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SYNTHIVAN Tablets (Atazanavir + Ritonavir)

Black Box Warning

Drug-drug interactions leading to potentially serious and/or life threatening reactions
Co-administration of ritonavir with several classes of drugs including sedative hypnotics, antiarrhythmics, or ergot alkaloid preparations may result in potentially serious and/or life-threatening adverse events due to possible effects of ritonavir on the hepatic metabolism of certain drugs. Review medications taken by patients prior to prescribing ritonavir or when prescribing other medications to patients already taking ritonavir .

Composition

SYNTHIVAN
Each tablet contains
Atazanavir sulfate ..... 300 mg
Ritonavir .....100 mg

Dosage Form

Oral tablet

Description

SYNTHIVAN Tablets are fixed dose combination tablets of atazanavir (300 mg) and ritonavir (100 mg). Both atazanavir and ritonavir belong to the class of protease inhibitors.

Pharmacology

▶ Pharmacodynamics

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 the formation of mature virions.
Cardiac Electrophysiology
Concentration- and dose-dependent prolongation of the PR interval in the electrocardiogram (ECG) has been observed in healthy volunteers receiving atazanavir. In a placebo-controlled study (AI424-076), the mean (±SD) maximum change in the PR interval from the pre-dose value was 24 (±15) milliseconds (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 ECG (see WARNINGS AND PRECAUTIONS, *Cardiac Conduction Abnormalities*).

Electrocardiographic effects of atazanavir were determined in a clinical pharmacology study of 72 healthy subjects. Oral doses of 400 mg (maximum recommended dose) and 800 mg (twice the maximum recommended dosage) were compared with placebo; there was no concentration-dependent effect of atazanavir on the QTc interval (using Fridericia's correction). In 1793 HIV-infected patients receiving antiretroviral regimens, QTc prolongation was comparable in the atazanavir and comparator regimens. No atazanavir-treated healthy subject or HIV-infected patient had a QTc interval >500 msec (see WARNINGS AND PRECAUTIONS, *Cardiac Conduction Abnormalities*).

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.

Low doses of ritonavir (100 mg) have been used as a pharmacokinetic booster, to boost plasma levels of concomitantly administered protease inhibitors. Boosted protease inhibitors are currently considered the standard of care in HIV therapy.

Cardiac Electrophysiology

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

PR interval prolongation was also noted in subjects receiving ritonavir in the same study on Day 3. The maximum mean (95% confidence interval) difference from placebo in the PR interval after baseline correction was 22 (25) msec for 400 mg twice-daily ritonavir (see WARNINGS AND PRECAUTIONS - *PR Interval Prolongation*).

▶ Pharmacokinetics

The pharmacokinetics of atazanavir/ritonavir were evaluated in healthy adult volunteers and in HIV-infected patients after administration of atazanavir 300 mg with ritonavir 100 mg once daily (see Table 1).

Table 1: Steady-state pharmacokinetics of atazanavir/ritonavir in healthy subjects or HIV-infected patients in the fed state

Parameter	300 mg with ritonavir 100 mg once daily	
	Healthy subjects (n=28)	HIV-infected patients (n=10)
C_{max} (ng/mL)		
Geometric mean (CV%)	6129 (31)	4422 (58)
Mean (SD)	6450 (2031)	5233 (3033)
T_{max} (h)		
Median	2.7	3.0
AUC (ng•h/mL)		
Geometric mean (CV%)	57039 (37)	46073 (66)
Mean (SD)	61435 (22911)	53761 (35294)

T-half (h)		
Mean (SD)	18.1 (6.2)[a]	8.6 (2.3)
C_{min} (ng/mL)		
Geometric mean (CV%)	1227 (53)	636 (97)
Mean (SD)	1441 (757)	862 (838)

[a] n=26

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

Absorption

Atazanavir is rapidly absorbed with a T_{max} of approximately 2.5 hours. Atazanavir demonstrates non-linear 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.

Effect of Food on Oral Absorption

Atazanavir

Administration of atazanavir with food enhances bioavailability and reduces pharmacokinetic variability. Co-administration of a single 300 mg dose of atazanavir and a 100 mg dose of ritonavir with a light meal (336 kcal, 5.1 g fat, 9.3 g protein) resulted in a 33% increase in the AUC and a 40% increase in both the C_{max} and the 24-hour concentration of atazanavir relative to the fasting state. Co-administration with a high-fat meal (951 kcal, 54.7 g fat, 35.9 g protein) did not affect the AUC of atazanavir relative to fasting conditions and the C_{max} was within 11% of fasting values. The 24-hour concentration following a high-fat meal was increased by approximately 33% due to delayed absorption; the median T_{max} increased from 2.0 to 5.0 hours. Co-administration of atazanavir with ritonavir with either a light or a high-fat meal decreased the coefficient of variation of AUC and C_{max} by approximately 25%, compared to the fasting state.

Ritonavir

Following the administration of a 100 mg tablet dose of Ritonavir, C_{max} and AUC_{inf} of ritonavir were decreased by 21-23% under moderate fat (857 Kcal, 30% from fat) or high fat conditions (917 Kcal, 60% calories from fat) relative to fasting conditions.

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

Atazanavir is extensively metabolized in humans. The major biotransformation pathways of atazanavir in humans consisted of mono-oxygenation 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.

Special Populations

Gender, Race and Age

Ritonavir

No age-related pharmacokinetic differences have been observed in adult patients (18 to 63 years). Ritonavir pharmacokinetics have not been studied in older patients.

A study of ritonavir pharmacokinetics in healthy males and females showed no statistically significant differences in the pharmacokinetics of ritonavir. Pharmacokinetic differences due to race have not been identified.

Renal Impairment

Atazanavir

Atazanavir is not recommended for use in HIV-treatment-experienced patients with end stage renal disease managed with hemodialysis (see, DOSAGE AND ADMINISTRATION).

Ritonavir

Ritonavir pharmacokinetics have not been studied in patients with renal impairment, however, since renal clearance is negligible, a decrease in total body clearance is not expected in patients with renal impairment.

Hepatic Impairment

A dose of 300 mg is recommended for patients with moderate hepatic impairment (Child-Pugh Class B) who have not experienced prior virologic failure as increased concentrations of atazanavir are expected. Atazanavir is not recommended for use in patients with severe hepatic impairment. The pharmacokinetics of atazanavir in combination with ritonavir has not been studied in subjects with hepatic impairment; thus, coadministration of atazanavir with ritonavir is not recommended for use in patients with any degree of hepatic impairment (see DOSAGE AND ADMINISTRATION).

Pregnancy

Atazanavir

The pharmacokinetic data from HIV-infected pregnant women receiving Atazanavir capsules with ritonavir are presented in Table 2.

Table 2: Steady-State pharmacokinetics of atazanavir with ritonavir in hiv-infected pregnant women in the fed state

Pharmacokinetic parameter	Atazanavir 300 mg with ritonavir 100 mg		
	2nd Trimester (n=5[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 (4-12 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.

Ritonavir

Based on evaluation of the published literature, ritonavir exposures are reduced during pregnancy relative to postpartum.

Indications

SYNTHIVAN Tablets are indicated for treatment of HIV infection in adults.

Dosage And Administration

▶ Overview

SYNTHIVAN Tablets must be taken with food.

The recommended oral dosage of SYNTHIVAN Tablets depends on the treatment history of the patient and the use of other co-administered drugs. When co-administered with H2-receptor antagonists or proton-pump inhibitors, dose separation may be required. (See WARNING AND PRECAUTIONS, Drug Interactions).

Atazanavir without ritonavir is not recommended for treatment-experienced adult patients with prior virologic failure.

Efficacy and safety of atazanavir with ritonavir when ritonavir is administered in doses greater than 100 mg once daily have not been established. The use of higher ritonavir doses may alter the safety profile of atazanavir (cardiac effects, hyperbilirubinemia) and, therefore, is not recommended. Prescribers should consult the complete prescribing information for ritonavir when using ritonavir.

▶ Testing Prior to Initiation and During Treatment with Atazanavir

Renal laboratory testing should be performed in all patients prior to initiation of Atazanavir and continued during treatment with Atazanavir. Renal laboratory testing should include serum creatinine, estimated creatinine clearance, and urinalysis with microscopic examination (see WARNINGS AND PRECAUTIONS).

Hepatic laboratory testing should be performed in patients with underlying liver disease prior to initiation of Atazanavir and continued during treatment with Atazanavir (see WARNINGS AND PRECAUTIONS).

▶ Recommended Adult Dosage

Dose Recommendations for Therapy-Naïve Patients

One SYNTHIVAN tablet once daily with food.

Concomitant Therapy

One SYNTHIVAN tablet once daily with food if combined with any of the following:

- Tenofovir
- *H2-receptor antagonist:* The H2-receptor antagonist dose should not exceed a dose comparable to famotidine 40 mg twice daily. SYNTHIVAN tablets should be administered simultaneously with, and/or at least 10 hours after, the dose of the H2-receptor antagonist.
- *Proton-pump inhibitors:* 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 SYNTHIVAN Tablets dose.

Dose Recommendations for Therapy-Experienced Patients:

One SYNTHIVAN tablet once daily with food.

Concomitant Therapy

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

One SYNTHIVAN tablet once daily with food if taken with an H2-receptor antagonist.

Do not administer SYNTHIVAN Tablets if both tenofovir and an H_2-receptor antagonist has to be taken together.

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

Efavirenz: Do not co-administer SYNTHIVAN Tablets with efavirenz in treatment-experienced patients due to decreased atazanavir exposure.

(For these drugs and other antiretroviral agents for which dosing modification may be appropriate, see WARNINGS AND PRECAUTIONS, Drug Interactions).

Dosage Adjustments in Pregnant Patients

Table 3 includes the recommended dosage of Atazanavir capsules and ritonavir in treatment-naive and treatment-experienced pregnant patients. In these patients, Atazanavir must be administered with ritonavir. There are no dosage adjustments for postpartum patients (see WARNING AND PRECAUTIONS).

Table 3: Recommended dosage of atazanavir and ritonavir in pregnant patientsa

	Atazanavir OD dosage	Ritonavir OD dosage
Treatment-naïve and treatment-experienced		
Recommended regimen	300 mg	100 mg
Treatment-Experienced During the Second or Third Trimester When Co-administered with either H2RA or Tenofovir DF[b]		
In combination with either H2RA or tenofovir DF	400 mg	100 mg

[a] See WARNING AND PRECAUTIONS for instructions concerning coadministration of acid-reducing medications (eg, H2RA or PPIs), and other antiretroviral drugs (eg, efavirenz, tenofovir DF, and didanosine).

[b] Atazanavir is not recommended for treatment-experienced pregnant patients during the second and third trimester taking Atazanavir with both tenofovir DF and H2RA.

Dosage in patients with Renal Impairment

For patients with renal impairment, including those with severe renal impairment who are not managed with hemodialysis, no dose adjustment is required for atazanavir. Treatment-naïve patients with end-stage renal disease managed with hemodialysis should receive SYNTHIVAN Tablets. atazanavir should not be administered to HIV-treatmen--experienced patients with end-stage renal disease managed with hemodialysis. (see PHARMACOKINETICS, *special populations).*

▶ Dosage Adjustments in Patients with Hepatic Impairment

SYNTHIVAN Tablets can be administered in patients with moderate hepatic impairment (Child-Pugh Class B). The use of atazanavir in patients with severe hepatic impairment (Child-Pugh Class C) is not recommended. The coadministration of atazanavir with ritonavir in patients with any degree of hepatic impairment is not recommended.

Contraindications

SYNTHIVAN Tablets are contraindicated:

In patients with previously demonstrated clinically significant hypersensitivity (e.g. Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product;

When co-administered with drugs that are highly dependent on CYP3A or UGT1A1 for clearance, and for which elevated plasma concentrations of interacting drugs are associated with serious and/or life-threatening events. These and other contraindicated drugs are listed in Table 4.

When coadministered with drugs that strongly induce CYP3A and may lead to lower exposure and loss of efficacy of atazanavir sulphate.

Table 4: Drugs that are contraindicated with atazanavir

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.
Antipsychotics	Lurasidone	Potential for serious and/or life-threatening reactions if atazanavir is coadministered with ritonavir.
	Pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.

Benzodiazepines	Triazolam, orally administered midazolam[a]	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Co-administration 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.
Gastrointestinal (GI) Motility Agent	cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Hepatitis C Direct-Acting Antivirals	Elbasvir/grazoprevir	May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations.
Herbal Products	St. John's wort (*Hypericum perforatum*)	Coadministration of St. John’s wort and atazanavir sulfate may result in loss of therapeutic effect and development of resistance.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for serious reactions such as myopathy, including rhabdomyolysis.
PDE5 Enzyme inhibitor	Sildenafil[b], when dosed for the treatment of pulmonary arterial hypertension (PAH)	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.
Non-nucleoside Reverse Transcriptase Inhibitors	Nevirapine	Nevirapine substantially decreases atazanavir exposure which may result in loss of therapeutic effect and development of resistance. Potential risk for nevirapine-associated adverse reactions due to increased nevirapine exposures.

[a] See WARNINGS AND PRECAUTIONS, *Drug Interactions*, Table 6 for parenterally administered midazolam.

[b] See WARNINGS AND PRECAUTIONS, *Drug Interactions,* Table 6 for sildenafil when dosed for erectile dysfunction.

Table 5: Drugs that are contraindicated with ritonavir use (full dose)

Drug Class	Drugs Within Class That Are CONTRAINDICATED with ritonavir	Clinical comments
Alpha$_1$-adrenoreceptor antagonist	Alfuzosin HCL	Potential for hypotension
Antianginal	Ranolazine	Potential for serious and/or life-threatening reactions.
Anti-arrhythmic	amiodarone, dronedarone, flecainide, propafenone, quinidine	Potential for cardiac arrhythmias
Antifungal	Voriconazole	Voriconazole is contraindicated with ritonavir doses 400 mg every 12 hours or greater due to the potential for loss of antifungal response.
Anti-gout	Colchicine[a]	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Antipsychotics	Lurasidone Pimozide	Potential for serious and/or life-threatening reactions. Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products	St. John's Wort (*hypericum perforatum*)	May lead to loss of virologic response and possible resistance to ritonavir or to the class of protease inhibitors.
Ergot Derivatives	dihydroergotamine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by vasopasm and ischemia of the extremities and other tissues, including the central nervous system.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy, including rhabdomyolysis.
GI Motility Agent	cisapride	Potential for cardiac arrhythmias
PDE5 inhibitor	Sildenafil[b], when used for the treatment of pulmonary arterial hypertension (PAH)	Potential for sildenafil-associated adverse events, including visual abnormalities, hypotension, prolonged erection and syncope

Sedative/hypnotics	Oral midazolam[c], triazolam	Prolonged or increased sedation or respiratory depression

[a] (see WARNING AND PRECAUTIONS, Drug Interactions), Table 7 for colchicine doses in patients with normal hepatic and renal function.

[b] (see WARNING AND PRECAUTIONS, Drug Interactions), Table 7 for co-administration of sildenafil in patients with erectile dysfunction.

[c] (see WARNING AND PRECAUTIONS, Drug Interactions), Table 7 for parenterally administered midazolam.

Warnings And Precautions

▶ Atazanavir

Drug Interactions

Potential for Atazanavir to Affect Other Drugs

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

Atazanavir is a weak inhibitor of CYP2C8. Use of atazanavir without ritonavir is not recommended when coadministered with drugs highly dependent on CYP2C8 with narrow therapeutic indices (eg, paclitaxel, repaglinide). When atazanavir sulfate with ritonavir is coadministered with substrates of CYP2C8, clinically significant interactions are not expected.

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

Potential for Other Drugs to Affect Atazanavir

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

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

Established and Other Potentially Significant Drug Interactions

Table 6 provides dosing recommendations in adults as a result of drug interactions with atazanavir. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 6: Established and other potentially significant drug interactions: Alteration in dose or regimen may be recommended based on drug interaction studies 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	Co-administration of atazanavir with didanosine buffered tablets resulted in a marked decrease in atazanavir exposure. It is recommended that atazanavir be given (with food) 2 h before or 1 h after didanosine buffered formulations. Simultaneous administration of didanosine EC and atazanavir with food results in a decrease in didanosine exposure. Thus, atazanavir and didanosine EC should be administered at different times.
Nucleotide Reverse Transcriptase Inhibitors: tenofovir disoproxil fumarate (DF)	↓ atazanavir ↑ tenofovir	Tenofovir DF may decrease the AUC and C_{min} of atazanavir. When co-administered with tenofovir DF in adults, it is recommended that atazanavir 300 mg be given with ritonavir 100 mg and tenofovir DF 300 mg (all as a single daily dose with food). Atazanavir increases tenofovir concentrations. The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse reactions, including renal disorders. Patients receiving atazanavir and tenofovir DF should be monitored for tenofovir-associated adverse reactions. For pregnant women taking atazanavir with ritonavir *and* tenofovir DF (see DOSAGE AND ADMINISTRATION)
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs): efavirenz	↓ atazanavir	Efavirenz decreases atazanavir exposure. *In treatment-naïve patients:* If atazanavir is combined with efavirenz, atazanavir 400 mg (two 200mg capsules) should be administered with ritonavir 100 mg simultaneously once daily with food, and efavirenz 600 mg should be administered once daily on an empty stomach, preferably at bedtime. *In treatment-experienced patients:* Co-administration of atazanavir with efavirenz in treatment-experienced patients is not recommended due to decreased atazanavir exposure.
Protease Inhibitors: saquinavir (soft gelatin capsules)	↑ saquinavir	Appropriate dosing recommendations for this combination, with or without ritonavir, with respect to efficacy and safety have not been established. In a clinical study, saquinavir 1200 mg co-administered with atazanavir 400 mg and tenofovir DF 300 mg (all given once daily) plus nucleoside analogue reverse transcriptase inhibitors did not provide adequate efficacy.
ritonavir	↑ atazanavir	If atazanavir is co-administered with ritonavir, it is recommended that atazanavir 300 mg once daily be given with ritonavir 100 mg once daily with food in adults.

others	↑ other protease inhibitor	Although not studied, the co-administration of atazanavir/ritonavir and an additional protease inhibitors would be expected to increase exposure to the other protease inhibitor. Such co-administration is not recommended.
HCV Antiviral Agents		
Protease Inhibitors: Boceprevir	↓ atazanavir ↓ ritonavir	Concomitant administration of boceprevir and atazanavir/ritonavir resulted in reduced steady-state exposures to atazanavir and ritonavir. Coadministration of atazanavir sulfate/ritonavir and boceprevir is not recommended.
Other Agents		
Antacids and buffered medications	↓ atazanavir	Reduced plasma concentrations of atazanavir are expected if antacids, including buffered medications, are administered with atazanavir. Atazanavir should be administered 2 hours before or 1 hour after these medications.
Anti-arrhythmics: amiodarone, bepridil, lidocaine (systemic), quinidine	↑ amiodarone, bepridil, lidocaine (systemic), quinidine	Co-administration with atazanavir has the potential to produce serious and/or life-threatening adverse events and has not been studied. Caution is warranted and therapeutic concentration monitoring of these drugs is recommended if they are used concomitantly with atazanavir sulfate.
Anticoagulants: warfarin	↑ warfarin	Co-administration with atazanavir has the potential to produce serious and/or life-threatening bleeding and has not been studied. It is recommended that International Normalized Ratio (INR) be monitored.
Antidepressants: tricyclic antidepressants	↑ tricyclic antidepressants	Co-administration with atazanavir has the potential to produce serious and/or life-threatening adverse events and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with atazanavir.
trazodone	↑ trazodone	Concomitant use of trazodone and atazanavir with or without ritonavir may increase plasma concentrations of trazodone. Nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as atazanavir, the combination should be used with caution and a lower dose of trazodone should be considered.

Antiepileptics: carbamazepine	↓ atazanavir ↑ carbamazepine	Plasma concentrations of atazanavir may be decreased when carbamazepine is administered with atazanavir sulfate without ritonavir. Coadministration of carbamazepine and atazanavir sulfate without ritonavir is not recommended. Ritonavir may increase plasma levels of carbamazepine. If patients beginning treatment with atazanavir sulfate/ritonavir have been titrated to a stable dose of carbamazepine, a dose reduction for carbamazepine may be necessary.
phenytoin, phenobarbital	↓ atazanavir ↓ phenytoin ↓ phenobarbital	Plasma concentrations of atazanavir may be decreased when phenytoin or phenobarbital is administered with atazanavir sulfate without ritonavir. Coadministration of phenytoin or phenobarbital and atazanavir sulfate without ritonavir is not recommended. Ritonavir may decrease plasma levels of phenytoin and phenobarbital. When atazanavir sulfate with ritonavir is coadministered with either phenytoin or phenobarbital, a dose adjustment of phenytoin or phenobarbital may be required.
lamotrigine	↓ lamotrigine	Coadministration of lamotrigine and atazanavir sulfate with ritonavir may decrease lamotrigine plasma concentrations. Dose adjustment of lamotrigine may be required when coadministered with atazanavir sulfate and ritonavir. Coadministration of lamotrigine and atazanavir sulfate without ritonavir is not expected to decrease lamotrigine plasma concentrations. No dose adjustment of lamotrigine is required when coadministered with atazanavir sulfate without ritonavir.
Antifungals: ketoconazole, itraconazole	Atazanavir/ritonavir ↑ ketoconazole ↑ itraconazole	Co-administration of ketoconazole has only been studied with atazanavir without ritonavir (negligible increase in atazanavir AUC and C_{max}). Due to the effect of ritonavir on ketoconazole, high doses of ketoconazole and itraconazole (>200 mg/day) should be used cautiously with atazanavir/ritonavir.

voriconazole	*Atazanavir Sulfate/ ritonavir in subjects with a functional CYP2C19 allele:* ↓ voriconazole ↓ atazanavir *Atazanavir Sulfate/ ritonavir in subjects without a functional CYP2C19 allele:* ↑ voriconazole ↓ atazanavir	The use of voriconazole in patients receiving atazanavir sulfate/ritonavir is not recommended unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Patients should be carefully monitored for voriconazole-associated adverse reactions and loss of either voriconazole or atazanavir efficacy during the coadministration of voriconazole and atazanavir sulfate /ritonavir. Coadministration of voriconazole with atazanavir sulfate (without ritonavir) may affect atazanavir concentrations; however, no data are available.
Anti-gout: Colchicine	↑colchicine	The coadministration of atazanavir sulfate with colchicine in patients with renal or hepatic impairment is not recommended. *Recommended adult dosage of colchicine when administered with atazanavir:* *Treatment of gout flares*: 0.6 mg (1 tablet) for 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Not to be repeated before 3 days. *Prophylaxis of gout flares*: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. *Treatment of familial Mediterranean fever (FMF)*: maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
Antimycobacterials: rifabutin	↑ rifabutin	A rifabutin dose reduction of up to 75% (e.g., 150 mg every other day or 3 times per week) is recommended. Increased monitoring for rifabutin-associated adverse reactions including neutropenia is warranted.

Antipsychotics: quetiapine and lurasidone	↑ quetiapine Atazanavir/ritonavir ↑ lurasidone	Initiation of atazanavir sulfate with ritonavir in patients taking quetiapine: Consider alternative antiretroviral therapy to avoid increases in quetiapine exposures. If coadministration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring. Initiation of quetiapine in patients taking atazanavir sulfate with ritonavir: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine Atazanavir/ritonavir Use of Lurasidone is contraindicated
Benzodiazepines: parenterally administered midazolam[a]	↑ midazolam	Concomitant use of parenteral midazolam with atazanavir may increase plasma concentrations of midazolam. Co-administration 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. Co-administration 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. Co-administration 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	Plasma concentrations of atazanavir may be decreased when bosentan is administered with atazanavir without ritonavir. Co-administration of bosentan and atazanavir without ritonavir is not recommended. *Co-administration of bosentan in adult patients on Atazanavir/ritonavir*: For patients, who have been receiving atazanavir/ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day, based on individual tolerability. *Co-administration of Atazanavir/ritonavir in adult patients on bosentan:* Discontinue bosentan at least 36 hours before starting atazanavir/ritonavir. At least 10 days after starting atazanavir/ritonavir, resume bosentan at 62.5 mg once daily or every other day, based on individual tolerability.
HMG-CoA reductase inhibitors: atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Titrate atorvastatin dose carefully and use the lowest necessary dose. Rosuvastatin dose should not exceed 10 mg/day. The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including atazanavir, are used in combination with these drugs.
H2-Receptor antagonists	↓ atazanavir	Plasma concentrations of atazanavir were substantially decreased when atazanavir 400 mg once daily was administered simultaneously with famotidine 40 mg twice daily in adults, which may result in loss of therapeutic effect and development of resistance. *In treatment-naïve patients:* Atazanavir 300 mg/ritonavir 100 mg once daily with food should be administered simultaneously with, and/or at least 10 hours after, a dose of the H2-receptor antagonist (H2RA). An H2RA dose comparable to famotidine 20 mg once daily up to a dose comparable to famotidine 40 mg twice daily can be used with atazanavir 300 mg with ritonavir 100 mg in treatment-naïve patients. *In treatment-experienced patients:* Whenever an H2RA is given to a patient receiving atazanavir with ritonavir, the H2RA dose should not exceed a dose comparable to famotidine 20 mg twice daily, and the atazanavir and ritonavir doses should be administered simultaneously with, and/or at least 10 hours after, the dose of the H2-receptor antagonist. Atazanavir 300 mg/ritonavir 100 mg once daily (all as a single dose with food) if taken with an H2RA.

Immunosuppressants: cyclosporin, sirolimus, tacrolimus	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for these immunosuppressants when co-administered with atazanavir sulfate.
Inhaled beta agonist: Salmeterol	↑ salmeterol	Coadministration of salmeterol with Atazanavir is not recommended. Concomitant use of salmeterol and atazanavir may result in increased risk of cardiovascular adverse reactions associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Inhaled/nasal steroid: fluticasone	atazanavir/ritonavir ↑ fluticasone	Concomitant use of fluticasone propionate and atazanavir/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression, have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate or budesonides. Co-administration of fluticasone propionate and atazanavir/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see WARNINGS AND PRECAUTIONS).
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 co-administered with atazanavir. In addition, concentrations of the active metabolite 14-OH clarithromycin are significantly reduced; consider alternative therapy for indications other than infections due to *Mycobacterium avium* complex. Co-administration of atazanavir/ritonavir with clarithromycin has not been studied.

Hormonal contraceptives: ethinyl estradiol and norgestimate or norethindrone	↓ ethinyl estradiol ↑ norgestimate[b] ↑ ethinyl estradiol ↑ norethindrone[c]	Use with caution if co-administration of atazanavir or atazanavir/ritonavir with oral contraceptives is considered. If an oral contraceptive is administered with atazanavir/ritonavir, it is recommended that the oral contraceptive contain at least 35 mcg of ethinyl estradiol. Potential safety risks include substantial increases in progesterone exposure. The long-term effects of increases in concentration of the progestational agent are unknown and could increase the risk of insulin resistance, dyslipidemia, and acne. Co-administration of atazanavir or atazanavir/ritonavir with other hormonal contraceptives (e.g., contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestagens other than norethindrone or norgestimate, or less than 25 mcg of ethinyl estradiol, has not been studied; therefore, alternative methods of contraception are recommended.
Opioids: Buprenorphine	↑buprenorphine ↑ norbuprenorphine	Co-administration of buprenorphine and Atazanavir/ritonavir increases the plasma concentration of buprenorphine and norbuprenorphine. Co-administration of Atazanavir/ritonavir with buprenorphine warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered. Co- administration of buprenorphine and Atazanavir with ritonavir is not expected to decrease atazanavir plasma concentrations. Coadministration of buprenorphine and atazanavir without ritonavir may decrease atazanavir plasma concentrations. The coadminsitration of atazanavir sulfate and buprenorphine without ritonavir is not recommended

PDE5 inhibitors: sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Co-administration with atazanavir has not been studied but may result in an increase in PDE5 inhibitor-associated adverse reactions, including hypotension, syncope, visual changes, 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. *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. Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours, with increased monitoring for adverse reactions.

Proton-pump inhibitors: omeprazole	↓ atazanavir	Plasma concentrations of atazanavir were substantially decreased when atazanavir 400 mg or atazanavir 300 mg/ritonavir 100 mg once daily was administered with omeprazole 40 mg once daily, which may result in loss of therapeutic effect and development of resistance. *In treatment-naïve patients:* The proton-pump inhibitor (PPI) dose should not exceed a dose comparable to omeprazole 20 mg and must be taken approximately 12 hours prior to Atazanavir/ritonavir 300/100 mg. *In treatment-experienced patients:* The use of PPIs in treatment-experienced patients receiving atazanavir is not recommended.
[a] See Contraindications, Table 4, for orally administered midazolam. [b] In combination with atazanavir 300 mg and ritonavir 100 mg once daily. [c] In combination with atazanavir 400 mg once daily.		

Drugs with No Observed Interactions with atazanavir

No clinically significant drug interactions were observed when atazanavir was co-administered with methadone, fluconazole, acetaminophen or atenolol, or the nucleoside reverse transcriptase inhibitors lamivudine or zidovudine.

Cardiac Conduction Abnormalities

Atazanavir has been shown to prolong the PR interval of the electrocardiogram in some patients. In healthy volunteers and in patients, abnormalities in atrioventricular (AV) conduction were asymptomatic and generally limited to first-degree AV block. There have been reports of second-degree AV block and other conduction abnormalities (see UNDESIRABLE EFFECTS and OVERDOSAGE). In clinical trials that included electrocardiograms, asymptomatic first-degree AV block was observed in 5.9% of atazanavir-treated patients (n=920), 5.2% of lopinavir/ritonavir-treated patients (n=252), 10.4% of nelfinavir-treated patients (n=48), and 3.0% of efavirenz-treated patients (n=329). In Study AI424-045, asymptomatic first-degree AV block was observed in 5% (6/118) of atazanavir/ritonavir-treated patients and 5% (6/116) of lopinavir/ritonavir-treated patients who had on-study electrocardiogram measurements. Because of limited clinical experience in patients with preexisting conduction system disease (e.g., marked first-degree AV block or second- or third-degree AV block), ECG monitoring should be considered in these patients. (see PHARMACOLOGY).

Severe Skin Reactions

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

Hyperbilirubinemia

Most patients taking atazanavir sulfate experience asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT). This hyperbilirubinemia is reversible upon discontinuation of

atazanavir sulfate. Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies. No long-term safety data are available for patients experiencing persistent elevations in total bilirubin >5 times the upper limit of normal (ULN). Alternative antiretroviral therapy to atazanavir sulfate may be considered if jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for patients. Dose reduction of atazanavir is not recommended since long-term efficacy of reduced doses has not been established (see UNDESIRABLE EFFECTS).

Hepatotoxicity

Patients with underlying hepatitis B or C viral infections or marked elevations in transaminases before treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. In these patients, hepatic laboratory testing should be conducted prior to initiating therapy with atazanavir and during treatment. (see DOSING AND ADMINISTRATION, UNDESIRABLE EFFECTS).

Chronic Kidney Disease

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

Nephrolithiasis and Cholelithiasis

Cases of nephrolithiasis and/or cholelithiasis have been reported during post marketing surveillance 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. (See UNDESIRABLE EFFECTS).

Risk of Serious Adverse Reactions Due to Drug Interactions

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

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

Consider the potential for drug interactions prior to and during atazanavir/ritonavir therapy; review concomitant medications during atazanavir/ritonavir therapy; and monitor for the adverse reactions associated with the concomitant medications (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Diabetes Mellitus/Hyperglycemia

New-onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia

persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established. (See UNDESIRABLE EFFECTS).

Immune Reconstitution Syndrome

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

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) 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. 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 have been observed. Resistance to atazanavir may not preclude the subsequent use of other protease inhibitors.

▶ Ritonavir (Full dose)

Risk of serious adverse reactions due to Drug interactions:

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

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

Hepatotoxicity

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 postmarketing 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

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

PR Interval Prolongation

Ritonavir prolongs the PR interval in some patients. Postmarketing 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, pre-existing 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. (see PHARMACOLOGY, Pharmacodynamics).

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. Triglycerides and cholesterol testing should be performed prior to initiating ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate, taking into account any potential drug-drug interactions with ritonavir and HMG CoA reductase inhibitors. (see CONTRAINDICATIONS).

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.

▶ Pregnancy

Pregnancy category B

Atazanavir and ritonavir (full dose) are classified under pregnancy category B. Complete details regarding animal reproduction studies on both atazanavir and ritonavir (full dose) can be found in their respective prescribing information.

Risk Summary

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

Clinical Considerations

Dose Adjustments during Pregnancy and the Postpartum Period

Atazanavir must be administered with ritonavir in pregnant women.

No dosage adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir exposures could be higher during the first 2 months after delivery (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY).

Maternal Adverse Reactions

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

Hyperbilirubinemia occurs frequently in patients who take Atazanavir.

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

Data

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 ULN). There were no cases of lactic acidosis observed in clinical trial AI424-182.

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

Based on prospective reports from the APR of approximately 1600 live births following exposure to atazanavir-containing regimens (including 1037 live births in infants exposed in the first trimester and 569 exposed in second/third trimesters), there was no difference between atazanavir and overall birth defects compared with the background birth defect rate. In the U.S. general population, the estimated background risk of major birth defects in clinically recognized pregnancies is 2-4%.

Animal Data

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

▶ Lactation

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 and ritonavir (full dose) is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving SYNTHIVAN Tablets.

▶ Pediatric Use

Atazanavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients 3 months of age and older weighing at least 5 kg. Atazanavir is not recommended for use in pediatric patients below the age of 3 months due to the risk of kernicterus. All atazanavir contraindications, warnings, and precautions apply to pediatric patients.
The safety, pharmacokinetic profile, and virologic response of atazanavir in pediatric patients at least 3 months of age and older weighing at least 5 kg were established in three open-label, multicenter clinical trials: PACTG 1020A, AI424-451, and AI424-397. The safety profile in pediatric patients was generally similar to that observed in adults.

▶ Geriatric Use

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

▶ Age/Gender

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

▶ Impaired Renal Function

Atazanavir is not recommended for use in HIV-treatment-experienced patients with end stage renal disease managed with hemodialysis (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY).

▶ Impaired Hepatic Function

Atazanavir is not recommended for use in patients with severe hepatic impairment. Atazanavir/ritonavir is not recommended in patients with any degree of hepatic impairment (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY).

Undesirable Effects

▶ Atazanavir

The following adverse reactions are discussed in greater detail in other sections of the labeling:
cardiac conduction abnormalities (see WARNINGS AND PRECAUTIONS)
rash (see WARNINGS AND PRECAUTIONS)
hyperbilirubinemia (see WARNINGS AND PRECAUTIONS)
Chronic kidney disease (see WARNINGS AND PRECAUTIONS)
nephrolithiasis and cholelithiasis (see WARNINGS AND PRECAUTIONS)

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

Clinical Trial Experience in Adults

Adverse Reactions in Treatment-Naïve Adult Patients

The safety profile of atazanavir in treatment-naïve adults is based on 1625 HIV-1-infected patients in clinical trials. 536 patients received atazanavir 300 mg with ritonavir 100 mg and 1089 patients received atazanavir 400 mg or higher (without ritonavir).

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

Selected clinical adverse reactions of moderate or severe intensity reported in ≥2% of treatment-naïve patients receiving combination therapy, including atazanavir 300 mg with ritonavir 100 mg, are presented in Table 7.

Table 7: Selected treatment-emergent adverse eventsa of moderate or severe intensity reported in ≥2% of adult treatment-naïve patientb (Study AI424-138)

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

* None reported in this treatment arm.

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

[b] Based on regimens containing atazanavir.

[c] Median time on therapy.

[d] As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

Adverse Events in Treatment-Experienced Adult 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 were jaundice/scleral icterus and myalgia.

Selected clinical adverse events of moderate or severe intensity in ≥2% of treatment-experienced patients receiving atazanavir/ritonavir are presented in Table 8.

Table 8: Selected treatment-emergent adverse eventsa of moderate or severe intensity reported in ≥2% of adult treatment-experienced patientsb (Study AI424-045)

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

* None reported in this treatment arm.

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

[b] Based on the regimen containing atazanavir.

[c] Median time on therapy.

[d] As a fixed-dose combination.

Laboratory Abnormalities in Treatment-Naïve Patients:

The percentages of adult treatment-naïve patients treated with combination therapy, including atazanavir sulfate 300 mg with ritonavir 100 mg, and having Grade 3–4 laboratory abnormalities are presented in Table 9.

Table 9: Grade 3–4 laboratory abnormalities reported in ≥2% of adult treatment-naïve patientsa (Study AI424-138)

Variable	Limit[d]	96 weeks[b] atazanavir 300 mg with ritonavir 100 mg (once daily) and tenofovir DF with emtricitabine[c] (n=441)	96 weeks [b] lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir DF with emtricitabine[c] (n=437)
Chemistry	High		
SGOT/AST	≥5.1 x ULN	3%	1%
SGPT/ALT	≥5.1 x ULN	3%	2%
Total bilirubin	≥2.6 x ULN	44%	<1%
Lipase	≥2.1 x ULN	2%	2%

Creatine kinase	≥5.1 x ULN	8%	7%
Total cholesterol	≥240 mg/dL	11%	25%
Hematology	Low		
Neutrophils	<750 cells/mm^3	5%	2%

[a] Based on the regimen containing atazanavir.

[b] Median time on therapy.

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

[d] ULN = upper limit of normal.

Lipids, Change from Baseline in Treatment-Naïve Patients

For Study AI424-138, changes from baseline in fasting LDL-cholesterol, HDL-cholesterol, total cholesterol, and fasting triglycerides are shown in Table 10.

Table 10: 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 (n=428[e])	mg/dl (n=372[e])	Change[d] (n=372[e])	mg/dL (n=342[e])	Change[d] (n=335)	mg/dl (n=424[e])	mg/dl (n=335[e])	Change[d] (n=335[e])	mg/dL (n=291[e])	Change[d] (n=291[e])
LDL-cholesterol[f]	92	105	+14%	105	+14%	93	111	+19%	110	+17%
HDL-cholesterol[f]	37	46	+29%	44	+21%	36	48	+37%	46	+29%
Total cholesterol[f]	149	169	+13%	169	+13%	150	187	+25%	186	+25%
Triglycerides[f]	126	145	+15%	140	+13%	129	194	+52%	184	+50%

[a] Atazanavir 300 mg with ritonavir 100 mg once daily with the fixed-dose combination of 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% of patients in the lopinavir/ritonavir treatment arm and 1% in the atazanavir/ritonavir arm. Through week 48, serum lipid-reducing agents were used in 8% of patients 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 of 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.

Laboratory Abnormalities in Treatment-Experienced Adult Patients

The percentages of adult treatment-experienced patients treated with combination therapy, including atazanavir/ritonavir, and having Grade 3–4 laboratory abnormalities are presented in Table 11.

Table 11: Grade 3–4 laboratory abnormalities reported in ≥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 (n=119)	48 weeks[b] lopinavir/ritonavir 400/100 mg twice daily[d] + tenofovir + NRTI (n=118)
Chemistry	High		
SGOT/AST	≥5.1 x ULN	3%	3%
SGPT/ALT	≥5.1 x ULN	4%	3%
Total bilirubin	≥2.6 x ULN	49%	<1%
Lipase	≥2.1 x ULN	5%	6%
Creatine kinase	≥5.1 x ULN	8%	8%
Total cholesterol	≥240 mg/dL	25%	26%
Triglycerides	≥751 mg/dL	8%	12%
Glucose	≥251 mg/dL	5%	<1%
Hematology	Low		
Platelets	<50,000 cells/mm^3	2%	3%
Neutrophils	<750 cells/mm^3	7%	8%

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

[b] Median time on therapy.

[c] ULN = upper limit of normal.

[d] As a fixed-dose combination.

Change in Lipids from Baseline in Treatment-Experienced Adult Patients

For Study AI424-045, changes from baseline in fasting LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglycerides are shown in Table 12. 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 12: 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) b.i.d. + tenofovir DF + 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.

Postmarketing Experience

The events given below have been identified during the 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)

Gastrointestinal System: pancreatitis

Hepatic System: hepatic function abnormalities

Hepatobiliary Disorders: *cholelithiasis* (see WARNINGS AND PRECAUTIONS), *cholecystitis, cholestasis*

Metabolic System and Nutrition Disorders: hyperglycemia, diabetes mellitus (see WARNINGS and PRECAUTIONS, *Diabetes Mellitus/Hyperglycemia*)

Musculoskeletal System: arthralgia

Renal System: nephrolithiasis (see WARNINGS and PRECAUTIONS), *interstitial nephritis, granulomatous interstitial nephritis, chronic kidney disease* (see WARNINGS AND PRECAUTIONS).

Skin and Appendages: alopecia, maculopapular rash (see WARNINGS and PRECAUTIONS) pruritus, angioedema

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024.

By reporting side effects, you can help provide more information on the safety of this product.

Overdosage

▶ Atazanavir

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

▶ Ritonavir (Full dose)

Acute overdosage
Human experience of acute overdose with ritonavir is limited. in clinical trials, 1 patient took ritonavir 1500 mg/day for 2 days. The patient reported paresthesias, which resolved after the dose was decreased. A postmarketing case of renal failure with eosinophilia has been reported with ritonavir overdose.

The approximate lethal dose 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 consists of general supportive measures, including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with 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 ritonavir is extensively metabolized by the liver and is highly protein-bound, dialysis is unlikely to be beneficial in significant removal of the drug.

Storage And Handling Instructions

Store in a cool dry place.

Packaging Information

SYNTHIVAN Tablets .....Bottle of 30 tablets
Last Updated: Dec 2017
Last Reviewed: Dec 2017

SYNTHIVAN Tablets