mg once daily) with ritonavir (100 mg once daily) to lopinavir with ritonavir (400/100 mg twice daily), each in combination with fixed-dose tenofovir with emtricitabine (300/200 mg once daily), in 878 antiretroviral treatment-naive treated patients. Patients had a mean age of 36 years (range: 19–72), 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<sup>3</sup> (range: 2 to 810 cells/mm<sup>3</sup>) and the mean baseline plasma HIV-1 RNA level was 4.94 log<sub>10</sub> copies/mL (range: 2.60 to 5.88 log<sub>10</sub> copies/mL). Treatment response and outcomes through Week 96 are presented in Table 17.

**Table 17: Outcomes of Treatment Through Week 48 (Study AI424-138)**

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

<sup>a.</sup> As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

<sup>b.</sup> Patients achieved confirmed HIV RNA <50 copies/mL at Week 48. Roche Amplicor<sup>®</sup>, v1.5 ultra-sensitive assay.

<sup>c.</sup> Pre-specified ITT analysis using as-randomized cohort: ATV/RTV 78% and LPV/RTV 76% [difference estimate: 1.7 (95% confidence interval: -3.8, 7.1)].

<sup>d.</sup> Pre-specified ITT analysis at Week 96 using as-randomized cohort: ATV/RTV 74% and LPV/RTV

- 
- e. Includes viral rebound and failure to achieve confirmed HIV RNA <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  $\geq 100,000$  copies/mL) was comparable for the atazanavir/ritonavir (164 of 223 patients, 74%) and lopinavir/ritonavir (161 of 222 patients, 73%) arms. The median increase from baseline in CD4+ cell count was 191 cells/mm<sup>3</sup> for the atazanavir/ritonavir arm and 200 cells/mm<sup>3</sup> 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 + 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 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<sup>3</sup> (range: 14 to 154<sup>3</sup> cells/mm<sup>3</sup>) and the mean baseline plasma HIV-1 RNA level was 4.4 log<sub>10</sub> copies/mL (range: 2.6 to 5.88 log<sub>10</sub> copies/mL).

Treatment outcomes through Week 48 for the atazanavir/ritonavir and lopinavir/ritonavir treatment arms are presented in Table 18. 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. [See *Clinical Pharmacology, Tables 13 (12.4).*]

**Table 18: Outcomes of Treatment Through Week 48 in Study AI424-045 (Patients with Prior Antiretroviral Experience)**

<b>Outcome</b>	<b>atazanavir 300 mg + ritonavir 100 mg once daily + tenofovir + 1 NRTI (n=119)</b>	<b>lopinavir/ritonavir (400/100 mg) twice daily + tenofovir + 1 NRTI (n=118)</b>	<b>Difference<sup>a</sup> (atazanavir/lopinavir/ ritonavir) (CI)</b>
HIV RNA Change from Baseline (log <sub>10</sub> copies/mL) <sup>b</sup>	-1.58	-1.70	+0.12 <sup>c</sup> (-0.17, 0.41)
CD4+ Change from Baseline (cells/mm <sup>3</sup> ) <sup>d</sup>	116	123	-7 (-67, 52)
Percent of Patients Responding <sup>e</sup>			
HIV RNA <400 copies/mL <sup>b</sup>	55%	57%	-2.2% (-14.8%, 10.5%)
HIV RNA <50 copies/mL <sup>b</sup>	38%	45%	-7.1% (-19.6%, 5.4%)

<sup>a.</sup> 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.

<sup>b.</sup> Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.5.

<sup>c.</sup> Protocol-defined primary efficacy outcome measure.

<sup>d.</sup> Based on patients with baseline and Week 48 CD4+ cell count measurements (atazanavir/ritonavir, n=85; lopinavir/ritonavir, n=93).

<sup>e.</sup> Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL (<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.

In Study AI424-045, the mean change from baseline in plasma HIV-1 RNA for atazanavir 400 mg with saquinavir (n=115) was -1.55 log<sub>10</sub> copies/mL, and the time-averaged difference in change in HIV-1 RNA levels versus lopinavir/ritonavir was 0.33. The corresponding mean increase in CD4+ cell count was 72 cells/mm<sup>3</sup>. Through 48 weeks of treatment, the proportion of patients in this treatment arm with plasma HIV-1 RNA <400 (<50) copies/mL was 38% (26%). In this study, coadministration of atazanavir and saquinavir did not provide adequate efficacy [see *Drug Interactions* (7)].

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

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

### **14.3 Pediatric Patients**

Assessment of the pharmacokinetics, safety, tolerability, and efficacy of atazanavir, a component of Atazanavir Sulfate and Ritonavir Tablets, is based on data from the open-label, multicenter clinical trial PACTG 1020A conducted in patients from 3 months to 21 years of age. In this study, 193 patients (86 antiretroviral-naïve and 107 antiretroviral-experienced) received once daily atazanavir, with or without ritonavir, in combination with two NRTIs.

One-hundred and 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-naïve and -experienced patients with HIV RNA <400 copies/mL at Week 96 were 51% (22/43) and 34% (21/62), respectively. The overall proportions of antiretroviral-naïve and -experienced patients with HIV RNA <50 copies/mL at Week 96 were 47% (20/43) and 24% (15/62), respectively. The median increase from baseline in absolute CD4 count at 96 weeks of therapy was 335 cells/mm<sup>3</sup> in antiretroviral-naïve patients and 220 cells/mm<sup>3</sup> in antiretroviralexperienced patients.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

Atazanavir Sulfate and Ritonavir Tablets are available in the following package sizes:

Atazanavir Sulfate and Ritonavir Tablets, 300 mg\*/100 mg

Atazanavir Sulfate and Ritonavir Tablets Bilayer, film coated, capsule shaped, biconvex tablet having one layer plain with pale yellow to yellow color and a white to off-white layer debossed with “M777”.

Bottles of 30 tablets (NDC 65015-120-14)

Bottles of 90 tablets (NDC 65015-120-18)

Bottles of 120 tablets (NDC 65015-120-20)

#### Recommended Storage

Store film-coated tablets at 25°C (77°F); excursions permitted to 15°-30°C (59° to 86°F) [see USP controlled room temperature].

*\* Each film-coated tablet contain atazanavir sulfate equivalent to 300 mg of atazanavir and 100 mg of ritonavir*

## 17 PATIENT COUNSELING INFORMATION

*See proposed Patient Labeling.*

A statement to patients and healthcare providers is included on the product’s bottle label:

**ALERT: Find out about medicines that should NOT be taken with Atazanavir Sulfate and Ritonavir Tablets.**

Patients should be informed that atazanavir is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease.

### 17.1 Dosing Instructions

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. 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 sulfate and Ritonavir Tablets must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with

their doctor. If a dose of Atazanavir Sulfate and Ritonavir Tablets is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose. They should pay special attention to accurate administration of their dose to minimize the risk of accidental overdose or underdose of drug.

For their health and the health of others, it is important that they always practice safer sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood. They should also be advised to never re-use or share needles.

### **17.2 Drug Interactions**

Atazanavir Sulfate and Ritonavir Tablets may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, nonprescription medication, or herbal products, particularly St. John's wort.

Patients receiving a PDE5 inhibitor and Atazanavir Sulfate and Ritonavir Tablets should be advised that they may be at an increased risk of PDE5 inhibitor-associated adverse events including hypotension, syncope, visual disturbances, and priapism, and should promptly report any symptoms to their doctor.

Patients should be informed that REVATIO<sup>®</sup> (used to treat pulmonary arterial hypertension) is contraindicated with Atazanavir Sulfate and Ritonavir Tablets and that dose adjustments are necessary when Atazanavir Sulfate and Ritonavir Tablets is used with CIALIS<sup>®</sup>, LEVITRA<sup>®</sup>, or VIAGRA<sup>®</sup> (used to treat erectile dysfunction), or ADCIRCA<sup>®</sup> (used to treat pulmonary arterial hypertension).

If they are receiving estrogen-based hormonal contraceptives a dose adjustment of the oral contraceptive may be needed, or additional or alternate contraceptive measures may need to be used during therapy with Atazanavir Sulfate and Ritonavir Tablets.

### **17.3 Cardiac Conduction Abnormalities**

Patients should be informed that Atazanavir and Ritonavir tablets may produce changes in the electrocardiogram (eg, PR prolongation). Patients should consult their physician if they are experiencing symptoms such as dizziness or lightheadedness, abnormal heart rhythm or loss of consciousness.

#### **17.4 Rash**

Patients should be informed that mild rashes without other symptoms have been reported with Atazanavir Sulfate and Ritonavir Tablets use. Patients should be advised to contact their healthcare provider to determine if treatment should be continued or an alternative antiretroviral regimen used. There have been a few reports of severe skin reactions (eg, Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions). Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by one or more of the following: fever, general malaise, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must discontinue Atazanavir Sulfate and Ritonavir Tablets and seek medical evaluation immediately.

#### **17.5 Hyperbilirubinemia**

Patients should be informed 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. It is unknown whether long-term use of atazanavir will result in a lower incidence of lipodystrophy than with other protease inhibitors.

### **17.7 Hepatic Reactions**

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. Patients should be advised 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. Your patients should let you know of signs and symptoms (nausea, vomiting, and abdominal pain) that might be suggestive of pancreatitis.

### **17.9 Lipid Elevations**

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**

New onset of diabetes or exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported. Patients should be advised 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 ritonavir 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.

## **Patient Information**

### **Atazanavir Sulfate and Ritonavir Tablets**

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

**ALERT: Find out about medicines that should NOT be taken with Atazanavir Sulfate and Ritonavir Tablets.** Read the section “What important information should I know about taking Atazanavir Sulfate and Ritonavir Tablets with other medicines?”

#### **What is Atazanavir Sulfate and Ritonavir Tablets?**

Atazanavir Sulfate and Ritonavir Tablets are a prescription medicine used with other anti-HIV medicines to treat people 6 years of age and older who are infected with the human immunodeficiency virus (HIV). HIV is the virus that causes acquired immune deficiency syndrome (AIDS). Atazanavir Sulfate and Ritonavir Tablets contain a type of anti-HIV medicine called a protease inhibitor. HIV infection destroys CD4+ (T) cells, which are important to the immune system. The immune system helps fight infection. After a large number of (T) cells are destroyed, AIDS develops. Atazanavir Sulfate and Ritonavir Tablets helps to block HIV protease, an enzyme that is needed for the HIV virus to multiply. Atazanavir Sulfate and Ritonavir Tablets may lower the amount of HIV in your blood, help your body keep its supply of CD4+ (T) cells, and reduce the risk of death and illness associated with HIV.

#### **Does Atazanavir Sulfate and Ritonavir Tablets cure HIV or AIDS?**

**Atazanavir Sulfate and Ritonavir Tablets do not cure HIV infection or AIDS.** At present there is no cure for HIV infection. People taking Atazanavir Sulfate and Ritonavir Tablets may still get opportunistic infections or other conditions that happen with HIV infection. Opportunistic infections are infections that develop because the immune

system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections. **It is very important that you see your healthcare provider regularly while taking this medication.**

For your health and the health of others, it is important to always practice safer sex by using a latex or polyurethane condom or other barrier to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

### **Who should not take Atazanavir Sulfate and Ritonavir Tablets?**

#### **Do not take Atazanavir Sulfate and Ritonavir Tablets if you:**

- **are taking certain medicines.** (See “What important information should I know about taking Atazanavir Sulfate and Ritonavir Tablets with other medicines?”) Serious life-threatening side effects or death may happen. Before you take Atazanavir Sulfate and Ritonavir Tablets, 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 Sulfate and Ritonavir Tablets or to any of its ingredients.** The active ingredient is atazanavir sulfate and ritonavir . See the end of this leaflet for a complete list of ingredients in Atazanavir Sulfate and Ritonavir Tablets. 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?**

#### **Tell your healthcare provider:**

- **If you are pregnant or plan to become pregnant.** It is not known if Atazanavir Sulfate and Ritonavir Tablets can harm your unborn baby. Pregnant women have experienced serious side effects when taking Atazanavir Sulfate and Ritonavir Tablets with other HIV medicines called nucleoside analogues. You and your healthcare provider will need to decide if Atazanavir Sulfate and Ritonavir Tablets is right for you.

- **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 breast-feeding.** You should not breast-feed if you are HIV-positive because of the chance of passing HIV to your baby. Also, it is not known if Atazanavir Sulfate and Ritonavir Tablets can pass into your breast milk and if it can harm your baby. If you are a woman who has or will have a baby, talk with 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**, you should tell your doctor before taking Atazanavir Sulfate and Ritonavir Tablets.
- **If you have end stage kidney disease** managed with hemodialysis.
- **If you have diabetes.** See “What are the possible side effects of Atazanavir Sulfate and Ritonavir Tablets?”
- **If you have hemophilia.** See “What are the possible side effects of Atazanavir Sulfate and Ritonavir Tablets?”
- **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 with other medicines?” and “Who should not take Atazanavir Sulfate and Ritonavir Tablets?” Some medicines can cause serious side effects if taken with Atazanavir Sulfate and Ritonavir Tablets.

### **How should I take Atazanavir Sulfate and Ritonavir Tablets?**

- **Take** Atazanavir Sulfate and Ritonavir Tablets **once every day exactly as instructed by your healthcare provider.**
- **Always take** Atazanavir Sulfate and Ritonavir Tablets **with food** (a meal or snack) to help it work better. Swallow the tablets whole. Take Atazanavir Sulfate and Ritonavir Tablets at the same time each day.
- **If you are taking antacids or didanosine (VIDEX<sup>®</sup> or VIDEX<sup>®</sup> EC)**, take Atazanavir Sulfate and Ritonavir Tablets 2 hours before or 1 hour after these medicines.

- **If you are taking medicines for indigestion, heartburn, or ulcers such as AXID<sup>®</sup> (nizatidine), PEPCID AC<sup>®</sup> (famotidine), TAGAMET<sup>®</sup> (cimetidine), ZANTAC<sup>®</sup> (ranitidine), AcipHex<sup>®</sup> (rabeprazole), NEXIUM<sup>®</sup> (esomeprazole), PREVACID<sup>®</sup> (lansoprazole), PRILOSEC<sup>®</sup> (omeprazole), or PROTONIX<sup>®</sup> (pantoprazole),** talk to your healthcare provider.
- **Do not change your dose or stop taking** Atazanavir Sulfate and Ritonavir Tablets **without first talking with your healthcare provider.** It is important to stay under a healthcare provider's care while taking Atazanavir Sulfate and Ritonavir Tablets.
- **When your supply of** Atazanavir Sulfate and Ritonavir Tablets **starts to run low,** get more from your healthcare provider or pharmacy. It is important not to run out of Atazanavir Sulfate and Ritonavir Tablets. The amount of HIV in your blood may increase if the medicine is stopped for even a short time.
- **If you miss a dose of** Atazanavir Sulfate and Ritonavir Tablets, 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 Sulfate and Ritonavir Tablets **or your other anti-HIV medicines.**
- **If you take more than the prescribed dose of** Atazanavir Sulfate and Ritonavir Tablets, call your healthcare provider or poison control center right away.

#### **What are the possible side effects of** Atazanavir Sulfate and Ritonavir Tablets?

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.

**The following side effects have been reported with** Atazanavir Sulfate and Ritonavir Tablets:

- **mild rash** (redness and itching) without other symptoms sometimes occurs in patients taking Atazanavir Sulfate and Ritonavir Tablets, most often in the first few weeks after the medicine is started. Tell your healthcare provider if rash occurs.

- **severe rash:** Rash may develop in association with other symptoms which could be serious and potentially cause death.

**If you develop a rash with any of the following symptoms stop using Atazanavir Sulfate and Ritonavir Tablets and call your healthcare provider right away:**

- shortness of breath
  - general ill feeling or “flu-like” symptoms
  - fever
  - muscle or joint aches
  - conjunctivitis (red or inflamed eyes, like “pink eye”)
  - blisters
  - mouth sores
  - swelling of your face
- 
- **yellowing of the skin or 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).** Call your healthcare provider right away if you get dizzy or lightheaded. These could be symptoms of a heart problem.
  - **diabetes and high blood sugar (hyperglycemia)** sometimes happen in patients taking protease inhibitor medicines like atazanavir sulfate and ritonavir. Some patients had diabetes before taking protease inhibitors while others did not. Some patients may need changes in their diabetes medicine.
  - **if you have liver disease** including hepatitis B or C, your liver disease may get worse when you take anti-HIV medicines like Atazanavir Sulfate and Ritonavir Tablets.
  - **kidney stones** have been reported in patients taking Atazanavir Sulfate and Ritonavir Tablets. If you develop signs or symptoms of kidney stones (pain in your side, blood in your urine, pain when you urinate) tell your healthcare provider promptly.

- **some patients with hemophilia** have increased bleeding problems with protease inhibitors like atazanavir sulfate and ritonavir.
- **changes in body fat.** These changes may include an increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.
- **immune reconstitution syndrome.** In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started.
- **Some patients develop serious problems with their pancreas which may cause death.** Tell your doctor if you have nausea, vomiting, or stomach pain.
- **Increases in triglycerides and cholesterol**

Other common side effects of Atazanavir Sulfate and Ritonavir Tablets taken with other anti-HIV medicines include feeling weak; nausea; headache; stomach pain; vomiting; diarrhea; loss of appetite; depression; fever; dizziness; trouble sleeping; numbness, tingling, or burning of hands or feet; and muscle pain.

**Gallbladder disorders** (which may include gallstones and gallbladder inflammation) have been reported in patients taking Atazanavir Sulfate and Ritonavir Tablets.

**What important information should I know about taking Atazanavir Sulfate and Ritonavir Tablets with other medicines?**

**Do not take Atazanavir Sulfate and Ritonavir Tablets if you take the following medicines (not all brands may be listed; tell your healthcare provider about all the medicines you take). Atazanavir Sulfate and Ritonavir Tablets may cause serious, life-threatening side effects or death when used with these medicines.**

- Ergot medicines: dihydroergotamine, ergonovine, ergotamine, and methylergonovine such as CAFERGOT<sup>®</sup>, MIGRANAL<sup>®</sup>, D.H.E. 45<sup>®</sup>, ergotrate maleate, METHERGINE<sup>®</sup>, and others (used for migraine headaches).
- ORAP<sup>®</sup> (pimozide, used for Tourette’s disorder).

- PROPULSID<sup>®</sup> (cisapride, used for certain stomach problems).
- Triazolam, also known as HALCION<sup>®</sup> (used for insomnia).
- Midazolam, also known as VERSED<sup>®</sup> (used for sedation), when taken by mouth.

**Do not take the following medicines with Atazanavir Sulfate and Ritonavir Tablets because of possible serious side effects:**

- CAMPTOSAR<sup>®</sup> (irinotecan, used for cancer).
- CRIXIVAN<sup>®</sup> (indinavir, used for HIV infection).
- Cholesterol-lowering medicines MEVACOR<sup>®</sup> (lovastatin) or ZOCOR<sup>®</sup> (simvastatin).
- UROXATRAL<sup>®</sup> (alfuzosin, used to treat benign enlargement of the prostate).
- REVATIO<sup>®</sup> (sildenafil, used to treat pulmonary arterial hypertension).
- Medicines for abnormal heart rhythm: CORDARONE<sup>®</sup> (amiodarone), lidocaine, quinidine (also known as CARDIOQUIN<sup>®</sup>, QUINIDEX<sup>®</sup>, and others).
- VASCOR<sup>®</sup> (bepridil, used for chest pain).

**Do not take the following medicines with Atazanavir Sulfate and Ritonavir Tablets because they may lower the amount of drug in your blood.** This may lead to an increased HIV viral load. Resistance to atazanavir sulfate and ritonavir or cross-resistance to other HIV medicines may develop:

- Rifampin (also known as RIMACTANE<sup>®</sup>, RIFADIN<sup>®</sup>, RIFATER<sup>®</sup>, or RIFAMATE<sup>®</sup>, used for tuberculosis).
- St. John's wort (*Hypericum perforatum*), an herbal product sold as a dietary supplement, or products containing St. John's wort.
- SUSTIVA<sup>®</sup> (efavirenz, used for HIV infection).
- VIRAMUNE<sup>®</sup> (nevirapine, used for HIV infection).

**The following medicines are not recommended with Atazanavir Sulfate and Ritonavir Tablets:**

- SEREVENT DISKUS<sup>®</sup> (salmeterol) and ADVAIR<sup>®</sup> (salmeterol with fluticasone), used to treat asthma, emphysema/chronic obstructive pulmonary disease also known as COPD.

**The following medicines may require your healthcare provider to monitor your therapy more closely (for some medicines a change in the dose or dose schedule may be needed):**

- CIALIS<sup>®</sup> (tadalafil), LEVITRA<sup>®</sup> (vardenafil), or VIAGRA<sup>®</sup> (sildenafil), used to treat erectile dysfunction. ATAZANAVIR SULPHATE may increase the chances of serious side effects that can happen with CIALIS, LEVITRA, or VIAGRA. Do not use CIALIS, LEVITRA, or VIAGRA while you are taking Atazanavir sulphate unless your healthcare provider tells you it is okay.
- ADCIRCA<sup>®</sup> (tadalafil) or TRACLEER<sup>®</sup> (bosentan), used to treat pulmonary arterial hypertension.
- LIPITOR<sup>®</sup> (atorvastatin) or CRESTOR<sup>®</sup> (rosuvastatin). There is an increased chance of serious side effects if you take Atazanavir sulphate with this cholesterol-lowering medicine.
- MYCOBUTIN<sup>®</sup> (rifabutin, an antibiotic used to treat tuberculosis).
- BUPRENEX<sup>®</sup>, SUBUTEX<sup>®</sup>, SUBOXONE<sup>®</sup>, (buprenorphine or buprenorphine/naloxone, used to treat pain and addiction to narcotic painkillers).
- COUMADIN<sup>®</sup> (warfarin).
- Tricyclic antidepressants such as ELAVIL<sup>®</sup> (amitriptyline), NORPRAMIN<sup>®</sup> (desipramine), SINEQUAN<sup>®</sup> (doxepin), SURMONTIL<sup>®</sup> (trimipramine), TOFRANIL<sup>®</sup> (imipramine), or VIVACTIL<sup>®</sup> (protriptyline).
- Medicines to prevent organ transplant rejection: SANDIMMUNE<sup>®</sup> or NEORAL<sup>®</sup> (cyclosporin), RAPAMUNE<sup>®</sup> (sirolimus), or PROGRAF<sup>®</sup> (tacrolimus).
- The antidepressant trazodone (DESYREL<sup>®</sup> and others).
- Fluticasone propionate (FLONASE<sup>®</sup>, FLOVENT<sup>®</sup>), given by nose or inhaled to treat allergic symptoms or asthma. Your doctor may choose not to keep you on fluticasone, especially if you are also taking RITONAVIR<sup>®</sup>.

- Colchicine (COLCRYS<sup>®</sup>), used to prevent or treat gout or treat familial Mediterranean fever.
- VFEND<sup>®</sup> (voriconazole), used to treat serious fungal infections.

**The following medicines may require a change in the dose or dose schedule of either Atazanavir Sulfate and Ritonavir Tablets or the other medicine:**

- INVIRASE<sup>®</sup> (saquinavir).
- Antacids or buffered medicines.
- VIDEX<sup>®</sup> (didanosine).
- VIREAD<sup>®</sup> (tenofovir disoproxil fumarate).
- MYCOBUTIN<sup>®</sup> (rifabutin).
- Calcium channel blockers such as CARDIZEM<sup>®</sup> or TIAZAC<sup>®</sup> (diltiazem), COVERA-HS<sup>®</sup> or ISOPTIN SR<sup>®</sup> (verapamil) and others.
- BIAXIN<sup>®</sup> (clarithromycin).
- Medicines for indigestion, heartburn, or ulcers such as AXID<sup>®</sup> (nizatidine), PEPCID AC<sup>®</sup> (famotidine), TAGAMET<sup>®</sup> (cimetidine), or ZANTAC<sup>®</sup> (ranitidine).

**Talk to your healthcare provider about choosing an effective method of contraception.** Atazanavir Sulfate and Ritonavir Tablets may affect the safety and effectiveness of hormonal contraceptives such as birth control pills or the contraceptive patch. Hormonal contraceptives do not prevent the spread of HIV to others.

**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.**

**General information about Atazanavir Sulfate and Ritonavir Tablets**

This medicine was prescribed for your particular condition. Do not use Atazanavir Sulfate and Ritonavir Tablets for another condition. Do not give Atazanavir Sulfate and Ritonavir Tablets to other people, even if they have the same symptoms you have. It may harm them.

**Keep Atazanavir Sulfate and Ritonavir Tablets 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. 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.

### **How Should I Store Atazanavir Sulfate and Ritonavir Tablets?**

- Keep Atazanavir Sulfate and Ritonavir Tablets and all other medicines out of the reach of children.
- Store film-coated tablets at 25°C (77°F); excursions permitted to 15° to 30°C (59°-86° F) [Room temperature].
- Use tablets by the expiration date on the bottle.

Do not keep medicine that is out of date or that you no longer need. Be sure that if you throw any medicine away, it is out of the reach of children.

### **What are the ingredients in Atazanavir Sulfate and Ritonavir Tablets?**

Active ingredients: Atazanavir sulfate and ritonavir

Inactive ingredients:

**Film coated tablets:** Lactose monohydrate, crospovidone, microcrystalline cellulose, Magnesium stearate copovidone, sorbitan monolaurate, methylene chloride, colloidal silicon dioxide, sodium chloride, sodium stearyl fumarate, corn starch, sorbitol, hypromellose and polyethylene glycol.

For more information, call Matrix Laboratories Limited, at 1-877-4-INFO-RX (1-877-446-3679).

Manufactured in India by:

Matrix Laboratories Limited

Secunderabad - 500 003, India

\* The brands listed are trademarks of their respective owners and are not trademarks of Matrix Laboratories. The makers of these brands are not affiliated with and do not endorse Matrix Laboratories or its products.

November 2011