1. NAME OF THE MEDICINAL PRODUCT

Atazanavir sulfate and Ritonavir Tablets 300mg/100mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains Atazanavir sulfate equivalent to 300 mg of Atazanavir and 100 mg of Ritonavir USP

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet

Description: Yellow, modified capsule shaped, bevel edged biconvex film coated tablets, debossed with 'J' on one side and '73' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atazanavir and Ritonavir Tablets, 300 mg/100 mg, a combination of a protease inhibitor and a protease inhibitor used as a pharmacokinetic enhancer, are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection (1)

4.2 Posology and method of administration

General Dosing Recommendations:

- Atazanavir and Ritonavir Tablets, 300 mg/100 mg must be taken with food.
- When coadministered with H_2-receptor antagonists or proton-pump inhibitors, dose separation may be required.
- When co-administered with didanosine buffered or enteric-coated formulations, Atazanavir and Ritonavir Tablets, 300 mg/100 mg should be given (with food) 2 hours before or 1 hour after didanosine.

Recommended Dosage

Adults and pediatric patients (at least 6 years of age and weighing 40 kg): The recommended dosage of Atazanavir and Ritonavir Tablets, 300 mg/100 mg is shown in Table 1.

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

Treatment-Naive Patients	**One tablet once daily**
Do not coadminister with efavirenz in treatment–naïve pa	
When combined with any of the following: Tenofovir H_2-receptor antagonist Proton-pump inhibitor	**One tablet once daily**
• The H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 40 mg twice daily. Administer Atazanavir and Ritonavir Tablets, 300 mg/100 mg with, and/or at least 10 hours after the H_2-receptor antagonist. • The proton-pump inhibitor dose should not exceed a dose comparable to omeprazole 20 mg daily and must be taken approximately 12 hours prior to Atazanavir and Ritonavir Tablets, 300 mg/100 mg.	
Do not coadminister with both tenofovir and an H_2-receptor antagonist because higher doses of atazanavir are required.	
Treatment-Experienced Patients	**One tablet once daily**
Do not coadminister with both tenofovir and an H_2-receptor antagonist because higher doses of atazanavir are required.	
Do not co-administer with proton-pump inhibitors or efavirenz in treatment-experienced patients.	
When given with an H_2-receptor antagonist	**One tablet once daily**
• The H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 20 mg twice daily. Administer Atazanavir and Ritonavir Tablets, 300 mg/100 mg with, and/or at least 10 hours after the H_2-receptor antagonist.	

[For these drugs and other antiretroviral agents for which dosing modification may be appropriate]

Pregnancy

Dosing During Pregnancy and the Postpartum Period:

- It should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir, one component of Atazanavir and Ritonavir Tablets.
- Not recommended for treatment-experienced pregnant women during the second or third trimester, when coadministered with either an H_2-receptor antagonist or tenofovir because higher doses of atazanavir are required. There are insufficient data to recommend an atazanavir dose for use with both an H_2-receptor antagonist and tenofovir in treatment-experienced pregnant women.
- No dose adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir, one component of Atazanavir and Ritonavir Tablets, exposures could be higher during the first 2 months after delivery.

Renal Impairment

Treatment-naïve patients:

No dose adjustment is required for patients with renal impairment, including treatment-naive patients with end stage renal disease managed with hemodialysis.

Treatment-experienced patients:

Atazanavir and Ritonavir Tablets should not be administered to HIV-treatment-experienced patients with end stage renal disease managed with hemodialysis. No dose adjustment is required for other treatment-experienced patients with renal impairment.

Hepatic Impairment

Atazanavir and Ritonavir Tablets are not recommended for use in patients with hepatic impairment, because atazanavir with ritonavir has not been studied in that population.

4.3 Contraindications

Atazanavir and Ritonavir Tablets, 300 mg/100 mg are contraindicated:

- in patients with known hypersensitivity (e.g., erythema multiforme, toxic skin eruptions, or Stevens-Johnson syndrome) to any of components of this product.
- when co-administered with drugs that are highly dependent on CYP3A or UGT1A1 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These and other contraindicated drugs are listed in Table 2.

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

Drug Class	**Drugs within class that are contraindicated with atazanavir**	**Clinical Comment**
Alpha 1-Adrenoreceptor Antagonist	Alfuzosin	Potential for increased alfuzosin concentrations, which can result in hypotension.
Antimycobacterials	Rifampin	Rifampin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect and development of resistance.
Antineoplastics	Irinotecan	Atazanavir inhibits UGT1A1 and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.
Benzodiazepines	Triazolam, orally administered midazolam[a]	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally

		administered midazolam with atazanavir may cause large increases in the concentration of these benzodiazepines. Potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
Ergot Derivatives	Dihydroergotamine, ergotamine, ergonovine, methylergonovine	Potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	Cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Drug Class	**Drugs within class that are contraindicated with atazanavir**	**Clinical Comment**
Herbal Products	St. John's wort (*Hypericum perforatum*)	Patients taking atazanavir should not use products containing St. John's wort because coadministration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for serious reactions such as myopathy including rhabdomyolysis.
Neuroleptic	Pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
PDE5 Inhibitor	Sildenafil[b] when dosed for the treatment of pulmonary arterial hypertension	A safe and effective dose in combination with atazanavir has not been established for sildenafil when used for the treatment of pulmonary hypertension. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, priapism, and syncope).
Protease Inhibitors	Indinavir	Both atazanavir and indinavir are associated with indirect (unconjugated) hyperbilirubinemia.

[a] See *Drug Interactions, Table 9 (7)* for parenterally administered midazolam

[b] See *Drug Interactions, Table 9 (7)* for sildenafil when dosed for erectile dysfunction.

4.4 Special warnings and precautions for use

Drug Interactions

See Table 2 for a listing of drugs that are contraindicated for use with Atazanavir and Ritonavir Tablets due to significant interactions that may lead to potentially life-threatening adverse events,

or loss of virologic activity. Please refer to Table 9 for established and other potentially significant drug interactions.

Cardiac Conduction Abnormalities/PR interval prolongation

Atazanavir

Atazanavir has been shown to prolong the PR interval of the electrocardiogram in some patients. In healthy volunteers and in patients, abnormalities in atrioventricular (AV) conduction were asymptomatic and generally limited to first-degree AV block. There have been reports of second-degree AV block and other conduction abnormalities. In clinical trials that included electrocardiograms, asymptomatic first-degree AV block was observed in 5.9% of atazanavir-treated patients (n=920), 5.2% of lopinavir/ritonavir-treated patients (n=252), 10.4% of nelfinavir-treated patients (n=48), and 3% of efavirenz-treated patients (n=329). In Study AI424-045 asymptomatic first-degree AV block was observed in 5% (6/118) of atazanavir/ritonavir-treated patients and 5% (6/116) of lopinavir/ritonavir-treated patients who had on-study electrocardiogram measurements. Because of limited clinical experience in patients with preexisting conduction system disease (e.g, marked first-degree AV block or second- or third-degree AV block), atazanavir should be used with caution in these patients.

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. Pharmacokinetic studies between atazanavir and other drugs that prolong the PR interval including beta blockers [other than atenolol], verapamil, and digoxin have not been performed. An additive effect of atazanavir and these drugs cannot be excluded; therefore, caution should be exercised when atazanavir is given concurrently with these drugs, especially those that are metabolized by CYP3A (e.g, verapamil).

Ritonavir

Ritonavir prolongs the PR interval in some patients. Cases of second- or third-degree atrioventricular block have been reported in patients.

Ritonavir should be used with caution in patients with underlying structural heart disease, preexisting conduction system abnormalities, ischemic heart disease, cardiomyopathies, as these

patients may be at increased risk for developing cardiac conduction abnormalities.

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

Hepatotoxicity/Hepatic Reactions

Atazanavir

Caution should be exercised when administering Atazanavir to patients with hepatic impairment because atazanavir concentrations may be increased. Patients with underlying hepatitis B or C viral infections or marked elevations in transaminases before treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. In these patients, hepatic laboratory testing should be conducted prior to initiating therapy with Atazanavir and during treatment.

Ritonavir

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

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

Pancreatitis

Pancreatitis has been observed in patients receiving ritonavir therapy, including those who developed hypertriglyceridemia. In some cases fatalities have been observed. Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis. 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.

Allergic Reactions/Hypersensitivity/Rash

Atazanavir

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

Ritonavir

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

Hyperbilirubinemia

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

Lipid Disorders

Treatment with ritonavir therapy alone or in combination with saquinavir has resulted in substantial increases in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing should be performed prior to initiating ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate, taking into account any potential drug-drug interactions with ritonavir and HMG CoA reductase inhibitors.

Nephrolithiasis and Cholelithiasis

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

Diabetes Mellitus/Hyperglycemia

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

Immune Reconstitution Syndrome

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

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

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.

Hemophilia

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

Resistance/Cross-resistance

Various degrees of cross-resistance among protease inhibitors, including Atazanavir and ritonavir have been observed. Resistance to atazanavir may not preclude the subsequent use of other protease inhibitors.

Laboratory Tests

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

4.5 Interaction with other medicinal products and other forms of interaction

Potential to Affect Other Drugs

Atazanavir

Atazanavir is an inhibitor of CYP3A and UGT1A1. Coadministration of Atazanavir and drugs primarily metabolized by CYP3A or UGT1A1 may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects.

When atazanavir with ritonavir is coadministered with substrates of CYP2C8, clinically significant interactions are not expected.

Ritonavir

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

Ritonavir also inhibits CYP2D6 to a lesser extent. Co-administration of substrates of CYP2D6 with

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

Potential for Other Drugs to Affect Atazanavir

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

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

Established and Other Potentially Significant Drug Interactions

Table 2 provides dosing and clinical recommendations as a result of drug interactions with one or both components of Atazanavir 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 2: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
HIV Antiviral Agents		
Nucleoside Reverse Transcriptase Inhibitors (NRTIs): didanosine buffered formulations enteric-coated (EC) capsules	↓ atazanavir ↓ didanosine	Coadministration of atazanavir with didanosine buffered tablets resulted in a marked decrease in atazanavir exposure. It is recommended that atazanavir be given (with food) 2 h before or 1 h after didanosine buffered formulations. Simultaneous administration of didanosine EC and atazanavir with food results in a decrease in didanosine exposure. Thus, atazanavir and didanosine EC should be administered at different times.
Nucleotide Reverse Transcriptase Inhibitors: tenofovir disoproxil fumarate	↓ atazanavir ↑ tenofovir	Tenofovir may decrease the AUC and C_{min} of atazanavir. When coadministered with tenofovir, it is recommended that atazanavir and

		ritonavir tablets be given with tenofovir 300 mg (all as a single daily dose with food). **Atazanavir without ritonavir should not be coadministered with tenofovir.** 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. For pregnant women taking atazanavir with ritonavir *and* tenofovir.
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs): Efavirenz	↓ atazanavir	Efavirenz decreases atazanavir exposure. Do not co-administer atazanavir with efavirenz due to decreased atazanavir exposure.
Protease Inhibitors: saquinavir (soft gelatin capsules)	↑ saquinavir	Appropriate dosing recommendations for this combination, with or without ritonavir, with respect to efficacy and safety have not been established. In a clinical study, saquinavir 1200 mg coadministered with atazanavir 400 mg and tenofovir 300 mg (all given once daily) plus nucleoside analogue reverse transcriptase inhibitors did not provide adequate efficacy.
Protease Inhibitors: others	↑ other protease inhibitor	Although not studied, the coadministration of atazanavir and ritonavir and other protease inhibitors would be expected to increase exposure to the other protease inhibitor. Such coadministration is not recommended.

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
HCV Antiviral Agents		

Protease Inhibitors: Boceprevir	↓ atazanavir ↓ ritonavir	Concomitant administration of boceprevir and atazanavir and ritonavir resulted in reduced steady-state exposures to atazanavir and ritonavir. Coadministration of atazanavir andritonavir and boceprevir is not recommended.
Protease Inhibitors: telaprevir	↓ telaprevir ↑ atazanavir	Concomitant administration of telaprevir and atazanavir and ritonavir resulted in reduced steady-state telaprevir exposure, while steady-state atazanavir exposure was increased.
Other Agents		
Antacids and buffered medications	↓ atazanavir	Reduced plasma concentrations of atazanavir are expected if antacids, including buffered medications, are administered with atazanavir. Atazanavir should be administered 2 hours before or 1 hour after these medications.
Antiarrhythmics: amiodarone, bepridil, lidocaine (systemic), quinidine	↑ amiodarone, bepridil, lidocaine (systemic), quinidine	Coadministration with atazanavir has the potential to produce serious and/or life-threatening adverse events and has not been studied. Caution is warranted and therapeutic concentration monitoring of these drugs is recommended if they are used concomitantly with Atazanavir.
Anticoagulants: warfarin	↑ warfarin	Coadministration with atazanavir has the potential to produce serious and/or life-threatening bleeding and has not been studied. It is recommended that INR (International Normalized Ratio) be monitored.
Antidepressants: tricyclic antidepressants	↑ tricyclic antidepressants	Coadministration with atazanavir has the potential to produce serious and/or life-threatening adverse events and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with atazanavir.
Trazodone	↑ trazodone	Concomitant use of trazodone and atazanavir with or without ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea,

		dizziness, hypotension, and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as atazanavir, the combination should be used with caution and a lower dose of trazodone should be considered.

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
Antiepileptics: Carbamazepine	↓ atazanavir ↑ carbamazepine	Ritonavir may increase plasma levels of carbamazepine. If patients beginning treatment with atazanavir and ritonavir have been titrated to a stable dose of carbamazepine, a dose reduction for carbamazepine may be necessary.
phenytoin, phenobarbital	↓ atazanavir ↓ phenytoin ↓ phenobarbital	Ritonavir may decrease plasma levels of phenytoin and phenobarbital. When atazanavir and ritonavir is coadministered with either phenytoin or phenobarbital, a dose adjustment of phenytoin or phenobarbital may be required.
Lamotrigine	↓ lamotrigine	Coadministration of lamotrigine and atazanavir and ritonavir may decrease lamotrigine plasma concentrations. Dose adjustment of lamotrigine may be required when coadministered with atazanavir and ritonavir.
Antifungals: ketoconazole, itraconazole	↑ ketoconazole ↑ itraconazole	Coadministration of ketoconazole has only been studied with atazanavir without ritonavir (negligible increase in atazanavir AUC and C_{max}). Due to the effect of ritonavir on ketoconazole, high doses of ketoconazole and itraconazole (>200 mg/day) should be used cautiously with atazanavir and ritonavir.
Antifungals: voriconazole	**In subjects with a functional CYP2C19 allele:**	Voriconazole should not be administered to patients receiving atazanavir and ritonavir, unless an

	↓ voriconazole ↓ atazanavir **In subjects without a functional CYP2C19 allele:** ↑ voriconazole ↓ atazanavir	assessment of the benefit/risk to the patient justifies the use of voriconazole. Patients should be carefully monitored for voriconazole-associated adverse events and loss of either voriconazole or atazanavir efficacy during the coadministration of voriconazole and atazanavir and ritonavir. Coadministration of voriconazole with atazanavir (without ritonavir) may affect atazanavir concentrations; however, no data are available.
Antigout: colchicine	↑ colchicine	Atazanavir should not be coadministered with colchicine to patients with renal or hepatic impairment. ***Recommended dosage of colchicine when administered with atazanavir:*** ***Treatment of gout flares:*** 0.6 mg (1 tablet) for 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Not to be repeated before 3 days.

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
		Prophylaxis of gout flares: If the original regimen was 0.6 mg *twice* a day, the regimen should be adjusted to 0.3 mg *once a day*. If the original regimen was 0.6 mg *once* a day, the regimen should be adjusted to 0.3 mg *once every other day*. ***Treatment of familial Mediterranean fever (FMF):*** Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimycobacterials: rifabutin	↑ rifabutin	A rifabutin dose reduction of up to 75% (eg, 150 mg every other day or 3 times per week) is recommended. Increased monitoring for rifabutin-associated adverse reactions including

		neutropenia is warranted.
Benzodiazepines: parenterally administered midazolam[b]	↑ midazolam	Concomitant use of parenteral midazolam with atazanavir may increase plasma concentrations of midazolam. Coadministration should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Coadministration of oral midazolam with atazanavir is CONTRAINDICATED.
Calcium channel blockers: diltiazem	↑ diltiazem and desacetyl-diltiazem	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.
felodipine, nifedipine, nicardipine, and verapamil	↑ calcium channel blocker	Caution is warranted. Dose titration of the calcium channel blocker should be considered. ECG monitoring is recommended.
Endothelin receptor antagonists: bosentan	↓ atazanavir ↑ bosentan	***Coadministration of bosentan in patients on atazanavir and ritonavir:*** For patients who have been receiving atazanavir and ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based on individual tolerability. ***Coadministration of atazanavir and ritonavir in patients on bosentan:*** Discontinue bosentan at least 36 hours before starting atazanavir andritonavir. At least 10 days after starting atazanavir and ritonavir,

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
		resume bosentan at 62.5 mg once daily

		or every other day based on individual tolerability.
HMG-CoA reductase inhibitors: atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Titrate atorvastatin dose carefully and use the lowest necessary dose. Rosuvastatin dose should not exceed 10 mg/day. The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including atazanavir, are used in combination with these drugs.
H_2-Receptor antagonists	↓ atazanavir	***In treatment-naive patients:*** Atazanavir 300 mg with ritonavir 100 mg once daily with food should be administered simultaneously with, and/or at least 10 hours after, a dose of the H_2-receptor antagonist. An H_2-receptor antagonist dose comparable to famotidine 20 mg once daily up to a dose comparable to famotidine 40 mg twice daily can be used with atazanavir 300 mg with ritonavir 100 mg in treatment-naive patients.
		In treatment-experienced patients: Whenever an H_2-receptor antagonist is given to a patient receiving atazanavir with ritonavir, the H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 20 mg twice daily, and the atazanavir and ritonavir doses should be administered simultaneously with, and/or at least 10 hours after, the dose of the H_2-receptor antagonist. • Atazanavir 300 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with an H_2-receptor antagonist. For pregnant women taking atazanavir with ritonavir and an H_2-receptor antagonist. • Atazanavir and ritonavir tablets should not be taken with both tenofovir and an H_2-receptor antagonist because higher doses of atazanavir are required.
Hormonal contraceptives:	↓ ethinyl estradiol	Use with caution if coadministration of

ethinyl estradiol and norgestimate or norethindrone	↑ norgestimate[c] ↑ ethinyl estradiol	atazanavir or atazanavir/ritonavir with oral contraceptives is considered. If an oral contraceptive is administered with atazanavir and ritonavir, it is recommended that the oral contraceptive contain at least 35 mcg of ethinyl estradiol. If atazanavir is administered without ritonavir, the oral contraceptive should contain no more than 30 mcg of ethinyl estradiol.

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
		Potential safety risks include substantial increases in progesterone exposure. The long-term effects of increases in concentration of the progestational agent are unknown and could increase the risk of insulin resistance, dyslipidemia, and acne. Coadministration of atazanavir and ritonavir with other hormonal contraceptives (eg, contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestogens other than norethindrone or norgestimate, or less than 25 mcg of ethinyl estradiol, has not been studied; therefore, alternative methods of contraception are recommended.
Immunosuppressants: cyclosporin, sirolimus, tacrolimus	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with Atazanavir.
Inhaled beta agonist: salmeterol	↑ salmeterol	Coadministration of salmeterol with atazanavir is not recommended. Concomitant use of salmeterol and atazanavir may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.

Inhaled/nasal steroid: fluticasone	↑ fluticasone	Concomitant use of fluticasone propionate and atazanavir and 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 clinical use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Coadministration of fluticasone propionate and atazanavir and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.
Macrolide antibiotics: clarithromycin	↑ clarithromycin ↓ 14-OH clarithromycin ↑ atazanavir	Increased concentrations of clarithromycin may cause QTc prolongations; therefore, a dose reduction of clarithromycin by 50% should be considered when it is coadministered with atazanavir. In addition, concentrations of the active metabolite 14-OH clarithromycin are significantly reduced;

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
		consider alternative therapy for indications other than infections due to *Mycobacterium avium* complex. Coadministration of atazanavir and ritonavir with clarithromycin has not been studied.
Opioids: Buprenorphine	↑ buprenorphine ↑ norbuprenorphine	Coadministration of buprenorphine and atazanavir with or without ritonavir increases the plasma concentration of buprenorphine and norbuprenorphine. Coadministration of atazanavir plus ritonavir with buprenorphine warrants clinical

		monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered. Coadministration of buprenorphine and atazanavir with ritonavir is not expected to decrease atazanavir plasma concentrations. Coadministration of buprenorphine and atazanavir without ritonavir may decrease atazanavir plasma concentrations. atazanavir without ritonavir should not be coadministered with buprenorphine.
PDE5 inhibitors: sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Coadministration with atazanavir has not been studied but may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances, and priapism. ***Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH):*** Use of sildenafil for the treatment of pulmonary hypertension (PAH) is contraindicated with atazanavir. The following dose adjustments are recommended for the use of tadalafil with atazanavir: Coadministration of tadalafil in patients on atazanavir (with or without ritonavir): • For patients receiving atazanavir (with or without ritonavir) for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability. Coadministration of atazanavir (with or without ritonavir) in patients on tadalafil: • Avoid the use of tadalafil when starting atazanavir (with or without ritonavir). Stop tadalafil at least 24 hours before starting atazanavir (with

		or without ritonavir). At least one week after starting atazanavir (with or without ritonavir), resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability.
Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
		Use of PDE5 inhibitors for erectile dysfunction: Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Use tadalafil with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. ***Atazanavir and ritonavir:*** Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events.
Proton-pump inhibitors: omeprazole	↓ atazanavir	Plasma concentrations of atazanavir were substantially decreased when atazanavir 300 mg/ritonavir 100 mg once daily was administered with omeprazole 40 mg once daily, which may result in loss of therapeutic effect and development of resistance.
		In treatment-naive patients: The proton-pump inhibitor dose should not exceed a dose comparable to omeprazole 20 mg and must be taken approximately 12 hours prior to the atazanavir 300 mg with ritonavir 100 mg dose.
		In treatment-experienced patients: Proton-pump inhibitors should not be used in treatment-experienced patients receiving atazanavir.

[a] For magnitude of interactions see *Clinical Pharmacology, Table 12.*

[b] See *Contraindications (4), Table 2* for orally administered midazolam.

[c] In combination with atazanavir 300 mg and ritonavir 100 mg once daily.

Drugs with No Observed or Predicted Interactions with Atazanavir

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

Based on known metabolic profiles, clinically significant drug interactions are not expected between atazanavir sulfate and dapsone, trimethoprim/sulfamethoxazole, azithromycin, or erythromycin. Atazanavir does not interact with substrates of CYP2D6 (e.g, nortriptyline, desipramine, metoprolol). Additionally, no clinically significant drug interactions were observed when Atazanavir was coadministered with methadone, fluconazole, acetaminophen, or atenolol

Pharmacodynamic interactions

Effects on Electrocardiogram

Atazanavir

Concentration- and dose-dependent prolongation of the PR interval in the electrocardiogram has been observed in healthy volunteers receiving atazanavir. In a placebo-controlled study (AI424-076), the mean (±SD) maximum change in PR interval from the predose value was 24 (±15) msec following oral dosing with 400 mg of atazanavir (n=65) compared to 13 (±11) msec following dosing with placebo (n=67). The PR interval prolongations in this study were asymptomatic. There is limited information on the potential for a pharmacodynamic interaction in humans between atazanavir and other drugs that prolong the PR interval of the electrocardiogram.

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 greater than 500 msec.

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.

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.

Pharmacokinetic interactions

Table 3: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Atazanavir[a]

Coadministered Drug	**Coadministered Drug Dose/Schedule**	**Atazanavir Dose/Schedule**	**Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without atazanavir; No Effect = 1**		
			C_{max}	**AUC**	**C_{min}**
Acetaminophen	1 gm BID, d 1−20 (n=10)	300 mg QD/ritonavir 100 mg QD, d 11−20 (n=10)	0.87 (0.77, 0.99)	0.97 (0.91, 1.03)	1.26 (1.08, 1.46)
Atenolol	50 mg QD, d 7−11 (n=19) and d 19−23	400 mg QD, d 1−11 (n=19)	1.34 (1.26, 1.42)	1.25 (1.16, 1.34)	1.02 (0.88, 1.19)
Coadministered Drug	**Coadministered Drug Dose/Schedule**	**Atazanavir Dose/Schedule**	**Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without atazanavir; No Effect = 1**		
			C_{max}	**AUC**	**C_{min}**
Boceprevir	800 mg TID, d 1-6, 25-31	300 mg QD/ ritonavir 100 mg QD, d 10-31	0.93 (0.80, 1.08)	0.95 (0.87, 1.05)	0.82 (0.68, 0.98)
Clarithromycin	500 mg BID, d 7−10 (n=21) and	400 mg QD, d 1−10 (n=21)	1.50 (1.32, 1.71)	1.94 (1.75, 2.16)	2.60 (2.35, 2.88)

	d 18−21		OH-clarithromycin: 0.28 (0.24, 0.33)	OH-clarithromycin: 0.30 (0.26, 0.34)	OH-clarithromycin: 0.38 (0.34, 0.42)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)[b]	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose (n=31)	400 mg x 1 dose 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 (0.97, 1.03)	NA d4T: 1.04 (0.94, 1.16)
ddI (enteric-coated [EC] capsules)[c]	400 mg d 1 (fasted), d 8 (fed) (n=34)	400 mg QD, d 2−8 (n=34)	0.64 (0.55, 0.74)	0.66 (0.60, 0.74)	1.13 (0.91, 1.41)
	400 mg d 1 (fasted), d 19 (fed) (n=31)	300 mg QD/ritonavir 100 mg QD, d 9−19 (n=31)	0.62 (0.52, 0.74)	0.66 (0.59, 0.73)	1.25 (0.92, 1.69)
Diltiazem	180 mg QD, d 7−11 (n=28) and d 19−23	400 mg QD, d 1−11 (n=28)	1.98 (1.78, 2.19) desacetyl-diltiazem: 2.72 (2.44, 3.03)	2.25 (2.09, 2.16) desacetyl-diltiazem: 2.65 (2.45, 2.87)	2.42 (2.14, 2.73) desacetyl-diltiazem: 2.21 (2.02, 2.42)
ethinyl estradiol & norethindrone[d]	Norethindrone (0.5 mg + ethinyl estradiol 0.035 mg) QD, d 1−29 (n=19)	400 mg QD, d 16−29 (n=19)	ethinyl estradiol: 1.15 (0.99, 1.32) norethindrone: 1.67 (1.42, 1.96)	ethinyl estradiol: 1.48 (1.31, 1.68) norethindrone: 2.10 (1.68, 2.62)	ethinyl estradiol: 1.91 (1.57, 2.33) norethindrone: 3.62 (2.57, 5.09)
ethinyl estradiol & norgestimate[e]	Norgestimate (0.180 mg) + ethinyl estradiol (0.035 mg) QD, d 1–28 (n=18), then Norgestimate (0.180 mg) + ethinyl estradiol (0.025 mg) QD, d 29–42[f] (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:[g] 1.68 (1.51, 1.88)	ethinyl estradiol: 0.81 (0.75, 0.87) 17-deacetyl norgestimate:[g] 1.85 (1.67, 2.05)	ethinyl estradiol: 0.63 (0.55, 0.71) 17-deacetyl norgestimate:[g] 2.02 (1.77, 2.31)
Fluconazole	200 mg QD, d 1−10 (n=11) and 200 mg QD, d 11−20	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, 1.15)

	(n=29)				
Methadone	Stable maintenance dose, d 1−15 (n=16)	400 mg QD, d 2−15 (n=16)	(R)-methadone[h] 0.91	(R)-methadone[h] 1.03	(R)-methadone[h] 1.11
Coadministered Drug	**Coadministered Drug Dose/Schedule**	**Atazanavir Dose/Schedule**	**Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without atazanavir; No Effect = 1**		
			C_{max}	**AUC**	**C_{min}**
			(0.84, 1) total: 0.85 (0.78, 0.93)	(0.95, 1.10) total: 0.94 (0.87, 1.02)	(1.02, 1.20) total: 1.02 (0.93, 1.12)
nevirapine[i,j]	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[k]	40 mg single dose, d 7 and d 20 (n=16)	400 mg QD, d 1−12 (n=16)	1.24 (1.04, 1.47)	1.45 (1.20, 1.76)	NA
Rifabutin	300 mg QD, d 1−10 then 150 mg QD, d 11−20 (n=3)	600 mg QD,[l] d 11−20 (n=3)	1.18 (0.94, 1.48) 25-O-desacetyl-rifabutin: 8.20 (5.90, 11.40)	2.10 (1.57, 2.79) 25-O-desacetyl-rifabutin: 22.01 (15.97, 30.34)	3.43 (1.98, 5.96) 25-O-desacetyl-rifabutin: 75.6 (30.1, 190)
	150 mg twice weekly, d 1−15 (n=7)	300 mg QD/ritonavir 100 mg QD, d 1−17 (n=7)	2.49[m] (2.03, 3.06) 25-O-desacetyl-rifabutin: 7.77 (6.13, 9.83)	1.48[m] (1.19, 1.84) 25-O-desacetyl-rifabutin: 10.90 (8.14, 14.61)	1.40[m] (1.05, 1.87) 25-O-desacetyl-rifabutin: 11.45 (8.15, 16.10)
pitavastatin	4 mg QD for 5 days	300 mg QD for 5 days	1.60 (1.39, 1.85)	1.31 (1.23, 1.39)	NA
rosiglitazone[n]	4 mg single dose, d 1, 7, 17 (n=14)	400 mg QD, d 2–7, then 300 mg QD/ritonavir 100 mg QD, d	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

		8–17 (n=14)			
Rosuvastatin	10 mg single dose	300 mg QD/ ritonavir 100 mg QD for 7 days	↑ 7-fold[o]	↑ 3-fold[o]	NA
saquinavir[p] (soft gelatin capsules)	1200 mg QD, d 1−13 (n=7)	400 mg QD, d 7−13 (n=7)	4.39 (3.24, 5.95)	5.49 (4.04, 7.47)	6.86 (5.29, 8.91)
Telaprevir	750 mg q8h for 10 days (n=14)	300 mg QD/ ritonavir 100 mg QD for 20 days (n=14)	0.79 (0.74, 0.84)	0.80 (0.76, 0.85)	0.85 (0.75, 0.98)
tenofovir[q]	300 mg QD, d 9−16 (n=33) and d 24−30 (n=33)	400 mg QD, d 2−16 (n=33)	1.14 (1.08, 1.20)	1.24 (1.21, 1.28)	1.22 (1.15, 1.30)
	300 mg QD, d 1−7 (pm) (n=14) d 25−34 (pm) (n=12)	300 mg QD/ritonavir 100 mg QD, d 25−34 (am) (n=12)[r]	1.34 (1.20, 1.51)	1.37 (1.30, 1.45)	1.29 (1.21, 1.36)
Coadministered Drug	**Coadministered Drug Dose/Schedule**	**Atazanavir Dose/Schedule**	**Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without atazanavir; No Effect = 1**		
			C_{max}	**AUC**	**C_{min}**
Voriconazole (Subjects with at least one functional CYP2C19 allele	200 mg BID, d 2-3, 22-30; 400 mg BID, d 1, 21 (n=20)	300 mg/ritonavir 100 mg QD, d 11-30 (n=20)	0.90 (0.78, 1.04)	0.67 (0.58, 0.78)	0.61 (0.51, 0.72)
Voriconazole (Subjects without a functional CYP2C19 allele)	50 mg BID, d 2-3, 22-30; 100 mg BID, d 1, 21 (n=8)	300 mg/ritonavir 100 mg QD, d 11-30 (n=8)	4.38 (3.55, 5.39)	5.61 (4.51, 6.99)	7.65 (5.71, 10.2)
lamivudine + zidovudine	150 mg lamivudine + 300 mg zidovudine BID, d 1−12 (n=19)	400 mg QD, d 7−12 (n=19)	lamivudine: 1.04 (0.92, 1.16) zidovudine: 1.05 (0.88, 1.24) zidovudine glucuronide:	lamivudine: 1.03 (0.98, 1.08) zidovudine: 1.05 (0.96, 1.14) zidovudine glucuronide: 1	lamivudine: 1.12 (1.04, 1.21) zidovudine: 0.69 (0.57, 0.84) zidovudine glucuronide:

			0.95 (0.88, 1.02)	(0.97, 1.03)	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 25 mcg with atazanavir relative to ethinyl estradiol 35 mcg without atazanavir, the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 0.82 (0.73, 0.92), 1.06 (0.95, 1.17), and 1.35 (1.11, 1.63), respectively.
[e] Upon further dose normalization of ethinyl estradiol 35 mcg with atazanavir/ritonavir relative to ethinyl estradiol 25 mcg without atazanavir/ritonavir, the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 1.17 (1.03, 1.34), 1.13 (1.05, 1.22), and 0.88 (0.77, 1), respectively.
[f] All subjects were on a 28 day lead-in period.
[g] 17-deacetyl norgestimate is the active component of norgestimate.
[h] (R)-methadone is the active isomer of methadone.
[i] Study was conducted in HIV-infected individuals.
[j] Subjects were treated with nevirapine prior to study entry.
[k] Omeprazole was used as a metabolic probe for CYP2C19. Omeprazole was given 2 hours after atazanavir on Day 7; and was given alone 2 hours after a light meal on Day 20.
[l] Not the recommended therapeutic dose of atazanavir.
[m] When compared to rifabutin 150 mg QD alone d1−10 (n=14). Total of Rifabutin + 25-O-desacetyl-rifabutin: AUC 2.19 (1.78, 2.69).
[n] Rosiglitazone used as a probe substrate for CYP2C8.
[o] Mean ratio (with/without coadministered drug). ↑indicates an increase in rosuvastatin exposure.
[p] The combination of atazanavir and saquinavir 1200 mg QD produced daily saquinavir exposures similar to the values produced by the standard therapeutic dosing of saquinavir at 1200 mg TID. However, the C_{max} is about 79% higher than that for the standard dosing of saquinavir (soft gelatin capsules) alone at 1200 mg TID.
[q] Note that similar results were observed in a study where administration of tenofovir and atazanavir was separated by 12 hours.
[r] Administration of tenofovir and atazanavir was temporally separated by 12 hours.
NA = not available.

4.6 Pregnancy and lactation

Atazanavir: Pregnancy Category B

Risk Summary

Atazanavir 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 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 should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir.
- 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.

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

Atazanavir drug concentrations in fetal umbilical cord blood were approximately 12 to 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

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.

Ritonavir: **Pregnancy Category B**

Human data: There are no adequate and well-controlled studies in pregnant women. Ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry Data: As of January 2012, the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 3860 exposures to ritonavir containing regimens (1567 exposed in the first trimester and 2293 exposed in the second and third trimester). Birth defects occurred in 35 of the 1567 (2.2%) live births (first trimester exposure) and 59 of the 2293 (2.6%) 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 ritonavir and overall birth defects observed in the APR.

Animal data: No treatment related malformations were observed when ritonavir was administered to pregnant rats or rabbits. Developmental toxicity observed in rats (early resorptions, decreased fetal body weight and ossification delays and developmental variations) occurred at a maternally toxic dosage at an exposure equivalent to approximately 30% of that achieved with the proposed therapeutic dose. A slight increase in the incidence of cryptorchidism was also noted in rats at an

exposure approximately 22% of that achieved with the proposed therapeutic dose. Developmental toxicity observed in rabbits (resorptions, decreased litter size and decreased fetal weights) also occurred at a maternally toxic dosage equivalent to 1.8 times the proposed therapeutic dose based on a body surface area conversion factor.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed 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 breastfeed if they are taking Atazanavir and Ritonavir Tablets, 300 mg/100 mg.**

4.7 Effects on ability to drive and use machine.

No studies on the effects on ability to drive and use machines have been performed.

4.8 Undesirable Effects

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

- Drug interactions
- Cardiac conduction abnormalities/PR interval prolongation
- Allergic reactions/Hypersensitivity/Rash
- Hepatotoxicity/Hepatic Reactions Hyperbilirubinemia
- Nephrolithiasis and cholelithiasis
- Pancreatitis

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

Clinical Trial Experience in Adults

Treatment-Emergent Adverse Reactions in Treatment-Naive Patients

The safety profile of Atazanavir 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.

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

Selected clinical adverse reactions of moderate or severe intensity reported in greater than or equal

to 2% of treatment-naive patients receiving combination therapy including Atazanavir 300 mg with ritonavir 100 mg is presented in Table 3.

Table 4: Selected Treatment-Emergent Adverse Reactions[a] of Moderate or Severe Intensity Reported in greater than or equal to 2% of Adult Treatment-Naive Patients,[b] Study AI424-138

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

* None reported in this treatment arm.

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

[b] Based on the regimen containing atazanavir.

[c] Median time on therapy.

[d] As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

Treatment-Emergent Adverse Reactions in Treatment-Experienced Patients

The safety profile of atazanavir in treatment-experienced adults is based on 119 HIV-1 infected patients in clinical trials.

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

Selected clinical adverse reactions of moderate or severe intensity reported in greater than or equal to 2% of treatment-experienced patients receiving Atazanavir/ritonavir are presented in Table 4.

Table 5: Selected Treatment-Emergent Adverse Reactions[a] of Moderate or Severe Intensity Reported in greater than or equal to 2% of Adult Treatment-Experienced Patients,[b] Study AI424 045

	48 weeks[c] atazanavir/ritonavir 300/100 mg once daily + tenofovir + NRTI	48 weeks[c] lopinavir/ritonavir 400/100 mg twice daily + tenofovir + NRTI

	(n=119)	(n=118)
Body as a Whole		
Fever	2%	*
Digestive System		
Jaundice/scleral icterus	9%	*
Diarrhea	3%	11%
Nausea	3%	2%
Nervous System		
Depression	2%	<1%
Musculoskeletal System		
Myalgia	4%	*

* None reported in this treatment arm.

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

[b] Based on the regimen containing atazanavir.

[c] Median time on therapy.

Laboratory Abnormalities in Treatment-Naive Patients

The percentages of adult treatment-naive patients treated with combination therapy including Atazanavir 300 mg with ritonavir 100 mg with Grade 3 to 4 laboratory abnormalities are presented in Table 5.

Table 6: Grade 3 to 4 Laboratory Abnormalities Reported in greater than or equal to 2% of Adult Treatment-Naive Patients,[a] Study AI424-138

Variable	Limit[c]	96 weeks[b] atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine[d] (n=441)	96 weeks[b] lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir with emtricitabine[d] (n=437)
Chemistry	High		
SGOT/AST	≥5.1 x ULN	3%	1%
Variable	**Limit[c]**	**96 weeks[b] atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine[d] (n=441)**	**96 weeks[b] lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir with emtricitabine[d] (n=437)**
SGPT/ALT	≥5.1 x ULN	3%	2%

Total Bilirubin	≥2.6 x ULN	44%	<1%
Lipase	≥2.1 x ULN	2%	2%
Creatine Kinase	≥5.1 x ULN	8%	7%
Total Cholesterol	≥240 mg/dL	11%	25%
Hematology	Low		
Neutrophils	<750 cells/mm^3	5%	2%

[a] Based on the regimen containing Atazanavir.

[b] Median time on therapy.

[c] 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/ritonavir with Grade 3 to 4 laboratory abnormalities are presented in Table 6.

Table 7: Grade 3 to 4 Laboratory Abnormalities Reported in greater than or equal to 2% of Adult Treatment-Experienced Patients, Study AI424-045[a]

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

[a] Based on regimen(s) containing Atazanavir.

[b] Median time on therapy.

[c] ULN = upper limit of normal.

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 7.**Table 8: Lipid Values, Mean Change from Baseline, Study AI424-138**

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

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

[b] Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 1% in the lopinavir/ritonavir treatment arm and 1% in the Atazanavir/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. Through Week 96, serum lipid-reducing agents were used in 10% in the lopinavir/ritonavir treatment arm and 3% in the Atazanavir/ritonavir arm.

[c] Lopinavir 400 mg with ritonavir 100 mg twice daily with the fixed-dose combination 300 mg tenofovir, 200 mg emtricitabine once daily.

[d] The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 or Week 96 values and is not a simple difference of the baseline and Week 48 or Week 96 mean values, respectively.

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

[f] Fasting.

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 8. 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 9: Lipid Values, Mean Change from Baseline, Study AI424-045						
	atazanavir/ritonavir[a,b]			lopinavir/ritonavir[b,c]		
	Baseline mg/dL (n=111[e])	Week 48 mg/dL (n=75[e])	Week 48 Change[d] (n=74[e])	Baseline mg/dL (n=108[e])	Week 48 mg/dL (n=76[e])	Week 48 Change[d] (n=73[e])
LDL-Cholesterol[f]	108	98	−10%	104	103	+1%
HDL-Cholesterol	40	39	−7%	39	41	+2%
Total Cholesterol	188	170	−8%	181	187	+6%
Triglycerides[f]	215	161	−4%	196	224	+30%

[a] Atazanavir 300 mg once daily + ritonavir + tenofovir + 1 NRTI.
[b] Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 4% in the lopinavir/ritonavir treatment arm and 4% in the Atazanavir/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.
[c] Lopinavir/ritonavir (400/100 mg) BID + tenofovir + 1 NRTI.
[d] 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.
[e] Number of patients with LDL-cholesterol measured.
[f] Fasting.

Clinical Trial Experience in Pediatric Patients

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

The safety profile of atazanavir 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 to 4 adverse events (greater than or equal to 5%, regardless of causality) reported in pediatric patients were cough (21%), fever (18%), jaundice/scleral icterus (15%), rash (14%), vomiting (12%), diarrhea (9%), headache (8%), peripheral edema (7%), extremity pain (6%), nasal congestion (6%), oropharyngeal pain (6%), wheezing (6%), and rhinorrhea (6%). Asymptomatic second-degree atrioventricular block was reported in less than 2% of patients. The most common Grade 3 to 4 laboratory abnormalities occurring in pediatric patients were elevation of total bilirubin (greater than or equal to 3.2 mg/dL, 58%), neutropenia (9%), and hypoglycemia (4%). All other Grade 3 to 4 laboratory abnormalities occurred with a frequency of less than 3%.

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

Vomiting, diarrhea, and skin rash/allergy were the only drug-related clinical adverse events of

moderate to severe intensity observed in greater than or equal to 2% of pediatric patients enrolled in ritonavir clinical trials.

Laboratory Abnormalities

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

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 greater than 5 times ULN developed in 10% (6/60) of the atazanavir/ritonavir-treated patients and 8% (4/50) of the lopinavir/ritonavir-treated patients. AST levels greater than 5 times ULN developed in 10% (6/60) of the Atazanavir/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 greater than 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 greater than 5 times ULN developed in 10% (2/20) of the atazanavir/ritonavir-treated patients and 6% (1/18) of the lopinavir/ritonavir-treated patients.

Clinical Experience

Atazanavir, one component of Atazanavir 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)*].

Gastrointestinal System*:* pancreatitis

Hepatic System*:* hepatic function abnormalities

Hepatobiliary Disorders*:* cholelithiasis, cholecystitis, cholestasis.

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

Musculoskeletal System*:* arthralgia

Renal System*:* nephrolithiasis [see *Warnings and Precautions (5.8)*], interstitial nephritis

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

Ritonavir, one component of Atazanavir and Ritonavir Tablets

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

Body as a Whole

Dehydration, usually associated with gastrointestinal symptoms, and sometimes resulting in hypotension, or renal insufficiency has been reported. Syncope, orthostatic hypotension, and renal insufficiency have also been reported without known dehydration.

Coadministration of ritonavir with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system.

Cardiovascular System

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

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

Endocrine System

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

Nervous System

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

Skin and subcutaneous tissue disorders

Toxic epidermal necrolysis (TEN) has been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the authority ADR reporting tool; search for authority Adverse Reactions Reporting Tool in the Google Play Store.

4.9 Overdose

Atazanavir

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

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

Ritonavir

Acute Overdosage - Human Overdose Experience

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

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

Management of Overdosage

Treatment of overdose with ritonavir, one component of Atazanavir 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.

5 PHARMACEUTICAL PARTICULARS

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiretroviral

ATC code: J05AE08 - Atazanavir sulfate

J05AR10 - Ritonavir

Mechanism of action

Atazanavir: Atazanavir (ATV) is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.

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

Antiviral Activity in Cell Culture

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

(abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, 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.

Ritonavir: The activity of ritonavir was assessed in acutely infected lymphoblastoid cell lines and in peripheral blood lymphocytes. The concentration of drug that inhibits 50% (EC50) value of viral replication ranged from 3.8 to 153 nM depending upon the HIV-1 isolate and the cells employed. The average EC50 value for low passage clinical isolates was 22 nM (n = 13). In MT4 cells, ritonavir demonstrated additive effects against HIV-1 in combination with either didanosine (ddI) or zidovudine (ZDV). Studies which measured cytotoxicity of ritonavir on several cell lines showed that greater than 20 μM was required to inhibit cellular growth by 50% resulting in a cell culture therapeutic index of at least 1000.

Resistance

In Cell Culture*:*

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

Ritonavir: The activity of ritonavir was assessed in acutely infected lymphoblastoid cell lines and in peripheral blood lymphocytes. The concentration of drug that inhibits 50% (EC50) value of viral replication ranged from 3.8 to 153 nM depending upon the HIV-1 isolate and the cells employed. The average EC50 value for low passage clinical isolates was 22 nM (n = 13). In MT4 cells, ritonavir demonstrated additive effects against HIV-1 in combination with either didanosine (ddI) or zidovudine (ZDV). Studies which measured cytotoxicity of ritonavir on several cell lines showed that greater than 20 μM was required to inhibit cellular growth by 50% resulting in a cell culture therapeutic index of at least 1000.

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

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

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

Clinical Studies of Treatment-Naive Patients Receiving atazanavir 300 mg With Ritonavir 100 mg: In Phase III study AI424-138, an as-treated genotypic and phenotypic analysis was conducted on samples from patients who experienced virologic failure (HIV-1 RNA greater than or equal to 400 copies/mL) or discontinued before achieving suppression on ATV/RTV (n=39; 9%) and LPV/RTV (n=39; 9%) through 96 weeks of treatment. In the ATV/RTV arm, one of the virologic failure isolates had a 56-fold decrease in ATV susceptibility emerge on therapy with the development of PI resistance-associated substitutions L10F, V32I, K43T, M46I, A71I, G73S, I85I/V, and L90M. The NRTI resistance-associated substitution M184V also emerged on treatment in this isolate conferring emtricitabine resistance. Two ATV/RTV-virologic failure isolates had baseline phenotypic ATV resistance and IAS-defined major PI resistance-associated substitutions at baseline. The I50L substitution emerged on study in one of these failure isolates and was associated with a 17-fold decrease in ATV susceptibility from baseline and the other failure isolate with baseline ATV resistance and PI substitutions (M46M/I and I84I/V) had additional IAS-defined

major PI substitutions (V32I, M46I, and I84V) emerge on ATV treatment associated with a 3-fold decrease in ATV susceptibility from baseline. Five of the treatment failure isolates in the ATV/RTV arm developed phenotypic emtricitabine resistance with the emergence of either the M184I (n=1) or the M184V (n=4) substitution on therapy and none developed phenotypic tenofovir disoproxil resistance. In the LPV/RTV arm, one of the virologic failure patient isolates had a 69-fold decrease in LPV susceptibility emerge on therapy with the development of PI substitutions L10V, V11I, I54V, G73S, and V82A in addition to baseline PI substitutions L10L/I, V32I, I54I/V, A71I, G73G/S, V82V/A, L89V, and L90M. Six LPV/RTV virologic failure isolates developed the M184V substitution and phenotypic emtricitabine resistance and two developed phenotypic tenofovir disoproxil resistance.

Clinical Studies of Treatment-Experienced Patients*:* In studies of treatment-experienced patients treated with ATV or ATV/RTV, most ATV-resistant isolates from patients who experienced virologic failure developed substitutions that were associated with resistance to multiple PIs and displayed decreased susceptibility to multiple PIs. The most common protease substitutions to develop in the viral isolates of patients who failed treatment with ATV 300 mg once daily and RTV 100 mg once daily (together with tenofovir 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.

Ritonavir: HIV-1 isolates with reduced susceptibility to ritonavir have been selected in cell culture. Genotypic analysis of these isolates showed mutations in the HIV-1 protease gene leading to amino acid substitutions I84V, V82F, A71V, and M46I. Phenotypic (n = 18) and genotypic (n = 48) changes in HIV-1 isolates from selected patients treated with ritonavir were monitored in phase I/II trials over a period of 3 to 32 weeks. Substitutions associated with the HIV–1 viral protease in isolates obtained from 43 patients appeared to occur in a stepwise and ordered fashion at positions V82A/F/T/S, I54V, A71V/T, and I36L, followed by combinations of substitutions at an additional

5 specific amino acid positions (M46I/L, K20R, I84V, L33F and L90M). Of 18 patients for whom both phenotypic and genotypic analysis were performed on free virus isolated from plasma, 12 showed reduced susceptibility to ritonavir in cell culture. All 18 patients possessed one or more substitutions in the viral protease gene. The V82A/F substitution appeared to be necessary but not sufficient to confer phenotypic resistance. Phenotypic resistance was defined as a greater than or equal to 5-fold decrease in viral sensitivity in cell culture from baseline.

Cross-Resistance

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

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

Baseline Genotype/Phenotype and Virologic Outcome Analyses

Atazanavir

Genotypic and/or phenotypic analysis of baseline virus may aid in determining ATV susceptibility before initiation of ATV/RTV therapy. An association between virologic response at 48 weeks and

the number and type of primary PI resistance-associated substitutions detected in baseline HIV-1 isolates from antiretroviral-experienced patients receiving ATV/RTV once daily or lopinavir (LPV)/RTV twice daily in a Study AI424-045 is shown in Table 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 to 2 PI substitutions, including one of these substitutions.

Table 11: HIV RNA Response by Number and Type of Baseline PI Substitution, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

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

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

F53L.

The response rates of antiretroviral-experienced patients in Study AI424-045 were analyzed by baseline phenotype (shift in susceptibility in cell culture relative to reference, Table 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 12: Baseline Phenotype by Outcome, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

Baseline Phenotype[a]	Virologic Response = HIV RNA <400 copies/mL[b]	
	ATV/RTV (n=111)	LPV/RTV (n=111)
0–2	71% (55/78)	70% (56/80)
>2–5	53% (8/15)	44% (4/9)
>5–10	13% (1/8)	33% (3/9)
>10	10% (1/10)	23% (3/13)

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

5.2 Pharmacokinetic properties

Pharmacokinetics in Adults

Atazanavir and Ritonavir Tablets: Atazanavir exposure following administration of Atazanavir and ritonavir combination tablets (300 mg/100 mg) was comparable to exposure following administration of Reyataz® (Atazanavir) Capsules and Norvir® (ritonavir) Tablets, when administered to healthy volunteers under fasted and fed conditions.

Atazanavir

The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected patients after administration of atazanavir 300 mg and ritonavir 100 mg once daily (see Table 10).

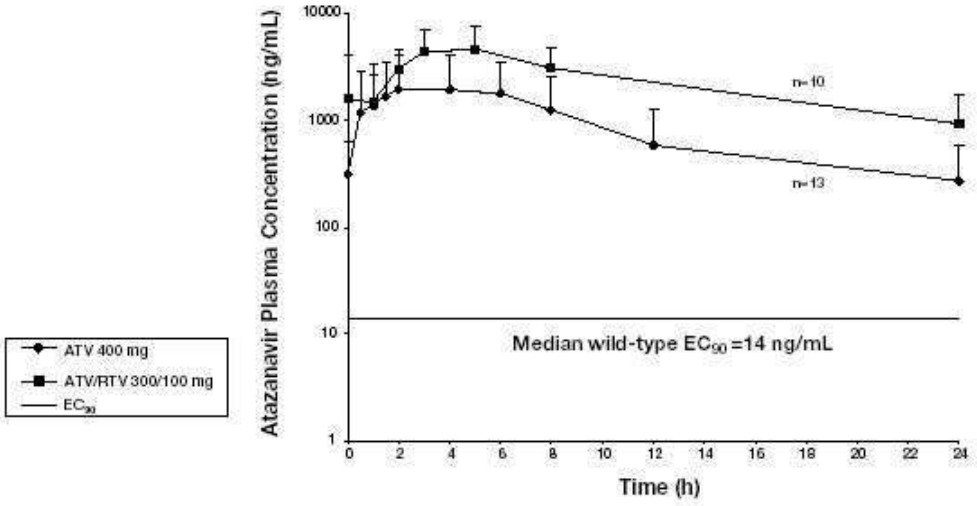
Table 13: Steady-State Pharmacokinetics of Atazanavir in Healthy Subjects or HIV-Infected Patients in the Fed State

	Atazanavir 300 mg and ritonavir 100 mg once daily	
Parameter	Healthy Subjects (n=28)	HIV-Infected Patients (n=10)
C_{max} (ng/mL)		
Geometric mean (CV%)	6129 (31)	4422 (58)

Mean (SD)	6450 (2031)	5233 (3033)
T_{max} (h)		
Median	2.7	3
AUC (ng•h/mL)		
Geometric mean (CV%)	57039 (37)	46073 (66)
Mean (SD)	61435 (22911)	53761 (35294)
T-half (h)		
Mean (SD)	18.1 (6.2)[a]	8.6 (2.3)
C_{min} (ng/mL)		
Geometric mean (CV %)	1227 (53)	636 (97)
Mean (SD)	1441 (757)	862 (838)
[a] n=26.		

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

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



Absorption

Atazanavir is rapidly absorbed with a T_{max} of approximately 2.5 hours. Atazanavir demonstrates nonlinear pharmacokinetics with greater than dose-proportional increases in AUC and C_{max} values over the dose range of 200 to 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 is 86% bound to human serum proteins and protein binding is independent of concentration. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively).

Metabolism

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

Elimination

Following a single 400-mg dose of ^{14}C-atazanavir, 79% and 13% of the total radioactivity was recovered in the feces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the feces and urine, respectively. The mean elimination half-life of atazanavir in healthy volunteers (n=214) and HIV-infected adult patients (n=13) was approximately 7 hours at steady state following a dose of 400 mg daily with a light meal.

In a study of five subjects receiving a 600 mg dose of ^{14}C-ritonavir oral solution, 11.3 ± 2.8% of the dose was excreted into the urine, with 3.5 ± 1.8% of the dose excreted as unchanged parent drug. In that study, 86.4 ± 2.9% of the dose was excreted in the feces with 33.8 ± 10.8% of the dose excreted as unchanged parent drug. Upon multiple dosing, ritonavir accumulation is less than predicted from a single dose possibly due to a time and dose-related increase in clearance.

Special Populations

Pediatrics

Atazanavir and Ritonavir Tablets should not be administered to HIV-1 infected pediatric patients less than 6 years of age and weighing less than 40kg.

Pregnancy

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

Table 14: Steady-State Pharmacokinetics of Atazanavir with ritonavir in HIV-Infected Pregnant Women in the Fed State

	Atazanavir 300 mg with ritonavir 100 mg		
Pharmacokinetic Parameter	**2nd Trimester (n=5[a])**	**3rd Trimester (n=20)**	**Postpartum[b] (n=34)**
C_{max} ng/mL	3078.85	3291.46	5721.21
Geometric mean (CV%)	(50)	(48)	(31)
AUC ng·h/mL	27657.1	34251.5	61990.4
Geometric mean (CV%)	(43)	(43)	(32)
C_{min} ng/mL[c]	538.70	668.48	1462.59
Geometric mean (CV%)	(46)	(50)	(45)

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

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

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

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Atazanavir: Long-term carcinogenicity studies in mice and rats were carried out with atazanavir for two years. In the mouse study, drug-related increases in hepatocellular adenomas were found in females at 360 mg/kg/day. The systemic drug exposure (AUC) at the NOAEL (no observable adverse effect level) in females, (120 mg/kg/day) was 2.8 times and in males (80 mg/kg/day) was 2.9 times higher than those in humans at the clinical dose (300 mg/day atazanavir boosted with 100 mg/day ritonavir, non-pregnant patients). In the rat study, no drug-related increases in tumor incidence were observed at doses up to 1200 mg/kg/day, for which AUCs were 1.1 (males) or 3.9 (females) times those measured in humans at the clinical dose.

Ritonavir: Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100 or 200 mg per kg per day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 0.3-fold for males that of the

exposure in humans with the recommended therapeutic dose (600 mg twice-daily). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 0.6-fold for the females that of the exposure in humans. In rats dosed at levels of 7, 15 or 30 mg per kg per day there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 6% that of the exposure in humans with the recommended therapeutic dose. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known.

Mutagenesis

Atazanavir: Atazanavir tested positive in an in vitro clastogenicity test using primary human lymphocytes, in the absence and presence of metabolic activation. Atazanavir tested negative in the in vitro Ames reverse-mutation assay, in vivo micronucleus and DNA repair tests in rats, and in vivo DNA damage test in rat duodenum (comet assay).

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

Impairment of Fertility

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, Crospovidone, Low substituted Hydroxypropyl cellulose, Povidone, Magnesium stearate, Copovidone, Colloidal silicon Dioxide, Sorbitan monolaurate, , Dibasic Calcium Phosphate Anhydrous, Sodium Stearyl Fumarate, Purified water and Opadry Yellow 16C82767 IHS.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

300mg/100mg

Blister pack: 30's HDPE Container

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/MANUFACTURER

7.1 Name and Address of Applicant

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7.2 Name and Address of Manufacturer

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