**Drug Interactions**

Atazanavir in combination with diltiazem increased diltiazem plasma concentration by 2-fold with an additive effect on the PR interval. When Atazanavir sulfate is a protease inhibitor indicated for use in combination with other antiretroviral agents.

### Dosage and Administration

**2.2 Recommended Pediatric Dosage**

Capsules: 150 mg, and 300 mg. (3, 16)

Hepatic impairment:

Concomitant therapy:

In a pharmacokinetic study between atazanavir 400 mg once daily and atenolol 50 mg once daily, no clinically significant additive effect was observed.

[For these drugs and other antiretroviral agents for which dosing modification may be appropriate, see 2.2 Recommended Pediatric Dosage]

Exceed the recommended adult dosage. Atazanavir sulfate Capsules must be taken with food. The data are insufficient to recommend dosing atazanavir sulfate 400 mg (without ritonavir) once daily with food.

### Adverse Reactions

- **6.1 Treatment-Emergent Adverse Reactions**
  - Wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism has not been established. [See 6.1 Treatment-Emergent Adverse Reactions]

- **6.2 Laboratory Abnormalities**
  - [See 6.2 Laboratory Abnormalities]

### Contraindications

- **4**
  - Use of PDE5 inhibitors for pulmonary arterial hypertension (e.g., tadalafil, vardenafil, sildenafil)
  - Increased risk of fatal cases of rhabdomyolysis, including cases of reactivation of latent infections such as cytomegalovirus (CMV) in patients using atazanavir sulfate in combination with ritonavir 100 mg.

- **5.1**
  - Drug Interactions

### Use in Specific Populations

**17.1 Pregnancy**

- Pregnancy Category C

**17.3 Cardiac Conduction Abnormalities**

**17.6 Fat Redistribution**

**17.7 Interstitial Lung Disease**

**17.8 Natural Killer Cell Lymphocytes**

**17.9 Immune Reconstitution Inflammatory Syndrome**

**17.10 Gastrointestinal Abnormalities**

**17.11 Neurological Abnormalities**

**17.12 Hepatitis**

**17.13 Mycobacterial Infections**

**17.14 Opportunistic Infections**

**17.15 Pneumocystis**

**17.16 Other Infections**

**17.17 Pathogen-Mediated Conditions**

**17.18 Viral Infections**

**18. USE IN SPECIFIC POPULATIONS**

**18.1 Pregnancy**

**18.2 Lactation**

**18.3 Children**

**18.4 Geriatric Use**

**18.5 Renal Impairment**

**18.6 Hepatic Impairment**

**18.7 Tumor Lysis Syndrome**

**18.8 Administration of Other Drugs**

### Laboratory Test Abnormalities

**8.3 Nursing Mothers**

### Drug Interactions

- **10.1 Drug-Drug Interactions**
  - Drugs that are highly dependent on CYP3A for metabolism may be affected by atazanavir sulfate. Be aware of the potential for increased concentrations of drugs such as irinotecan, lovastatin, simvastatin, indinavir, cisapride, pimozide, St. John’s wort, and sildenafil when taken approximately 12 hours prior to the atazanavir sulfate 300 mg and ritonavir 100 mg dose.

- **10.2 Increased Plasma Concentrations of Co-administered Drugs**

- **10.3 Decreased Plasma Concentrations of Co-administered Drugs**

- **10.4 Decreased Effectiveness of Atazanavir Sulfate**

- **10.5 Increased Effectiveness of Atazanavir Sulfate**

### Other Drugs

- **11**
  - Predictable effects.

- **11.1 Other Antiretroviral Agents**

### Use in Elderly Patients

- **13**
  - Use with caution.

### Adverse Reactions

**6.1 Treatment-Emergent Adverse Reactions**

**6.2 Laboratory Abnormalities**

**6.3 Unusual Adverse Reactions**

**6.4 Adverse Reactions During Discontinuation**

**6.5 Laboratory Test Abnormalities**

### Patient Counseling Information

**16.1 General Considerations**

**16.2 Drug Interactions**

**16.3 Laboratory Test Abnormalities**

**16.4 Other Considerations**

### Coadministration of Drugs

**10**

### Table 4: Selected Treatment-Emergent Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Atazanavir Sulfate &amp; Ritonavir</th>
<th>Locevir &amp; Ritonavir</th>
<th>Lopinavir &amp; Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>4%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>7%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Headache</td>
<td>7%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Fat Redistribution</td>
<td>44 ± 18%</td>
<td>48 ± 6%</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>4%</td>
<td>9%</td>
<td>3%</td>
</tr>
</tbody>
</table>

### Table 6: Selected Treatment-Emergent Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Atazanavir Sulfate &amp; Ritonavir</th>
<th>Locevir &amp; Ritonavir</th>
<th>Lopinavir &amp; Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>4%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>7%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Headache</td>
<td>7%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Fat Redistribution</td>
<td>44 ± 18%</td>
<td>48 ± 6%</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>4%</td>
<td>9%</td>
<td>3%</td>
</tr>
</tbody>
</table>

### Table 9: Grade 3 to 4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Experienced Patients, Study AI424-045

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Atazanavir Sulfate &amp; Ritonavir</th>
<th>Locevir &amp; Ritonavir</th>
<th>Lopinavir &amp; Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGOT/AST ≥5.1xULN</td>
<td>2%</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>Albumin</td>
<td>3%</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Creatinine</td>
<td>3%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Creatine Phosphokinase</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

### Table 10: Grade 3 to 4 Laboratory Abnormalities Reported in ≥2% of Pediatric Treatment-Experienced Patients, Study AI424-023

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Atazanavir Sulfate &amp; Ritonavir</th>
<th>Locevir &amp; Ritonavir</th>
<th>Lopinavir &amp; Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGOT/AST ≥5.1xULN</td>
<td>2%</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>Albumin</td>
<td>3%</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Creatinine</td>
<td>3%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Creatine Phosphokinase</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Atazanavir (ATV) is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag proteins. The primary mode of resistance is associated with substitutions at the protease cleavage sites. The extent of resistance is dependent on the number of substitutions. A single substitution, such as I84V or G48V, results in resistance to ATV. Greater than 60% of isolates containing L90M, G73S/T/C, A71V/T, and Y181C substitutions are resistant to ATV. In treatment-experienced patients, PI-resistant viral isolates that experienced patients experiencing virologic failure after long-term treatment. Protease cleavage site changes also emerged on ATV treatment. The resistance to ATV was 9% lower, AUC was 19% higher, and Cmax was 28% higher with ATV compared to nevirapine (n=16). Famotidine (0.95, 1.11) did not significantly alter the pharmacokinetics of ATV.

Effects on Electrocardiogram

In clinical trials, no QTc interval >500 msec was observed in atazanavir-treated healthy subjects or HIV-infected patients. No significant effect on QTc interval was observed in patients on concomitant medication with known QTc prolongation effects.

Study AI424-045: Atazanavir sulfate once daily + ritonavir once daily compared to atazanavir sulfate once daily + saquinavir (soft gelatin capsule) once daily. The study included 190 HIV-infected patients with virologic failure on current therapy. Baseline plasma HIV-1 RNA level was 4.7 log10 copies/mL. At baseline, the median CD4+ T-cell count was 171 cells/mm3. Patients were randomized to receive either atazanavir sulfate + ritonavir (n=95) or atazanavir sulfate + saquinavir (n=95) once daily for 96 weeks. The primary end point was HIV RNA response by number and type of baseline PI substitution.

Table 19: HIV RNA Response by Number and Type of Baseline PI Substitution, Antiretroviral-Experienced Patients in Study AI424-045,

<table>
<thead>
<tr>
<th>Baseline PI Substitution</th>
<th>Antiretroviral-Experienced Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA Response</td>
<td>Number of Patients</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/mL</td>
<td>99 (51.1%)</td>
</tr>
<tr>
<td>HIV RNA &gt;50 copies/mL</td>
<td>91 (48.9%)</td>
</tr>
</tbody>
</table>

The table shows that 99% of patients had HIV RNA <50 copies/mL, while 91% had HIV RNA >50 copies/mL. The study also evaluated the safety and tolerability of ATV + ritonavir compared to ATV + saquinavir. No significant difference in adverse events was observed between the two treatment groups. No new safety signals were identified.

Drug Interactions

- Coadministration with a high-fat meal (951 kcal, 54.7 g fat, 35.9 g protein) did not affect the AUC of ATV relative to fasting conditions.
- Discontinued for other reasons included: omeprazole (40 mg), ethinyl estradiol (35 mcg), rifampin (400 mg QD), rifabutin (600 mg QD), rifabutin (300 mg QD/ritonavir 100 mg QD), and rifabutin (300 mg QD/ritonavir 100 mg QD).
- Discontinued for other reasons: omeprazole (40 mg), ethinyl estradiol (35 mcg), rifampin (400 mg QD), rifabutin (600 mg QD), rifabutin (300 mg QD/ritonavir 100 mg QD), and rifabutin (300 mg QD/ritonavir 100 mg QD).