PRODUCT MONOGRAPH

[Pr]EVOTAZ*

atazanavir / cobicistat tablets

300 mg atazanavir (as atazanavir sulfate)/150 mg cobicistat

Azapeptide Inhibitor of HIV-1 Protease

Bristol-Myers Squibb Canada
Montreal, Canada

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atazanavir and cobicistat tablets 300 mg/150 mg
(as atazanavir sulfate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral	tablet, 300 mg atazanavir (as atazanavir sulfate), 150 mg cobicistat	Tablet core: microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, crospovidone, stearic acid, magnesium stearate, hydroxypropyl cellulose, and silicon dioxide. Film-coating: hypromellose, titanium dioxide, talc, triacetin, and red iron oxide

INDICATIONS AND CLINICAL USE

EVOTAZ (atazanavir and cobicistat) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.

Geriatrics (> 65 years of age):

Clinical studies of the components of EVOTAZ did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, EVOTAZ treatment for an elderly patient should reflect the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatrics (< 18 years of age):

Safety and effectiveness of EVOTAZ in children less than 18 years of age have not been established. EVOTAZ should not be administered to pediatric patients below the age of 3 months due to the risk of kernicterus.

CONTRAINDICATIONS

Patients with previously demonstrated clinically significant hypersensitivity (eg. Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any component of the product, including atazanavir and cobicistat, or container. For a complete listing see (DOSAGE FORMS, COMPOSITION AND PACKAGING).

Coadministration of EVOTAZ is contraindicated with drugs that are highly dependent on

CYP3A4 and/or UGT1A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events or loss of therapeutic effect. These drugs are listed in Table 1.

Table 1 : Drugs That Are Contraindicated With EVOTAZ

Drug Class	Drugs within class that are contraindicated with EVOTAZ	Clinical Comment
Alpha 1-Adrenoreceptor Antagonists	alfuzosin	Potential for increased alfuzosin concentrations, which can result in hypotension.
Antiarrhythmics	quinidine	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Anticonvulsants	carbamazepine, phenobarbital, phenytoin	Carbamazepine, a potent CYP3A inducer, decreases cobicistat plasma concentrations and that of atazanavir, which may result in loss of therapeutic effect and development of resistance. Coadministration of EVOTAZ with carbamazepine, phenobarbital, or phenytoin is contraindicated.
Antimycobacterials	rifampin	Rifampin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect of EVOTAZ and development of resistance to atazanavir.
Antineoplastics	irinotecan	Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan resulting in increased irinotecan toxicities.
Beta 2-adrenoceptor agonists	salmeterol	Coadministration of salmeterol with EVOTAZ may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Benzodiazepines	triazolam	Potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
Ergot Derivatives	dihydroergotamine, ergotamine, ergonovine	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.

Drug Class	Drugs within class that are contraindicated with EVOTAZ	Clinical Comment
Hepatitis C Direct-Acting Antivirals	elbasvir/grazoprevir	Contraindicated because of the potential increase in the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition.
Herbal Products	St. John's wort (*Hypericum perforatum*)	Patients taking EVOTAZ should not use products containing St. John's wort (*Hypericum perforatum*) because coadministration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect of EVOTAZ and development of resistance to atazanavir.
HMG-CoA Reductase Inhibitors	lovastatin, simvastatin	Potential for serious reactions such as myopathy, including rhabdomyolysis.
Neuroleptics	pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Phosphodiesterase-5 (PDE5) Inhibitors	sildenafil[1] when used for the treatment of pulmonary arterial hypertension	A safe and effective dose in combination with atazanavir, a component of EVOTAZ, 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.
	ritonavir or products containing ritonavir	The magnitude of increased atazanavir exposures and clinical implications are unknown.

[1] See Table 5 for sildenafil when dosed for erectile dysfunction.

WARNINGS AND PRECAUTIONS

General

EVOTAZ should not be used in combination with another antiretroviral that requires boosting (i.e., another protease inhibitor or VITEKTA), since dosing recommendations for such combinations have not been established.

Atazanavir is an inhibitor of CYP3A and UGT1A1. Cobicistat is a strong inhibitor of cytochrome P450 (CYP3A). Initiating treatment with EVOTAZ in patients receiving medications metabolized by CYP3A or initiating medications metabolized by CYP3A in patients already receiving EVOTAZ may result in increased plasma concentration of these concomitant medications. Higher plasma concentrations of concomitant medications can result in increased or prolonged therapeutic or adverse effects, potentially leading to severe, life-threatening or fatal events. Coadministration of EVOTAZ with drugs that induce CYP3A may result in decreased plasma concentration of cobicistat and consequently that of the concomitant medication, leading to loss of therapeutic effect and possible development of resistance. The potential for drug-drug

interactions must be considered prior to and during therapy with EVOTAZ. Review of other medications taken by patients and monitoring of patients for adverse effects is recommended during therapy with EVOTAZ (see CONTRAINDICATIONS and DRUG INTERACTIONS: Drug-Drug Interactions).

Due to inhibition of CYP3A4 by EVOTAZ, co-administration of EVOTAZ with quetiapine may result in increased quetiapine concentrations. Serious and/or life-threatening quetiapine-related adverse reactions, including severe sedation and coma, have been reported for concomitant use of HIV protease inhibitors and quetiapine. EVOTAZ should not be used in combination with quetiapine. If coadmnistration is necessary, reduce the quetiapine dose and monitor for quetiapine-associated adverse reactions as recommended in the quetiapine product monograph (see DRUG INTERACTIONS).

Carcinogenesis and Mutagenesis

The incidence of benign hepatocellular adenomas was increased in high-dose female mice at systemic exposures of atazanavir approximately 7-fold higher than those in humans at the recommended 400 mg clinical dose. There was no increase in the incidence of tumors in male mice or in male or female rats at any dose tested. The clinical significance of the carcinogenic findings in female mice is unknown as the benign hepatic tumors occurred only at doses that induced liver toxicity (see TOXICOLOGY: Carcinogenicity and Mutagenicity).

Cardiovascular

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 limited to first degree AV block with some exceptions (see OVERDOSAGE). There have been post-marketing reports of second-degree AV block, third-degree AV block, QTc prolongation, Torsades de Pointes and other conduction abnormalities in patients treated with atazanavir (see ADVERSE REACTIONS: Post-Market Adverse Drug Reactions). In clinical trials of atazanavir, asymptomatic first-degree AV block was observed in 5.9% of atazanavir-treated patients (n = 920), 3.0% of efavirenz treated patients (n = 329), 5.2% of lopinavir/ritonavir treated patients (n = 252) and 10.4% of nelfinavir-treated patients (n = 48). 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, atazanavir should be used with caution in patients with preexisting conduction system disease (e.g., marked first-degree AV block or second or third-degree AV block).

Dose related asymptomatic prolongations in PR interval with atazanavir have been observed in clinical studies. Caution should be used with medicinal products known to induce PR prolongations. In patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), EVOTAZ should be used with caution and only if the benefits exceed the risk. Particular caution should be used when prescribing EVOTAZ

in association with medicinal products which have the potential to increase the QT interval and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances) (see DETAILED PHARMACOLOGY).

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. When used in combination with EVOTAZ, 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, there was no substantial additive effect of atazanavir and atenolol on the PR interval. When used in combination with atazanavir, there is no need to adjust the dose of atenolol (see DRUG INTERACTIONS).

Pharmacokinetic studies between atazanavir and/or cobicistat 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 EVOTAZ is given concurrently with these drugs, especially those that are metabolized by CYP3A4 (e.g., verapamil) or CYP2D6 (eg, beta-blockers other than atenolol) (see DRUG INTERACTIONS).

Endocrine and Metabolism

Diabetes mellitus/Hyperglycemia: New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing 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.

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.

Hematologic

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.

Hepatic/Biliary

Hepatic Impairment and Toxicity: Atazanavir and cobicistat are principally metabolized by the liver. EVOTAZ is not recommended in patients with hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions). Patients with underlying hepatitis B or C viral infections or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. In these patients, test for liver enzymes before initiating therapy with EVOTAZ and monitor liver enzymes during treatment.

Hyperbilirubinemia: Most patients taking atazanavir experience elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT). This hyperbilirubinemia is generally reversible upon discontinuation of atazanavir. If hepatic transaminase elevations occur with hyperbilirubinemia while a patient is receiving EVOTAZ, consideration should be given to also evaluating alternative etiologies. No long-term safety data are available for patients experiencing persistent elevations in total bilirubin > 5 x ULN. Alternative antiretroviral therapy to EVOTAZ may be considered if jaundice or scleral icterus associated with bilirubin elevations present cosmetic concerns for patients.

Immune

Immune Reconstitution Inflammatory Syndrome: Immune reconstitution inflammatory syndrome has been reported in patients treated with combination antiretroviral therapy, including atazanavir, a component of EVOTAZ. During the initial phase of treatment, a patient whose immune system responds to therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as mycobacterium avium complex [MAC], cytomegalovirus [CMV], pneumocystis pneumonia [PCP] and tuberculosis [TB]), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Angioedema: Cases of angioedema have been reported in patients taking atazanavir (see ADVERSE REACTIONS: Post-market Adverse Drug Reactions).

Renal

Renal Impairment: In healthy subjects, approximately 7% of the dose of atazanavir is eliminated unchanged in the urine. Atazanavir has been studied in adult subjects with severe renal impairment (n=20), including those on hemodialysis, at multiple doses of 400 mg once daily. The impact of renal impairment on atazanavir elimination for patients without hemodialysis is anticipated to be low. Moderate increases in atazanavir clearance and decreased exposure levels were seen in patients managed with hemodialysis. EVOTAZ should not be administered to HIV-treatment-experienced patients with end stage renal disease managed with hemodialysis (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Nephrolithiasis and Cholelithiasis: Cases of nephrolithiasis and/or cholelithiasis were reported during post-marketing surveillance in HIV-infected patients receiving atazanavir, a component of EVOTAZ. 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.

Chronic kidney disease: Chronic kidney disease (CKD) has been reported in patients treated with atazanavir (a component of Evotaz), with or without ritonavir, during postmarketing surveillance. Some resulted in fatal outcomes or requiring hemodialysis. Evotaz should be used with caution, particularly in those patients with other risk factors for chronic kidney disease. Prescribers should consider the risk-benefit in continuing Evotaz therapy if patients develop signs and symptoms of CKD.Cholelithiasis, Cholecystitis, and Cholestasis: There have been post-marketing reports of cholelithiasis, cholecystitis, and cholestasis in patients treated with atazanavir with ritonavir as part of their ART regimen (see ADVERSE REACTIONS: Post-Market Adverse Drug Reactions).

Effects on serum creatinine: Cobicistat, a component of EVOTAZ, has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. This effect should be considered when interpreting changes in estimated creatinine clearance in patients initiating EVOTAZ particularly in patients with medical conditions or receiving drugs needing monitoring with estimated creatinine clearance. Dosing recommendations are not available for use of EVOTAZ in combination with other drugs that require dosing adjustment for renal impairment (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Patients with Renal Impairment). Consider alternative medications that do not require dosing adjustments.

Prior to initiating therapy with EVOTAZ, assess estimated creatinine clearance. Although cobicistat may cause modest increases in serum creatinine and modest declines in estimated creatinine clearance without affecting renal glomerular function, patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg per dL from baseline should be closely monitored for renal safety.

EVOTAZ should not be initiated in patients with creatinine clearance less than 70 mL/min if one or more co-administered agent requires dose adjustment based on creatinine clearance (eg, emtricitabine, lamivudine, tenofovir disoproxil fumarate or adefovir) (see ACTION AND CLINICAL PHARMACOLOGY: Pharmacocdynamics, Effect on Serum Creatinine, and CLINICAL TRIALS).

New Onset or Worsening Renal Impairment When Used with Tenofovir Disoproxil Fumarate

Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported when cobicistat is used in an antiretroviral regimen that contains tenofovir disoproxil fumarate (tenofovir DF).

- Do not initiate EVOTAZ as part of a regimen containing tenofovir DF in patients who have an estimated creatinine clearance below 70 mL/min because dose adjustment of tenofovir DF is required below 50 mL/min and such dose adjustments have not been established for coadministration with cobicistat.
- Document urine glucose and urine protein at baseline and perform routine monitoring of estimated creatinine clearance, urine glucose, and urine protein during treatment when EVOTAZ is used with tenofovir DF.
- Measure serum phosphorus in patients with or at risk for renal impairment.
- Avoid use of EVOTAZ with tenofovir DF in combination with concomitant or recent use of a nephrotoxic agent.

Resistance/Cross Resistance

Resistance: *In vitro* HIV-1 isolates with a decreased susceptibility to ATV have been selected *in vitro* and obtained from patients treated with ATV or atazanavir/ritonavir (ATV/RTV). HIV-1 isolates that were 93- to 183-fold resistant to ATV from three different viral strains were selected *in vitro* by 5 months. The mutations in these HIV-1 viruses that contributed to ATV resistance included I50L, N88S, I84V, A71V, and M46I. Changes were also observed at the protease cleavage sites following drug selection. Recombinant viruses containing the I50L mutation were growth impaired and displayed increased *in vitro* susceptibility 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.

Both genotypic and phenotypic resistances have developed during clinical studies (see MICROBIOLOGY: Resistance).

Cobicistat has no detectable antiviral activity against HIV-1, HBV, or HCV and does not antagonize the antiviral effect of HIV inhibitors.

Cross Resistance: Cross-resistance among PIs has been observed. Baseline phenotypic and genotypic analyses of clinical isolates from ATV clinical trials of PI-experienced subjects showed that isolates cross-resistant to multiple PIs were cross-resistant to ATV. Greater than 90% of the isolates with mutations 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 mutation in addition to other changes were resistant to ATV. Isolates resistant to ATV were also cross-resistant to other PIs with >90% of the isolates resistant to indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir,

and 80% resistant to amprenavir. In treatment-experienced patients, PI-resistant viral isolates that developed the I50L mutation in addition to other PI resistance-associated mutations were also cross-resistant to other PIs.

Genotypic and/or phenotypic analysis of baseline virus may aid in determining ATV susceptibility before initiation of EVOTAZ therapy.

Overall, both the number and type of baseline PI mutations affected response rates in treatment-experienced patients (see MICROBIOLOGY: Cross-Resistance).

Sexual Function/Reproduction

In a fertility and early embryonic development study in rats, atazanavir altered estrus cycling with no effects on mating, fertility or early embryonic development. Systemic drug exposure levels were equal (in male rats) or two times (in female rats) those at the human clinical dose (400 mg/day).

Skin

Rash: 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. Dosing with atazanavir was often continued without interruption in patients who developed rash. The discontinuation rate for rash in clinical trials was <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 (see CONTRAINDICATIONS).

Use with other antiretroviral products

EVOTAZ is indicated for use with other antiretrovirals for the treatment of HIV-1 infection. Do not use EVOTAZ in combination with products containing the same components (atazanavir or cobicistat), or with fixed-dose products that contain cobicistat. Do not use EVOTAZ in combination with another antiretroviral that requires a pharmacokinetic enhancer (eg, elvitegravir) because dosing recommendations for such combinations have not been established and may result in decreased plasma concentrations of the antiretroviral agent, leading to loss of therapeutic effect and development of resistance. Do not use EVOTAZ with other HIV-protease inhibitors. Do not use EVOTAZ in combination with nevirapine or efavirenz. (See Contraindications and DRUG INTERACTIONS)

Special Populations

Pregnant Women:

EVOTAZ should be used during pregnancy only if the potential benefit justifies the potential risk. There are no adequate and well-controlled studies in pregnant women with either

components of EVOTAZ (atazanavir or cobicistat). Cases of lactic acidosis, sometimes fatal, and symptomatic hyperlactatemia have been reported in patients (including pregnant women) receiving atazanavir in combination with nucleoside analogues, which are known to be associated with increased risk of lactic acidosis. Female gender and obesity are also known risk factors for lactic acidosis syndrome. The contribution of atazanavir to the risk of development of lactic acidosis syndrome has not been established.

Hyperbilirubinemia occurred frequently during treatment with atazanavir. It is not known whether EVOTAZ administered to the mother during pregnancy will exacerbate physiologic hyperbilirubinemia and lead to kernicterus in neonates and young infants. In the prepartum period, additional monitoring and alternative therapy should be considered. Atazanavir has been shown to cross the placenta.

In the pre-and post-natal development assessment in rats, atazanavir produced a transient reduction in body weight in the offspring at maternally toxic drug exposure levels two times those at the human clinical dose.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to EVOTAZ, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients,

http://www.apregistry.com
Telephone: (800) 258–4263
Fax: (800) 800-1052

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). There was no association between atazanavir and specific birth defects observed in the APR.

Nursing Women:

Atazanavir has been detected in human milk. It is not known whether cobicistat is excreted in human milk. No data are available regarding atazanavir or cobicistat effects on milk production. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving EVOTAZ.

Studies in rats have demonstrated that atazanavir and cobicistat are secreted in milk.

Pediatrics (< 18 years of age):

Safety and effectiveness of EVOTAZ in children less than 18 years of age have not been established.

Geriatrics (> 65 years of age):

There are no data available to make a dose recommendation for patients over the age of 65 years. In general, appropriate caution should be exercised in the administration and monitoring of EVOTAZ in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Drug Reaction Overview

The safety of atazanavir and cobicistat has been established in a Phase 3 randomized, active-controlled clinical study (Study 114) in which 692 treatment-naïve patients received atazanavir and cobicistat (n = 344) or atazanavir and ritonavir (n = 348) administered with emtricitabine and tenofovir DF fixed-dose combination for at least 48 weeks.

See Table 2 for the frequency of treatment-emergent adverse reactions (Grade 2-4) occurring in at least 2% of subjects receiving atazanavir and cobicistat with emtricitabine/tenofovir DF in Study 114. The most common adverse reactions (incidence greater than or equal to 5%) occurring in subjects receiving atazanavir and cobicistat with emtricitabine/tenofovir DF was jaundice, consistent with the safety profile of atazanavir.

Table 2 - Treatment-Emergent Adverse Drug Reactions[a] (Grades 2-4) Reported in ≥ 2% of Subjects Receiving atazanavir and cobicistat + emtricitabine/ tenofovir disoproxil fumarate in Study 114 (Week 48 analysis)

	Atazanavir and cobicistat with emtricitabine/tenofovir DF	Atazanavir and ritonavir with emtricitabine/tenofovir DF
	N=344	N=348
EYE DISORDERS		
Ocular icterus	3%	1%
GASTROINTESTINAL DISORDERS		
Nausea	2%	2%
HEPATOBILIARY DISORDERS		
Jaundice	6%	3%
Hyperbilirubinaemia	4%	3%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash[b]	4%	3%

a Frequencies of adverse reactions are based on Grade 2-4 treatment-emergent adverse events, attributed to study drugs
b Rash event includes rash, rash generalized, rash maculo-papular, rash macular, and rash morbilliform

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Treatment-emergent adverse drug reactions of at least moderate severity (≥Grade 2) occurring in less than 2% of subjects receiving atazanavir and cobicistat with emtricitabine/tenofovir DF in Study 114 are listed below.

Ear and Labyrinth Disorders: vertigo

Gastrointestinal Disorders: diarrhea, vomiting, constipation, abdominal pain, hyperchlorhydia

General Disorders and Administration Site Conditions: fatigue, asthenia

Immune System Disorders: drug hypersensitivity

Metabolism and Nutrition Disorders: increased appetite, decreased appetite, diabetes mellitus, hyperlipidaemia, hypertriclyceridaemia

Musculoskeletal and Connective Tissue Disorders: back pain, myalgia, rhabdomyolysis

Nervous System Disorders: headache

Pregnancy, Puerperium and Perinatal Conditions: abortion spontaneous

Psychiatric Disorders: insomnia, abnormal dreams, depression, affective disorder

Renal and Urinary Disorders: Fanconi syndrome acquired, nephrolithiasis, renal impairment, haematuria, hydronephrosis, nephropathy, renal colic

Reproductive System and Breast Disorders: premenstrual syndrome

Skin and Subcutaneous Tissue Disorders: dermatitis allergic, eosinophilic pustular folliculitis, hyperhidrosis, pruritus generalized

Laboratory Abnormalities: The frequency of treatment-emergent laboratory abnormalities (Grades 3-4) occurring in at least 1% of subjects receiving atazanavir boosted with cobicistat + emtricitabine/tenofovir DF in Study 114 are presented in Table 3.

Table 3: Laboratory Abnormalities (Grades 3-4) Reported in ≥1% of Subjects in the atazanavir boosted with cobicistat + emtricitabine/tenofovir disoproxil fumarate group in Study 114 (Week 48 analysis)

Laboratory Parameter Abnormality	Atazanavir and cobicistat with emtricitabine/tenofovir DF (n=344)	Atazanavir and ritonavir with emtricitabine/tenofovir DF (n=348)
Total Bilirubin (>2.5 × ULN)	65%	57%
Creatine Kinase (≥10.0 × ULN)	6%	6%
Serum Amylase[a] (>2.0 × ULN)	3%	2%
ALT (>5.0 × ULN)	3%	2%
Urine RBC (Hematuria) (> 75 RBC/HPF)	3%	2%
Neutrophils (< 750/mm3)	2%	1%
AST (>5.0 × ULN)	3%	2%
GGT (>5.0 × ULN)	2%	1%
Serum Glucose (> 250 mg/dL)	2%	1%
Urine Glucose (+4)	2%	1%

a. For subjects with serum amylase > 1.5 x upper limit of normal, lipase test was also performed. The frequency of increased lipase (Grade 3-4) occurring in atazanavir boosted with cobicistat + emtricitabine/tenofovir DF plus and atazanavir boosted with ritonavir + emtricitabine/tenofovir DF treatment groups was 5% (2/38) and 4% (1/28), respectively.

In addition to the laboratory abnormalities listed in Table 3, creatinine renal clearance decreased and glomerular filtration rate abnormal (≥ Grade 2) were reported in less than 2% of subjects receiving atazanavir boosted with cobicistat + emtricitabine/tenofovir DF in Study 114.

Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. An increase in serum creatinine due to cobicistat's inhibitory effect generally does not exceed 0.4 mg per dL (35.36 µmol/L) from baseline. In Study 114, decreases in estimated creatinine clearance occurred early in treatment with atazanavir boosted with cobicistat, after which they stabilized. The mean (± SD) change in estimated glomerular filtration rate (eGFR) by Cockcroft-Gault method after 48 weeks of treatment was -13.4 ± 15.2 mL/min in the atazanavir boosted with cobicistat + emtricitabine/tenofovir DF group and -8.7 ± 14.5 mL/min in the atazanavir boosted with

ritonavir emtricitabine/tenofovir DF group (see ACTION AND CLINICAL PHARMACOLOGY: Pharmacodynamics, Effects on Serum Creatinine).

Serum Lipids: Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides are presented in Table 4.

Table 4 Lipid Values, Mean Change from Baseline, Reported in Subjects Receiving Atazanavir and Cobicistat with Emtricitabine/Tenofovir DF or Atazanavir and Ritonavir with Emtricitabine/Tenofovir DF in Study 114 (Week 48 analysis)

	Atazanavir and cobicistat with emtricitabine/tenofovir DF		Atazanavir and ritonavir with emtricitabine/tenofovir DF	
	Baseline mg/dL	**Week 48 change from baseline[a]**	**Baseline mg/dL**	**Week 48 change from baseline[a]**
Total Cholesterol (fasted)	164 [N=323]	+5 [N=278]	166 [N=328]	+9 [N=287]
HDL-cholesterol (fasted)	43 [N=322]	+4 [N=277]	43 [N=328]	+3 [N=287]
LDL-cholesterol (fasted)	103 [N=322]	+6 [N=278]	104 [N=328]	+8 [N=288]
Triglycerides (fasted)	126 [N=323]	+19 [N=278]	132 [N=328]	+32 [N=287]

[a] The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values.

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.

Patients who entered clinical studies with atazanavir (AI424-138, AI424-045, AI424-008, or AI424-034) who were coinfected with chronic hepatitis B or C, were more likely to have baseline hepatic transaminase elevations than those without chronic viral hepatitis. The frequency of treatment-emergent hepatitis or transaminase elevations in coinfected patients was comparable between atazanavir and comparator regimens. No differences in frequency of bilirubin elevations were observed.

Post-Market Adverse Drug Reactions

The following events have been identified during post approval use of atazanavir. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, or causal connection to atazanavir, or a combination of these factors.

Body as a whole: edema

Cardiac disorders and vascular disorders: second-degree AV block, third-degree AV block, QTc prolongation, Torsades de Pointes, left bundle branch block

Gastrointestinal system: pancreatitis

Hepatic system: hepatic function abnormalities

Hepatobiliary disorders: cholelithiasis, cholecystitis, cholestasis

Immune system: angioedema

Metabolism and nutrition disorders: hyperglycemia, diabetes mellitus

Musculoskeletal system: arthralgia

Renal system: nephrolithiasis, interstitial nephritis, chronic kidney disease

Skin and appendages: pruritus, alopecia, maculopapular rash

DRUG INTERACTIONS

Serious Drug Interactions

Atazanavir is an inhibitor of CYP3A and UGT1A1. Cobicistat is a strong inhibitor of cytochrome P450 (CYP3A). Atazanavir and cobicistat are CYP3A4 substrates. Coadministration of EVOTAZ 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.

Drugs that induce CYP3A4 may decrease atazanavir and cobicistat plasma concentrations and reduce the therapeutic effect of EVOTAZ and may lead to development of resistance to atazanavir. (see **WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, and DRUG INTERACTIONS: Table 5 – Established and Other Potentially Significant Drug Interactions**).

Atazanavir is a weak to moderate inhibitor of CYP2C8. Caution should be used with coadministration of EVOTAZ and drugs highly dependent on CYP2C8 with narrow therapeutic indices (eg, paclitaxel, repaglinide).

- Refer to CONTRAINDICATIONS
- Refer to Table 5 for Established and Other Potentially Significant Drug Interactions

Overview

Drug interaction trials were not conducted for EVOTAZ (atazanavir and cobicistat). The recommendations shown in Table 5 are based either on drug interaction studies of unboosted atazanavir, atazanavir boosted with ritonavir, cobicistat, or predicted interactions due to the expected magnitude of the interaction and potential for serious adverse events or loss of therapeutic effect of EVOTAZ.

Atazanavir: Atazanavir is metabolized in the liver by the cytochrome P450 enzyme system, and is an inhibitor of CYP3A4. Atazanavir has been shown in vivo not to induce its own metabolism,

nor to increase the biotransformation of some drugs metabolized by CYP3A4. Atazanavir is a weak to moderate inhibitor of CYP2C8.

Cobicistat: Cobicistat is primarily metabolized in the liver by the cytochrome P450 enzyme system and is an inhibitor of CYP3A4. Cobicistat is a weak inhibitor of CYP2D6.

EVOTAZ:

- Coadministration of EVOTAZ and drugs primarily metabolized by CYP3A4 (eg, calcium channel blockers, some HMG-CoA reductase inhibitors, immunosuppressants, and phosphodiesterase (PDE5) inhibitors), UGT1A1, and/or CYP2D6, or drugs that are substrates of P-gp, BCP, OATP1B1, and/or OATP1B3 may result in increased plasma concentrations of the other drug that could increase or prolong both the therapeutic and adverse effects of the other drug.
- Coadministration of EVOTAZ and drugs that induce CYP3A4 (eg, rifampin) may decrease atazanavir and cobicistat plasma concentrations and reduce the therapeutic effect of EVOTAZ.
- Coadministration of EVOTAZ and drugs that inhibit CYP3A4 (eg, ketoconazole) may increase atazanavir and cobicistat plasma concentrations.
- Caution should be used with coadministration of EVOTAZ and drugs highly dependent on CYP2C8 with narrow therapeutic indices (eg, paclitaxel, repaglinide).

Drugs that are contraindicated with EVOTAZ are included in Table 1. Established and potentially significant drug interactions are included in Table 5. These recommendations are based on either drug interaction studies with the components of EVOTAZ, or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of therapeutic effect of EVOTAZ.

Table 5 - Established and Other Potentially Significant Drug Interactions: Alteration in dose or regimen of the following drugs may be recommended based on drug interaction studies or predicted interactions.

Concomitant Drug Class: ***Specific Drugs***	**Effect on Concentration**	**Clinical Comment**
HIV Antiviral Agents: *Nucleoside Reverse Transcriptase Inhibitors (NRTIs)*		
didanosine buffered formulations enteric-coated (EC) capsules	↓ atazanavir ↓ didanosine ↔ cobicistat	Coadministration of atazanavir with didanosine buffered tablets resulted in a marked decrease in atazanavir exposure. It is recommended that EVOTAZ be given with food 2 hours before or 1 hour after didanosine buffered formulations. Simultaneous administration of didanosine EC and atazanavir with food results in a decrease in didanosine exposure. Thus, EVOTAZ and didanosine EC should be administered at different times.

Table 5 - Established and Other Potentially Significant Drug Interactions: Alteration in dose or regimen of the following drugs may be recommended based on drug interaction studies or predicted interactions.

Concomitant Drug Class: ***Specific Drugs***	**Effect on Concentration**	**Clinical Comment**
tenofovir DF	↓ atazanavir ↑ tenofovir ↔ cobicistat	Tenofovir DF may decrease the AUC and C_{min} of atazanavir. When coadministered with tenofovir DF, it is recommended that EVOTAZ and tenofovir DF 300 mg be given together with food. Atazanavir increases tenofovir concentrations. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving EVOTAZ and tenofovir DF should be monitored for tenofovir-associated adverse events.
HIV Antiviral Agents: *Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)*		
delavirdine	↑ cobicistat ↑ delavirdine	Coadministration of delavirdine and cobicistat may increase delavirdine and/or cobicistat plasma concentration. The appropriate dose of delavirdine in combination with EVOTAZ has not been established. Coadministration is not recommended.
efavirenz	↓ atazanavir ↓ cobicistat ↔ efavirenz	Do not coadminister EVOTAZ with efavirenz. Efavirenz decreases atazanavir plasma concentration and is expected to decrease cobicistat plasma concentration. This may result in a loss of therapeutic effect of EVOTAZ and development of resistance to atazanavir.
etravirine	↓ atazanavir ↓ cobicistat	Do not coadminister EVOTAZ with etravirine because it expected to decrease cobicistat plasma concentration and consequently that of atazanavir, which may result in loss of therapeutic effect and development of resistance.
nevirapine	↓ atazanavir ↓ cobicistat ↑ nevirapine	Do not coadminister EVOTAZ with nevirapine. Nevirapine is expected to decrease cobicistat and atazanavir plasma concentrations, which may result in a loss of therapeutic effect of EVOTAZ and development of resistance to atazanavir. Coadministration of nevirapine and EVOTAZ is expected to increase nevirapine plasma concentration, which may increase the risk of nevirapine-associated toxicity.
rilpivirine	↑ rilpivirine ↔ cobicistat	Coadministration of rilpivirine and cobicistat is expected to increase the plasma concentration of rilpivirine. Rilpivirine is not expected to affect the plasma concentration of cobicistat. No dose adjustment of rilpivirine is required when coadministered with EVOTAZ.
Antiretroviral Agents: *CCR5 Antagonist*		
maraviroc	↑ maraviroc	Maraviroc is a substrate of CYP3A and its plasma concentration increases when coadministered with potent CYP3A inhibitors. When coadministering maraviroc and EVOTAZ, patients should receive maraviroc 150 mg twice daily. For further details, see the maraviroc Product Monograph. Maraviroc is not expected to have an impact on concentrations of atazanavir and cobicistat.

Table 5 - Established and Other Potentially Significant Drug Interactions: Alteration in dose or regimen of the following drugs may be recommended based on drug interaction studies or predicted interactions.

Concomitant Drug Class: ***Specific Drugs***	**Effect on Concentration**	**Clinical Comment**
Antiretroviral Agents: *Protease Inhibitors*		
saquinavir (soft gelatin capsules)	↑saquinavir	Appropriate dosing recommendations for the coadministration of EVOTAZ and saquinavir with respect to efficacy and safety have not been established.
Other HIV protease inhibitors	effects unknown	Do not use EVOTAZ in combination with other HIV protease inhibitors because coadministration may not provide adequate protease inhibitor exposure.
HCV Antiviral Agents: *Protease Inhibitors*		
boceprevir	↓ atazanavir ↔boceprevir	Concomitant administration of boceprevir with atazanavir/ritonavir resulted in reduced exposures to atazanavir. The effects of EVOTAZ on boceprevir exposures are unknown. Coadministration with boceprevir is not recommended.
OTHER AGENTS		
Antacids and buffered medications	↓ atazanavir	EVOTAZ should be administered 2 hours before or 1 hour after these medications.
Analeptics**:** modafinil	↓ atazanavir ↓ cobicistat	Coadministration of modafinil, a CYP3A inducer, may decrease cobicistat plasma concentrations and consequently that of atazanavir, which may result in loss of therapeutic effect and development of resistance. Alternative analeptics should be considered.
Antiarrhythmics		
amiodarone, disopyramide, flecainide, mexiletine, propafenone, lidocaine (systemic),	↑atazanavir ↑ antiarrhythmics	Coadministration with EVOTAZ has the potential to produce serious and/or life-threatening adverse events. Caution is warranted and therapeutic concentration monitoring of these antiarrhythmics is recommended if they are used concomitantly with EVOTAZ.
digoxin	↑ digoxin	When coadministering EVOTAZ with digoxin, titrate the digoxin dose and monitor digoxin concentrations.
Antibacterials (macrolide or ketolide antibiotics)		
clarithromycin erythromycin, telithromycin	↑ atazanavir ↑ cobicistat ↑ clarithromycin ↑ erythromycin ↑ telithromycin ↓ 14-OH clarithromycin	Clarithromycin, erythromycin, and telithromycin may increase concentrations of atazanavir and cobicistat. Exposure to these antibiotics is expected to increase. Alternative antibiotics should be considered.

Table 5 - Established and Other Potentially Significant Drug Interactions: Alteration in dose or regimen of the following drugs may be recommended based on drug interaction studies or predicted interactions.

Concomitant Drug Class: ***Specific Drugs***	**Effect on Concentration**	**Clinical Comment**
Anticancer Agents		
dasatinib nilotinib vinblastine vincristine	↑ anticancer agents	Concentrations of these drugs may increase when coadministered with EVOTAZ resulting in the potential for increased adverse events usually associated with these anticancer agents. A decrease in the dosage or an adjustment of the dosing interval of dasatinib and nilotinib may be necessary for coadministration with EVOTAZ. Consult the dasatinib and nilotinib Product Monographs for dosing instructions.
Anticoagulants		
warfarin	↑ warfarin	Coadministration with EVOTAZ has the potential to produce serious and/or life-threatening bleeding due to increased exposure to warfarin and has not been studied. It is recommended that the INR (International Normalized Ratio) be monitored.
Anticonvulsants		
oxcarbazepine	↓ atazanavir ↓ cobicistat	Coadministration of oxcarbazepine, a CYP3A inducer, may decrease cobicistat plasma concentrations and consequently that of atazanavir, which may result in loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered.
clonazepam, ethosuximide	↑ clonazepam ↑ethosuximide	Concentrations of clonazepam and ethosuximide may be increased when coadministered with EVOTAZ. Clinical monitoring is recommended upon coadministration with EVOTAZ.
lamotrigine	lamotrigine: effect unknown	Monitoring of lamotrigine concentrations is recommended with EVOTAZ coadministration.
Antidepressants		
Selective Serotonin Reuptake Inhibitors SSRIs (eg, paroxetine)	↑ SSRIs	Concentrations of selective serotonin reuptake inhibitors may be increased when coadministered with cobicistat, a component of EVOTAZ. Dose titration may be required for most drugs of the SSRI class when coadministered with EVOTAZ.
Tricyclic antidepressants: (eg, amitriptyline, desipramine, imipramine, nortriptyline)	↑ tricyclic antidepressants	Coadministration with EVOTAZ has the potential to produce serious and/or life-threatening adverse events due to increased exposure to these agents and has not been studied. The concentration of desipramine is increased when coadministered with cobicistat. Concentration monitoring of these drugs is recommended if they are used concomitantly with EVOTAZ.
Other antidepressants: trazodone	↑ trazodone	Concomitant use of trazodone and EVOTAZ may increase plasma concentrations of trazodone. If trazodone is used with EVOTAZ, the combination should be used with caution and a lower dose of trazodone should be considered.

Table 5 - Established and Other Potentially Significant Drug Interactions: Alteration in dose or regimen of the following drugs may be recommended based on drug interaction studies or predicted interactions.

Concomitant Drug Class: ***Specific Drugs***	**Effect on Concentration**	**Clinical Comment**
Antifungals		
ketoconazole, itraconazole	↑ atazanavir ↑ cobicistat ↑ ketoconazole ↑ itraconazole	Concentrations of ketoconazole, itraconazole, and/or cobicistat may increase with coadministration of EVOTAZ. Caution is warranted. Specific dosing recommendations are not available for coadministration of EVOTAZ with either itraconazole or ketoconazole.
voriconazole	effects unknown	Voriconazole should not be coadministered with EVOTAZ unless the benefit/risk assessment justifies the use of voriconazole. Clinical monitoring may be needed upon coadministration with EVOTAZ.
Antigout		
colchicine	↑ colchicine	EVOTAZ should not be coadministered with colchicine to patients with renal or hepatic impairment. Recommended dosage of colchicine when administered with EVOTAZ: ***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	↓cobicistat ↑ 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 and uveitis is warranted.
Antipsychotics		
quetiapine	↑ quetiapine	EVOTAZ should not be used in combination with quetiapine. Due to CYP3A4 inhibition by EVOTAZ, concentrations of quetiapine are expected to increase, which can result in serious and/or life-threatening adverse reactions. If coadministration is necessary, monitoring and quetiapine dose reduction may be required (see WARNINGS AND PRECAUTIONS, General).
Beta-Blockers		
metoprolol carvedilol timolol	↔atazanavir ↑ beta-blockers	Concentrations of beta-blockers may be increased when coadministered with cobicistat. Clinical monitoring is recommended and a dose reduction may be necessary when these agents are coadministered with EVOTAZ.

Table 5 - Established and Other Potentially Significant Drug Interactions: Alteration in dose or regimen of the following drugs may be recommended based on drug interaction studies or predicted interactions.

Concomitant Drug Class: ***Specific Drugs***	**Effect on Concentration**	**Clinical Comment**
Calcium channel blockers		
diltiazem	↑ diltiazem and desacetyl-diltiazem	Exposure to diltiazem and a metabolite, desacetyl-diltiazem, is increased when diltiazem is coadministered with atazanavir. A dose reduction of diltiazem by 50% should be considered, and electrocardiogram monitoring is recommended.
amlodipine, felodipine, nifedipine, and verapamil	↑ calcium channel blockers	Caution is warranted. Dose titration of the calcium channel blockers should be considered. Electrocardiogram monitoring is recommended.
Endothelin receptor antagonists		
bosentan	↓ atazanavir ↓ cobicistat ↑ bosentan	Bosentan is metabolized by CYP3A4 and is an inducer of CYP3A4. Coadministration of bosentan with EVOTAZ may lead to decreased concentrations of cobicistat and atazanavir, which may result in loss of therapeutic effect and development of resistance. ***Coadministration of bosentan in patients on EVOTAZ:*** For patients who have been receiving EVOTAZ for at least 10 days, start bosentan at 62.5 mg once daily or every other day based on individual tolerability. ***Coadministration of EVOTAZ in patients on bosentan:*** Discontinue bosentan at least 36 hours before starting EVOTAZ. At least 10 days after starting EVOTAZ, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability. ***Switching from ritonavir-boosted atazanavir to EVOTAZ:*** Maintain bosentan dose.
HMG-CoA reductase inhibitors		
atorvastatin	↑ atorvastatin	Titrate atorvastatin dose carefully and use the lowest necessary dose. The risk of myopathy, including rhabdomyolysis, may be increased.
rosuvastatin	↑ rosuvastatin	Rosuvastatin dose should not exceed 10 mg/day. The risk of myopathy, including rhabdomyolysis, may be increased.

Table 5 - Established and Other Potentially Significant Drug Interactions: Alteration in dose or regimen of the following drugs may be recommended based on drug interaction studies or predicted interactions.

Concomitant Drug Class: ***Specific Drugs***	**Effect on Concentration**	**Clinical Comment**
H_2-Receptor antagonists		
famotidine	↓ atazanavir	***Treatment-naive patients:*** • EVOTAZ once daily with food should be administered simultaneously with, and/or at least 10 hours after, a dose of the H_2-receptor antagonist. The dose of the H_2-receptor antagonist should not exceed a dose comparable to famotidine 40 mg twice daily. ***Treatment-experienced patients:*** • For treatment-experienced patients who are also receiving concomitant tenofovir DF: Do not coadminister EVOTAZ with an H2-receptor antagonist in these patients. • For treatment-experienced patients who are not receiving concomitant tenofovir DF: EVOTAZ once daily with food should be administered simultaneously with, and/or at least 10 hours after, a dose of the H2-receptor antagonist. The dose of the H2-receptor antagonist should not exceed a dose comparable to famotidine 20 mg twice daily.
Hormonal contraceptives		
eg, progestin/estrogen	progestin and estrogen: effects unknown	No data are available to make recommendations on the use of EVOTAZ with oral contraceptives. Concentrations of ethinyl estradiol and norethindrone are increased when a combined oral contraceptive containing those agents is coadministered with atazanavir. Alternative (nonhormonal) forms of contraception should be considered.
Immunosuppressants		
eg, cyclosporin, sirolimus, tacrolimus	↑ immuno-suppressants	Concentrations of these immunosuppressant agents may be increased when they are coadministered with EVOTAZ. Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with EVOTAZ.
Inhaled beta-agonist		
Corticosteroids (systemic): dexamethasone and other corticosteroids	↓ atazanavir ↓ cobicistat ↑ corticosteroids	Coadministration with dexamethasone or other corticosteroids that induce CYP3A may result in loss of therapeutic effect of EVOTAZ and development of resistance to atazanavir. Alternative corticosteroids should be considered. Coadministration with corticosteroids that are metabolized by CYP3A, particularly for long-term use, may increase the risk for development of systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Consider the potential benefit of treatment versus the risk of systemic corticosteroid effects.

Table 5 - Established and Other Potentially Significant Drug Interactions: Alteration in dose or regimen of the following drugs may be recommended based on drug interaction studies or predicted interactions.

Concomitant Drug Class: ***Specific Drugs***	**Effect on Concentration**	**Clinical Comment**
Inhaled/nasal corticosteroids		
Fluticasone and other inhaled or nasal steroids	↑ fluticasone ↑ other inhaled/nasal steroids	Concomitant use of fluticasone propionate or other inhaled or nasal corticosteroids and EVOTAZ are not recommended unless the potential benefit to the patient outweighs the risks. Consider alternatives particularly for long-term use.
Opioids		
eg, buprenorphine, naloxone, methadone, fentanyl, tramadol	↑ buprenorphine ↑ norbuprenor-phine naloxone and methadone: effects unknown ↑ fentanyl ↑ tramadol	***Buprenorphine/naloxone/methadone:*** Coadministration of buprenorphine and atazanavir increases the plasma concentration of buprenorphine and norbuprenorphine. Coadministration of EVOTAZ with buprenorphine warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered. ***Fentanyl:*** When EVOTAZ is coadministered with fentanyl, careful monitoring of therapeutic and adverse effects of fentanyl (including potentially fatal respiratory depression) is recommended. ***Tramadol:*** When EVOTAZ is coadministered with tramadol, a decreased dose of tramadol may be needed.
Neuroleptics		
perphenazine, risperidone	↑ neuroleptics	A decrease in the dose of neuroleptics metabolized by CYP3A or CYP2D6 may be required when coadministered with EVOTAZ.
PDE5 inhibitors used for the treatment of pulmonary arterial hypertension		
Concomitant use of EVOTAZ and PDE-5 inhibitors may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances, and priapism.		
tadalafil	↑tadalafil	Coadministration of EVOTAZ and tadalafil for the treatment of pulmonary hypertension is not recommended
PDE5 inhibitors used for the treatment of erectile dysfunction		
sildenafil tadalafil	↑sildenafil ↑tadalafil	Co administration of EVOTAZ and PDE5 inhibitors has not been studied. Coadministration of a protease inhibitor with a PDE5 inhibitor is expected to substantially increase the PDE5 inhibitor concentration and may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances and priapism. • Vardenafil should not be coadministered with EVOTAZ. • Sildenafil: reduced doses (25 mg every 48 hours) are recommended when coadministered with EVOTAZ. • Tadalafil: reduced doses (10 mg every 72 hours) are recommended when coadministered with EVOTAZ. Use with caution and monitor adverse events.

Table 5 - Established and Other Potentially Significant Drug Interactions: Alteration in dose or regimen of the following drugs may be recommended based on drug interaction studies or predicted interactions.

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
Proton-pump inhibitors		
omeprazole	↓atazanavir	In treatment-naive patients, administer EVOTAZ a minimum of 12 hours after administration of the proton pump inhibitor. The dose of the proton pump inhibitor should not exceed a dose comparable to omeprazole 20 mg daily. In treatment-experienced patients, coadministration of EVOTAZ with proton pump inhibitors is not recommended.
Sedatives/ hypnotics		
midazolam	↑ midazolam	*Parenteral midazolam:* Caution should be used with coadministration of EVOTAZ and parenteral midazolam. No data are available on concomitant use of EVOTAZ with intravenous midazolam; data from concomitant use of other protease inhibitors suggest a possible 3–4 fold increase in midazolam plasma levels. If EVOTAZ is coadministered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.
buspirone clorazepate diazepam flurazepam	↑ sedative /hypnotics	Concentrations of cobicistat may result in increased plasma concentrations of these drugs. Dose reduction may be necessary and concentration monitoring is recommended.

Clinically significant drug interactions are not expected between EVOTAZ and dapsone, trimethoprim/sulfamethoxazole, azithromycin or erythromycin. Additionally, no clinically significant drug interactions were observed when atazanavir, a component of EVOTAZ, was coadministered with fluconazole, acetaminophen, or atenolol and, accordingly, these drugs are also not expected to interact with EVOTAZ.

DOSAGE AND ADMINISTRATION

Dosing Considerations

General Dosing Recommendations:

- EVOTAZ Tablets must be taken with food.
- EVOTAZ Tablets should be taken whole and not broken, cut, or crushed.
- If patients are unable to take cobicistat, a component of EVOTAZ, please refer to the REYATAZ® full prescribing information for the use of atazanavir without cobicistat.

Recommended Dose and Dosage Adjustment

The recommended adult dosage of EVOTAZ is one tablet once daily taken orally with food.

For coadministration with drugs for which dosing modification may be appropriate (see Drug Interactions).

Geriatrics (>65 years of age)

Insufficient data are available on which to make a dose recommendation for patients over 65 years of age.

Pediatrics (<18 years of age)

EVOTAZ is not indicated for use in pediatric patients < 18 years of age.

Patients With Renal Impairment

EVOTAZ should not be administered to HIV-treatment-experienced patients with renal disease managed with hemodialysis.

Cobicistat, a component of EVOTAZ, has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. Consider this effect when EVOTAZ is coadministered with a drug that has dosing adjustment recommendations guided by estimated creatinine clearance (see WARNINGS AND PRECAUTIONS: Renal and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency).

Patients With Hepatic Impairment

EVOTAZ is not recommended in patients with hepatic impairment (see WARNINGS AND PRECAUTIONS: Hepatic/Biliary and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).

Missed Dose

If a dose of EVOTAZ is missed by 12 hours or less, the missed dose of EVOTAZ should be taken right away. The next dose of EVOTAZ should be taken at the usual time.

If a dose of EVOTAZ is missed by more than 12 hours, the patient should wait and take the next dose at the usual time. If a dose of EVOTAZ is missed, the patient should not double the next dose.

OVERDOSAGE

If overdose occurs with EVOTAZ, the patient must be monitored for evidence of toxicity. Treatment should consist of general supportive measures including monitoring of vital signs and ECG as well as observation of the patient's clinical status. There is no specific antidote for overdose with EVOTAZ. Since atazanavir and cobicistat are extensively metabolized by the liver, highly bound to plasma proteins, it is unlikely that EVOTAZ can be significantly removed by hemodialysis or peritoneal dialysis.

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 58.4 g of atazanavir in an HIV-infected patient (146 times the 400 mg recommended dose) was associated with asymptomatic bilateral bundle branch 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 cardiac conduction abnormalities, including PR and/or QT interval prolongations, may be observed. (See WARNINGS AND PRECAUTIONS: Cardiovascular, and DETAILED PHARMACOLOGY: Electrocardiogram)

Cobicistat: Limited clinical experience is available at doses higher than the therapeutic dose of cobicistat. In two studies, a single dose of cobicistat 400 mg was administered to a total of 60 healthy subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

For management of a suspected drug overdose, contact your regional Poison Control Centre Immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

EVOTAZ is a fixed-dose combination of the antiviral drug atazanavir sulfate boosted by the pharmacokinetic enhancer cobicistat.

Atazanavir is an azapeptide HIV-1 protease inhibitor. 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.

Cobicistat is a selective, mechanism-based inhibitor of cytochrome P450 of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates, such as atazanavir, where bioavailability is limited and half-life is shortened due to CYP3A-dependent metabolism.

Pharmacodynamics

Effects on Serum Creatinine

The effect of cobicistat on serum creatinine was investigated in a trial in subjects with normal renal function (eGFR ≥80 mL/min, N=12) and mild-to-moderate renal impairment (eGFR 50-79 mL/min, N=18). A statistically significant change of estimated glomerular filtration rate, calculated by Cockcroft-Gault method ($eGFR_{CG}$) from baseline, was observed after 7 days of treatment with cobicistat 150 mg among subjects with normal renal function (−9.9 ± 13.1 mL/min) and mild-to-moderate renal impairment (−11.9 ± 7.0 mL/min). No statistically significant changes in $eGFR_{CG}$ were observed compared to baseline for subjects with normal renal function or mild-to-moderate renal impairment 7 days after cobicistat was discontinued. The actual glomerular filtration rate, as determined by the clearance of probe drug iohexol, was

not altered from baseline following treatment of cobicistat among subjects with normal renal function and mild-to-moderate renal impairment, indicating that cobicistat inhibits tubular secretion of creatinine, reflected as a reduction in $eGFR_{CG}$, without affecting the actual glomerular filtration rate.

Pharmacokinetics

One EVOTAZ tablet provided comparable atazanavir exposures (90% confidence intervals within 80.0%-125.0%) to one atazanavir capsule (300 mg) plus one cobicistat tablet (150 mg) following single, oral dose administration with a light meal (336 kcal; 5.1 g fat, 63.3 g carbohydrates, and 9.3 g protein) in healthy, adult subjects (N=62) (see CLINICAL TRIALS, Comparative Bioavailability Studies).

The pharmacokinetic enhancing effect of cobicistat on atazanavir pharmacokinetics was evaluated in the pharmacokinetic substudy (N=48) of Study 114 in which HIV-1 infected subjects received atazanavir 300 mg coadministered with cobicistat 150 mg or atazanavir 300 mg coadministered with ritonavir 100 mg, both in combination with emtricitabine/tenofovir DF. The steady-state pharmacokinetic parameters of atazanavir were comparable when coadministered with cobicistat versus ritonavir as shown in Table 6 (see CLINICAL TRIALS).

Table 6 - Pharmacokinetic Parameters (Mean ± SD) of Atazanavir in the Pharmacokinetic Substudy of Study 114

Parameter	Atazanavir and cobicistat with emtricitabine/tenofovir DF (n=22)	Atazanavir and ritonavir with emtricitabine/tenofovir DF (n=26)
AUC (µg•h/mL)	46.13 ± 26.18	47.59 ± 24.39
C_{max} (µg/mL)	3.91 ± 1.94	4.76 ± 1.94
C_{tau} (µg/ml)	0.80 ± 0.72	0.85 ± 0.72

Absorption:

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

Cobicistat: Following oral administration of cobicistat with food in HIV-1 infected subjects, peak plasma concentrations were observed 3 hours post-dose for cobicistat. The steady-state mean Cmax, AUCtau, and Ctrough (mean ± SD) following multiple doses of cobicistat in HIV-1 infected patients (N=68), respectively, were 1.2 ± 0.3 µg/mL, 10.9 ± 3.8 µg•h/mL, and 0.07 ± 0.07 µg/mL. Cobicistat exposures are non-linear and greater than dose-proportional over the range of 50 mg to 400 mg, consistent with a mechanism-based CYP3A inhibitor.

Food effect

Administration of a single dose of EVOTAZ with a light meal (336 kcal, 5.1 g fat, 63.3 g carbohydrates, 9.3 g protein) resulted in a 42% increase in atazanavir C_{max}, a 28% increase in

atazanavir AUC, a 31% increase in cobicistat C_{max}, and a 24% increase in cobicistat AUC relative to the fasting state. Administration of a single dose of EVOTAZ with a high-fat meal (1038 kcal, 59 g fat, 89.7 g carbohydrates, 37 g protein) resulted in a 14% reduction in atazanavir C_{max} with no change in atazanavir AUC or cobicistat exposures (C_{max}, AUC) relative to the fasting state. The 24-hour atazanavir concentration following a high-fat meal was increased by approximately 23% due to delayed absorption; the median T_{max} increased from 2.0 to 3.5 hours.

Distribution:

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

Cobicistat: Cobicistat is 97-98% bound to human plasma proteins and the mean plasma-to-blood drug concentration ratio was 2.

Metabolism:

Atazanavir: Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that atazanavir is principally metabolized by CYP3A4 isozyme to oxygenated metabolites, which are then excreted in the bile as either free or glucuronidated metabolites. Additional minor metabolic pathways consist of N-dealkylation, hydrolysis and oxygenation with dehydrogenation.

Two minor metabolites of atazanavir in plasma have been characterized. Neither metabolite demonstrated *in vitro* antiviral activity.

Cobicistat: Cobicistat is metabolized via CYP3A (major)- and CYP2D6 (minor)-mediated oxidation and does not undergo glucuronidation. Following oral administration of [^{14}C]cobicistat, 99% of circulating radioactivity in plasma was unchanged cobicistat. Low levels of metabolites are observed in urine and feces and do not contribute to the CYP3A inhibitory activity of cobicistat.

Elimination:

Atazanavir: 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.

Cobicistat: Following oral administration of [^{14}C] 86% and 8.2% of the dose were recovered in feces and urine, respectively. The median terminal plasma half-life of cobicistat following administration of TYBOST is approximately 3-4 hours.

Special Populations and Conditions

Age/Gender/Race:

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 important pharmacokinetic differences observed due to age or gender. There are insufficient data to determine whether there are any effects of race on the pharmacokinetics of atazanavir. The pharmacokinetics of cobicistat have not been established in children (< 18 years) nor has it been fully evaluated in the elderly (> 65 years). No clinically relevant pharmacokinetic differences in gender and race have been observed between men and women for cobicistat.

Hepatic Insufficiency:

The impact of hepatic impairment on the pharmacokinetics of the combination of atazanavir and cobicistat has not been assessed.

Atazanavir: Atazanavir is metabolized and eliminated primarily by the liver. Atazanavir has been studied in adult patients with moderate to severe hepatic impairment (14 Child-Pugh B and 2 Child-Pugh C) after a single 400-mg dose. The mean AUC(0-∞) was 42% greater in patients with impaired hepatic function than in healthy volunteers. The mean half-life of atazanavir in hepatically impaired patients was 12.1 hours compared to 6.4 hours in healthy volunteers. Increased concentrations of atazanavir are expected in patients with moderately or severely impaired hepatic function.

Cobicistat: Cobicistat is primarily metabolized and eliminated by the liver. A study of the pharmacokinetics of cobicistat was performed in non-HIV-1 infected subjects with moderate hepatic impairment (Child-Pugh Class B). No clinically relevant differences in cobicistat pharmacokinetics were observed between subjects with moderate impairment and healthy subjects. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of cobicistat has not been studied.

Renal Insufficiency:

Atazanavir: In healthy subjects, approximately 7% of the dose of atazanavir is eliminated unchanged in the urine. Atazanavir has been studied in adult subjects with severe renal impairment (n=20), including those on hemodialysis, at multiple doses of 400 mg once daily. The mean atazanavir Cmax was 9% lower, AUC was 19% higher, and Cmin was 96% higher in subjects with severe renal impairment not undergoing hemodialysis (n=10), than in age, weight, and gender matched subjects with normal renal function. Atazanavir was not appreciably cleared during hemodialysis. In a 4-hour dialysis session, 2.1% of the administered dose was removed. Subjects on hemodialysis appeared to display lower exposures as compared to healthy subjects

and renally-impaired subjects without hemodialysis. The geometric means for ATV AUC, Cmax and Cmin, for atazanavir administered immediately following dialysis in subjects on hemodialysis (n=10) were 42%, 37% and 54% lower, respectively, relative to subjects with normal renal function. When atazanavir was administered 2 hours before a 4-hour hemodialysis session, the geometric means for ATV AUC, Cmax and Cmin in hemodialysis subjects were 28%, 25% and 43% lower, respectively, than subjects with normal renal function. The mechanism of this decrease is unknown.

Cobicistat: A study of the pharmacokinetics of cobicistat-boosted elvitegravir was performed in non–HIV-1 infected subjects with severe renal impairment (estimated creatinine clearance below 30 mL/min). No meaningful differences in cobicistat pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects, consistent with low renal clearance of cobicistat. (See DOSAGE AND ADMINISTRATION).

STORAGE AND STABILITY

EVOTAZ Tablets should be stored at 25°C, with excursions permitted to 15°C - 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

EVOTAZ is a fixed-dose combination tablet for oral administration containing 300 mg atazanavir (as atazanavir sulfate) and 150 mg cobicistat.

Inactive Ingredients:

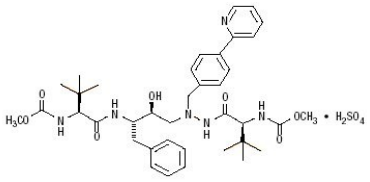
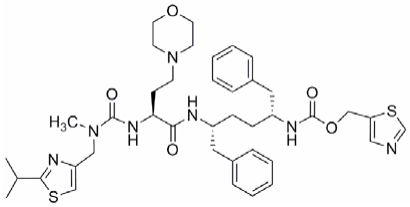
- Tablet core: microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, crospovidone, stearic acid, magnesium stearate, hydroxypropyl cellulose, and silicon dioxide.
- Film-coating: hypromellose, titanium dioxide, talc, triacetin, and red iron oxide

EVOTAZ Tablets are oval, biconvex, pink film-coated, debossed with “3641” on one side and plain on the other side. Each bottle contains 30 tablets, a silica gel desiccant and closed with a child-resistant closure.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name:	atazanavir sulfate	cobicistat
Chemical Name:	(3S,8S,9S,12S)-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate (1:1)	1,3-thiazol-5-ylmethyl [(2*R*,5*R*)-5-{[(2*S*)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]-4-(morpholin-4-yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate
Molecular Formula and Molecular Mass:	$C_{38}H_{52}N_6O_7 \bullet H_2SO_4$ 802.9 (sulfuric acid salt) 704.9 (free base)	$C_{40}H_{53}N_7O_5S_2$ 776.0
Structural Formula:		
Physicochemical Properties:	Atazanavir sulfate is a white to pale yellow crystalline powder. It is slightly soluble in water (4-5 mg/mL, free base equivalent) with the pH of a saturated solution in water being about 1.9 at 24 ± 3°C.	Cobicistat is adsorbed onto silicon dioxide. Cobicistat is a white to pale yellow solid. The solubility is approximately 0.1 mg/mL in water at 20°C. The partition coefficient (log P) is 4.3 (*n*-octanol/phosphate buffer pH 8.5) and the pKa is pKa1 = 1.8 (thiazole group), pKa2 = 2.5 (alkylthiazole group), pKa3 = 6.4 (morpholino group).

CLINICAL TRIALS

Study Demographics and Trial Design

The activity of cobicistat has been demonstrated in pharmacokinetic studies. In these pharmacokinetic studies, the exposure of atazanavir boosted with cobicistat 150 mg was consistent with that observed with ritonavir 100 mg (see ACTION AND CLINICAL PHARMACOLOGY: Pharmacodynamics, Effects on Pharmacokinetic Enhancement).

The safety and efficacy of atazanavir given with cobicistat was evaluated in a Phase 3 randomized, double-blind, active-controlled trial (Study 114) in antiretroviral treatment-naïve, HIV-1 infected subjects with baseline estimated creatinine clearance above 70 mL/min (N=692).

Randomization was stratified by screening HIV-1 RNA level (≤100,000 copies/mL or >100,000 copies/mL). Virologic response rate was evaluated in both treatment arms and defined as achieving an undetectable viral load (< 50 HIV-1 RNA copies/mL).

Demographic characteristics for Study 114 are presented in Table 7.

Table 7: Study Treatment and Demographic Characteristics of Antiretroviral Treatment-naïve HIV-1 Infected Adult Subjects in Study 114

Study	Dosage, Route of Administration	Demographics	
		Treatment Arm	Control Arm
114	Atazanavir 300 mg with cobicistat 100 mg (once daily) + emtricitabine/tenofovir DF or Atazanavir 300 mg with ritonavir 100 mg + emtricitabine/tenofovir DF	N=344 **Gender: n (%)** Male 287 (83.4) Female 57 (16.6) **Age: median (min-max)** 36 (19–62) **Race:** White – 198 (57.6) Black – 65 (18.9) Asian – 44 (12.8) Other – 37 (10.8) **Percentage of subjects with viral load > 100,000 copies/mL:** 38.4% **Median baseline CD4+ cell count (min-max), cells/mm^3:** 348 (1-1075) **Percentage of subjects with CD4+ cell count ≤ 200 cells/mm^3:** 17.4%	N=348 **Gender: n (%)** Male 287 (82.5) Female 61 (17.5) **Age: median (min-max)** 37 (19–70) **Race:** White – 215 (61.8) Black – 63 (18.1) Asian – 37 (10.6) Other – 33 (9.5) **Percentage of subjects with viral load > 100,000 copies/mL:** 41.1% **Median baseline CD4+ cell count (min-max), cells/mm^3:** 341 (10-1455) **Percentage of subjects with CD4+ cell count ≤ 200 cells/mm^3:** 16.4%

Treatment outcomes at 48 weeks are presented in Table 8.

Table 8: Virologic Outcomes of Randomized Treatment of Study 114 at Week 48[a]

	Atazanavir 300 mg with cobicistat 100 mg (once daily) + emtricitabine/tenofovir disoproxil fumarate (n=344)	Atazanavir 300 mg with ritonavir 100 mg + emtricitabine/tenofovir disoproxil fumarate (n=348)
HIV-1 RNA <50 copies/mL	85%	87%
Treatment Difference	−2.2% (95% Cl = −7.4%, 3.0%)	
Virologic Failure[b]	6%	4%
No Virologic Data at Week 48 Window	9% (31)	9% (30)
Discontinued Study Drug Due to AE or Death[c]	6% (22)	7% (23)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	3% (9)	2% (7)
Missing Data During Window but on Study Drug	0%	0%

a. Week 48 window is between Day 309 and 378 (inclusive).
b. Includes subjects who had ≥50 copies/mL in the Week 48 window, subjects who discontinued early due to lack or loss of efficacy, subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥50 copies/mL.
c. Includes subjects who discontinued due to adverse event or death at any time point from Day 1 through the Week 48 window resulting in no virologic data on treatment during the specified window.
d. Includes subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Atazanavir given with cobicistat + emtricitabine/tenofovir DF was non-inferior in achieving HIV-1 RNA < 50 copies/mL when compared to atazanavir given with ritonavir + emtricitabine/tenofovir DF.

In Study 114, the mean increase from baseline in CD4+ cell count at Week 48 was 213 cells/mm^3 in patients receiving atazanavir and cobicistat and 219 cells/mm^3 in patients receiving atazanavir and ritonavir.

Comparative Bioavailability Studies

A randomized, single-dose, open-label, 5-period, crossover comparative bioavailability study was conducted in 64 healthy subjects (40 males and 24 females) to examine the comparative bioavailability of atazanavir when co-administered with cobicistat as a fixed dose combination (FDC) tablet (1 x 300/150 mg) relative to the single agents (300 mg Atzanavir capsule + 150 mg Cobicistat tablet) following a light meal, the relative bioavailability of atazanavir when co-administered with cobicistat as a FDC tablet relative to the single agents under fasted conditions, and the effect of food on the bioavailability of atazanavir in the FDC tablet.

The results of the comparison of the bioavailability of atazanavir and cobicistat from the FDC tablet relative to the single agents (300 mg Atzanavir capsule + 150 mg Cobicistat tablet)

following administration with a light meal (336 kcal; 5.1 g fat (14%), 63.3 g carbohydrates (75%), and 9.3 g protein (11%)) are presented below (N=62).

Table 9 : Summary of Atazanavir Pharmacokinetic Parameters (Light meal)

Atazanavir (1 x 300 mg) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
$AUC_{(0-T)}$ (ng•h/mL)	34905.41 36871.94 (31)	32774.78 35661.43 (38)	106.5	101.2 - 112.0
$AUC_{(INF)}$ (ng•h/mL)	35672.92 37801.76 (32)	33522.82 36698.74 (39)	106.4	101.1 - 112.0
C_{max} (ng/mL)	4104.17 4335.97 (32)	3831.93 4188.87 (39)	107.3	101.2 - 113.7
C24 (ng/mL)	449.36 520.43 (52)	415.98 502.36 (58)	108.4	101.4 - 115.8
T_{max} ϵ (h)	2.50 (2.00 - 4.05)	3.00 (2.00 - 5.55)		
T-HALF¶ (h)	7.50 (35)	7.54 (39)		

* ATV/COBI 300/150 mg Fixed-Dose Combination (FDC) tablet with a light meal
† ATV 300 mg capsule (Bristol-Myers Squibb, USA) + COBI 150 mg tablet (Gilead, Canada) with a light meal
ϵ Expressed as the median (range) only
¶ Expressed as the arithmetic mean (CV%) only

Table 10: Summary of Cobicistat Pharmacokinetic Parameters (Light meal)

Cobicistat (1 x 150 mg) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	%Ratio of Geometric Means	90% Confidence Interval
$AUC_{(0-T)}$ (ng•h/mL)	8866.19 9582.17 (38)	8738.14 9577.31 (42)	101.9	98.3 - 105.7
$AUC_{(INF)}$ (ng•h/mL)	9178.99 10024.94 (41)	9045.14 10027.45 (45)	101.9	98.2 - 105.8
C_{max} (ng/mL)	1347.52 1404.58 (29)	1321.20 1394.54 (32)	102.3	99.1 - 105.7
T_{max} ϵ (h)	2.52 (1.00 - 5.00)	2.52 (1.00 - 5.00)		
T-HALF¶ (h)	4.33 (33)	4.34 (33)		

* ATV/COBI 300/150 mg Fixed-Dose Combination (FDC) tablet with a light meal
† ATV 300 mg capsule (Bristol-Myers Squibb, USA) + COBI 150 mg tablet (Gilead, Canada) with a light meal
ϵ Expressed as the median (range) only
¶ Expressed as the arithmetic mean (CV%) only

DETAILED PHARMACOLOGY

Effects on Electrocardiogram- Effect on PR and QT intervals

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 pre-dose 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 pharmacodynamic interaction in humans between atazanavir and other drugs that prolong the PR interval of the electrocardiogram (see WARNINGS AND PRECAUTIONS).

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 had a QTc interval > 500 msec.

Cobicistat: The electrocardiographic effects of cobicistat were determined in a study of 48 healthy adult subjects. Cobicistat did not prolong the QTcF interval at doses of 250 mg and 400 mg, providing exposures 2- and 4-fold above the recommended therapeutic dose, respectively. Prolongation of the PR interval was noted in subjects receiving cobicistat in the same study. The maximum mean (95% upper confidence bound) difference in PR from placebo after baseline-correction was 9.5 (12.1) ms for 250 mg dose and 20.2 (22.8) for 400-mg dose cobicistat. Because the proposed therapeutic dose of cobicistat is lower than the lowest dose studied in the thorough QT study, it is unlikely that treatment with cobicistat will result in clinically relevant PR prolongation.

In a human clinical study of 35 healthy subjects, echocardiograms performed at baseline and after receiving 150 mg cobicistat once daily for at least 15 days indicated no clinically significant change in left ventricular function.

Drug-Drug Interactions

See also CONTRAINDICATIONS and DRUG INTERACTIONS.

Atazanavir is metabolized in the liver by the cytochrome P450 enzyme system and inhibits CYP3A4 and UGT1A1 at clinically relevant concentrations with Ki of 2.35 μM (CYP3A4 isoform) and 1.9 μM. Cobicistat is a potent mechanism-based inhibitor of CYP3A4 and is an inhibitor of CYP2D6. EVOTAZ should not be administered concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4 and/or UGT1A1 (see CONTRAINDICATIONS). Drugs that induce CYP3A4 activity would be expected to increase the clearance of atazanavir, resulting in lowered plasma concentrations. Coadministration of EVOTAZ and other drugs that inhibit CYP3A4 may increase atazanavir plasma concentrations.

Atazanavir is a weak inhibitor of CYP2C8. Caution should be used when EVOTAZ is coadministered with drugs highly dependent on CYP2C8 with narrow therapeutic indicies (eg. paclitaxel, repaglinide).

Atazanavir has been shown *in vivo* not to induce its own metabolism, nor to increase the biotransformation of some drugs metabolized by CYP3A4. In a multiple-dose study, atazanavir decreased the urinary ratio of endogenous 6β-OH cortisol to cortisol versus baseline, indicating that CYP3A4 production was not induced.

Drug interaction studies were performed with atazanavir and cobicistat separately and other drugs likely to be coadministered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministered drugs on the exposure of atazanavir are shown in Table 11. The effects of atazanavir on the exposure of coadministered drugs are shown in Table **12**.

Table 11: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
				C_{max}	AUC	C_{min}
Atenolol	50 mg once daily, d 7-11 and d19-23	400 mg once daily, d 1-11	19	1.00 (0.89, 1.12)	0.93 (0.85,1.01)	0.74 (0.65, 0.86)
clarithromycin	500 mg BID, d 7-10 and d 18-21	400 mg once daily, d 1-10	29	1.06 (0.93, 1.20)	1.28 (1.16, 1.43)	1.91 (1.66, 2.21)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose simultaneously with ddI and d4T	31	0.11 (0.06, 0.18)	0.13 (0.08, 0.21)	0.16 (0.10, 0.27)
	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose 1 hour after ddI + d4T	31	1.12 (0.67, 1.18)	1.03 (0.64, 1.67)	1.03 (0.61, 1.73)
didanosine (ddI) (enteric-coated [EC] capsules)[b]	400 mg d 8 (fed)	400 mg once daily d 2-8	34	1.03 (0.93, 1.14)	0.99 (0.91, 1.08)	0.98 (0.89, 1.08)
	400 mg d 19 (fed)	300 mg/ritonavir 100 mg once daily d 9-19	31	1.04 (1.01, 1.07)	1.00 (0.96, 1.03)	0.87 (0.82, 0.92)
diltiazem	180 mg once daily, d 7-11 and d 19-23	400 mg once daily, d 1-11	30	1.04 (0.96, 1.11)	1.00 (0.95, 1.05)	0.98 (0.90, 1.07)
efavirenz	600 mg once daily, d 7-20	400 mg once daily, d 1-20	27	0.41 (0.33, 0.51)	0.26 (0.22, 0.32)	0.07 (0.05, 0.10)
famotidine	40 mg BID d 7-12 [c]	400 mg once daily d 1-12 [c]	15	0.53 (0.34, 0.82)	0.59 (0.40, 0.87)	0.58 (0.37, 0.89)
	40 mg BID d 7-12 [d]	400 mg once daily (pm) d 1-6, d 7-12 [d]	14	1.08 (0.82, 1.41)	0.95 (0.74, 1.21)	0.79 (0.60, 1.04)

Table 11: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
				C_{max}	AUC	C_{min}
	40 mg BID d 11-20 [c,e]	300 mg once daily / ritonavir 100 mg once daily d 1-20 [c,e]	14	0.86 (0.79, 0.94)	0.82 (0.75, 0.89)	0.72 (0.64, 0.81)
	20 mg BID, d 11-17	300 mg once daily /ritonavir 100 mg once daily /tenofovir 300 mg once daily, d 1-10 (am), then 300 mg once daily /ritonavir 100 mg once daily /tenofovir 300 mg once daily, d 11-17 (am) (simultaneous administration with am famotidine) [m, n]	18	0.91 (0.84, 0.99)	0.90 (0.82, 0.98)	0.81 (0.69, 0.94)
	40 mg once daily (pm), d 18-24	300 mg once daily /ritonavir 100 mg once daily /tenofovir 300 mg once daily, d 1-10 (am), then 300 mg once daily /ritonavir 100 mg once daily /tenofovir 300 mg once daily, d 18-24 (am) (12h after pm famotidine) [n]	20	0.89 (0.81, 0.97)	0.88 (0.80, 0.96)	0.77 (0.63, 0.93)
	40 mg BID, d 18-24	300 mg once daily /ritonavir 100 mg once daily /tenofovir 300 mg once daily, d 1-10 (am), then 300 mg once daily /ritonavir 100 mg once daily /tenofovir 300 mg once daily, d 18-24 (am) (10h after pm famotidine and 2h before am famotidine)[n]	18	0.74 (0.66, 0.84)	0.79 (0.70, 0.88)	0.72 (0.63, 0.83)
fluconazole	200 mg once daily, d 11-20	300 mg once daily /ritonavir 100 mg once daily, d 1-10, then 300 mg once daily /ritonavir 100 mg once daily, d 11-20	29	1.03 (0.95, 1.11)	1.04 (0.95, 1.13)	0.98 (0.85, 1.13)

Table 11: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
				C_{max}	AUC	C_{min}
ketoconazole	200 mg once daily, d 7-13	400 mg once daily, d 1-13	14	0.99 (0.77, 1.28)	1.10 (0.89, 1.37)	1.03 (0.53, 2.01)
nevirapine[f,g]	200 mg BID, d 1-23	300 mg once daily / ritonavir 100 mg once daily, d 4-13, then 400 mg once daily / ritonavir 100 mg once daily, d 14-23	23, 22[h]	0.72 (0.60, 0.86) 1.02 (0.85, 1.24)	0.58 (0.48, 0.71) 0.81 (0.65, 1.02)	0.28 (0.20, 0.40) 0.41 (0.27, 0.60)
omeprazole	40 mg once daily d 7-12 [i]	400 mg once daily d 1-12	16	0.04 (0.04, 0.05)	0.06 (0.05, 0.07)	0.05 (0.03, 0.07)
	40 mg once daily d 11-20 [i]	300 mg once daily/ ritonavir 100 mg once daily d 1-20	15	0.28 (0.24, 0.32)	0.24 (0.21, 0.27)	0.22 (0.19, 0.26)
	20 mg once daily, d 17-23 (am)	300 mg once daily /ritonavir 100 mg once daily, d 7-16 (pm), then 300 mg once daily /ritonavir 100 mg once daily, d 17-23 (pm) [o, p]	13	0.61 (0.46, 0.81)	0.58 (0.44, 0.75)	0.54 (0.41, 0.71)
rifabutin	150 mg once daily, d 15-28	400 mg once daily, d 1-28	7	1.34 (1.14, 1.59)	1.15 (0.98, 1.34)	1.13 (0.68, 1.87)
rifampin	600 mg once daily d 17-26	300 mg once daily/ ritonavir 100 mg once daily d 7-26	16	0.47 (0.41, 0.53)	0.28 (0.25, 0.32)	0.02 (0.02, 0.03)
ritonavir [j]	100 mg once daily, d 11-20	300 mg once daily, d 1-20	28	1.86 (1.69, 2.05)	3.38 (3.13, 3.63)	11.89 (10.23, 13.82)
tenofovir [k]	300 mg once daily with food d 9-16	400 mg once daily with food d 1-16	34	0.79 (0.73, 0.86)	0.75 (0.70, 0.81)	0.60 (0.52, 0.68)
tenofovir [k] and ritonavir	tenofovir [k] 300 mg once daily d 15-42	300 mg once daily with ritonavir 100 mg once daily d 1-42	10	0.72 [l] (0.50, 1.05)	0.75 [l] (0.58, 0.97)	0.77 [l] (0.54, 1.10)

Table 11: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
				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	300 mg/ritonavir 100 mg QD, d 11–30	20	0.87 (0.80, 0.96)	0.88 (0.82, 0.95)	0.80 (0.72, 0.90)
voriconazole (Subjects without a functional CYP2C19 allele)	50 mg BID, d 2-3, 22-30; 100 mg BID d 1, 21	300 mg/ritonavir 100 mg QD, d 11–30	8	0.81 (0.66, 1.00)	0.80 (0.65, 0.97)	0.69 (0.54, 0.87)

[a] N = number of subjects
[b] 400 mg ddI EC and atazanavir were administered together with food on Days 8 and 19.
[c] Simultaneous administration
[d] 10 hr after, 2 hr before famotidine
[e] Atazanavir 300 mg plus ritonavir 100 mg once daily coadministered with famotidine40 mg twice daily resulted in atazanavir geometric mean C_{max} that was similar and AUC and C_{min} values that were 1.79- and 4.46- fold higher relative to atazanavir 400 mg once daily alone.
[f] Study was conducted in HIV-infected individuals.
[g] Compared with atazanavir 400 mg historical data without nevirapine (n=13), the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 1.42 (0.98, 2.05), 1.64 (1.11, 2.42), and 1.25 (0.66, 2.36), respectively, for atazanavir/ritonavir 300/100 mg; and 2.02 (1.42, 2.87), 2.28 (1.54, 3.38), and 1.80 (0.94, 3.45), respectively, for atazanavir/ritonavir 400/100 mg.
[h] Parallel group design; n for atazanavir/ritonavir plus nevirapine, n for atazanavir 300 mg/ritonavir 100 mg without nevirapine. Subjects were treated with nevirapine prior to study entry.
[i] Omeprazole was administered on an empty stomach 2 hours before atazanavir.
[j] Compared with atazanavir 400 mg once daily historical data, administration of atazanavir/ritonavir 300/100 mg once daily increased the atazanavir geometric mean values of C_{max}, AUC, and C_{min} by 18%, 103%, and 671%, respectively. The geometric mean values of atazanavir pharmacokinetic parameters when coadministered with ritonavir were: C_{max} = 6129 ng/mL, AUC = 57039 ng•h/ml, and C_{min} = 1227 ng/mL.
[k] Tenofovir DF. Note that similar results were observed in studies where administration of tenofovir and atazanavir was separated by 12 hours.
[l] Ratio of atazanavir plus ritonavir plus tenofovir to atazanavir plus ritonavir. Atazanavir 300 mg plus ritonavir 100 mg results in higher atazanavir exposure than atazanavir 400 mg (see footnote [g]).
[m] Similar results were noted when famotidine 20 mg BID was administered 2 hours after and 10 hours before atazanavir 300 mg and ritonavir 100 mg plus tenofovir 300 mg.
[n] Atazanavir/ritonavir/tenofovir was administered after a light meal.
[o] Omeprazole 20 mg was administered 30 minutes prior to a light meal in the morning and atazanavir 300 mg plus ritonavir 100 mg in the evening after a light meal, separated by 12 hours from omeprazole.
[p] Atazanavir 300 mg plus ritonavir 100 mg once daily separated by 12 hours from omeprazole 20 mg daily resulted in increases in atazanavir geometric mean AUC (10%) and Cmin (2.4-fold), with a decrease in Cmax (29%) relative to atazanavir 400 mg once daily in the absence of omeprazole (study days 1–6).

The effects of coadministration of atazanavir on the AUC, C_{max}, and C_{min} of other drugs are summarized in Table 12.

Table 12: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Atazanavir:

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Atazanavir; No Effect = 1.00		
				C_{max}	AUC	C_{min}
acetaminophen	1 gm BID, d 1-20	300 mg once daily /ritonavir 100 mg once daily, d 11-20	10	0.87 (0.77, 0.99)	0.97 (0.91, 1.03)	1.26 (1.08, 1.46)
atenolol	50 mg once daily, d 7-11 and d 19-23	400 mg once daily, d 1-11	19	1.34 (1.26, 1.42)	1.25 (1.16, 1.34)	1.02 (0.88, 1.19)
buprenorphine	once daily stable maintenance dose with naloxone	400 mg once daily x 5 days	10	buprenorphine: 1.64 norbuprenorphine: 1.36	buprenorphine: 1.93 norbuprenorphine: 1.76	buprenorphine: 1.99 norbuprenorphine: 1.64
clarithromycin	500 mg BID, d 7-10 and d 18-21	400 mg once daily, d 1-10	21	1.50 (1.32, 1.71) OH-clarithromycin: 0.28 (0.24, 0.33)	1.94 (1.75, 2.16) OH-clarithromycin: 0.30 (0.26, 0.34)	2.60(2.35, 2.88) OH-clarithromycin: 0.38 (0.34, 0.42)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)	ddI: 200 mg x 1 dose d4T: 40 mg x 1 dose	400 mg x 1 dose simultaneous with ddI and d4T	31	ddI: 0.92 (0.84, 1.02) d4T: 1.08 (0.96, 1.22)	ddI: 0.98 (0.92, 1.05) d4T: 1.00 (0.97, 1.03)	NA d4T: 1.04 (0.94, 1.16)
didanosine (ddI) (enteric coated [EC] capsules)[b]	400 mg d 1 (fasted), 8 (fed)	400 mg once daily, d 2-8	34	0.64 (0.55, 0.74)	0.66 (0.60, 0.74)	1.13 (0.91, 1.41)
diltiazem	180 mg once daily, d 7-11 and d 19-23	400 mg once daily, d 1-11	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[c]	Ortho-Novum® 7/7/7 once daily, d 1-29	400 mg once daily, d 16-29	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)

Table 12: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Atazanavir:

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Atazanavir; No Effect = 1.00		
				C_{max}	AUC	C_{min}
ethinyl estradiol & norgestimate[d]	Tri-Cyclen® once daily, d 1-28, then Tri-Cyclen® LO once daily, d 29-42[e]	300 mg once daily /ritonavir 100 mg once daily, d 29-42	13	ethinyl estradiol: 0.84 (0.74, 0.95) 17-deacetyl norgestimate:[f] 1.68 (1.51, 1.88)	ethinyl estradiol: 0.81 (0.75, 0.87) 17-deacetyl norgestimate:[f] 1.85 (1.67, 2.05)	ethinyl estradiol: 0.63 (0.55, 0.71) 17-deacetyl norgestimate:[f] 2.02 (1.77, 2.31)
fluconazole	200 mg once daily, d 1-20	300 mg once daily /ritonavir 100 mg once daily, d 11-20	30	1.05 (0.99, 1.10)	1.08 (1.02, 1.15)	1.07 (1.00, 1.15)
methadone	stable maintenance dose, d 1-15	400 mg once daily, d 2-15	16	(R)-methadone[g] 0.91 (0.84, 1.0) total: 0.85 (0.78, 0.93)	(R)-methadone [g] 1.03 (0.95, 1.10) total: 0.94 (0.87, 1.02)	(R)-methadone[g] 1.11 (1.02, 1.20) total: 1.02 (0.93, 1.12)
nevirapine[h,i]	200 mg BID, d 1-23	300 mg once daily / ritonavir 100 mg once daily, d 4-13, then 400 mg once daily / ritonavir 100 mg once daily, d 14-23	23	1.17 (1.09, 1.25) 1.21 (1.11, 1.32)	1.25 (1.17, 1.34) 1.26 (1.17, 1.36)	1.32 (1.22, 1.43) 1.35 (1.25, 1.47)
omeprazole[j]	40 mg single dose d 7 and d 20	400 mg once daily d 1-12	16	1.24 (1.04, 1.47)	1.45 (1.20, 1.76)	NA
rifabutin	300 mg once daily, d 1-10 then 150 mg once daily, d 11-20	600 mg once daily[k] d 11-20	3	1.18 (0.94, 1.48) 25-O-desacetyl-rifabutin: 8.20 (5.90, 11.40)	2.10 (1.57, 2.79) 25-O-desacetyl-rifabutin: 22.01 (15.97, 30.34)	3.43 (1.98, 5.96) 25-O-desacetyl-rifabutin: 75.6 (30.1, 190.0)
	150 mg twice weekly, d 1-15	300 mg once daily / ritonavir 100 mg once daily, d 1-17	7	2.49 [l] (2.03, 3.06) 25-O-desacetyl-rifabutin: 7.77 (6.13, 9.83)	1.48 [l] (1.19, 1.84) 25-O-desacetyl-rifabutin: 10.90 (8.14, 14.61)	1.40 [l] (1.05, 1.87) 25-O-desacetyl-rifabutin: 11.45 (8.15, 16.10)

Table 12: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Atazanavir:

Coadministered Drug	Coadministered Drug Dose/Schedule	Atazanavir Dose/Schedule	N[a]	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Atazanavir; No Effect = 1.00		
				C_{max}	AUC	C_{min}
rosiglitazone[m]	4 mg single dose, d 1, 7,	400 mg once daily D 2-7	14	1.08 (1.03, 1.13)	1.35 (1.26, 1.44)	NA
saquinavir (soft gelatin capsules)	1200 mg once daily, d 1-13	400 mg once daily, d 7-13	7	4.39 (3.24, 5.95)	5.49 (4.04, 7.47)	6.86 (5.29, 8.91)
tenofovir[n]	300 mg once daily with food d 9-16 and d 24-30	400 mg once daily with food d 1-16	33	1.14 (1.08, 1.20)	1.24 (1.21, 1.28)	1.22 (1.15, 1.30)
voriconazole (Subjects with at least one functional CYP2C19 allele)	200 mg BID, d 2-3, 22-30; 400 mg BID d 1, 21	300 mg/ritonavir 100 mg QD, d 11–30	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	300 mg/ritonavir 100 mg QD, d 11–30	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	400 mg once daily, d 7-12	19	lamivudine: 1.04 (0.92, 1.16) zidovudine: 1.05 (0.88, 1.24) zidovudine glucuronide: 0.95 (0.88, 1.02)	Lamivudine: 1.03 (0.98, 1.08) zidovudine: 1.05 (0.96, 1.14) zidovudine glucuronide: 1.00 (0.97, 1.03)	Lamivudine: 1.12 (1.04, 1.21) zidovudine: 0.69 (0.57, 0.84) zidovudine glucuronide: 0.82 (0.62, 1.08)

[a] N = number of subjects

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

[c] Upon further dose normalization of ethinyl estradiol 25 mcg with atazanavir relative to ethinyl estradiol 35 mcg without atazanavir, the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 0.82 (0.73, 0.92), 1.06 (0.95, 1.17), and 1.35 (1.11, 1.63), respectively.

[d] Upon further dose normalization of ethinyl estradiol 35 mcg with atazanavir/ritonavir relative to ethinyl estradiol 25 mcg without atazanavir/ritonavir, the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 1.17 (1.03, 1.34), 1.13 (1.05, 1.22), and 0.88 (0.77, 1.00), respectively.

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

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

[g] (R)-methadone is the active isomer of methadone.

[h] Study was conducted in HIV-infected individuals.

[i] Subjects were treated with nevirapine prior to study entry.

[j] Omeprazole was used as a metabolic probe for CYP2C19. Omeprazole was given 2 hours after atazanavir on Day 7; and was given alone 2 hours after a light meal on Day 20.
[k] Not the recommended therapeutic dose of atazanavir.
[l] When compared to rifabutin 150 mg once daily alone d1-10 (n=14). Total of rifabutin + 25-O-desacetyl-rifabutin: AUC 2.19 (1.78, 2.69).
[m] Rosiglitazone used as a probe substrate for CYP2C8.
[n] Tenofovir DF. Note that similar results were observed in studies where administration of tenofovir and atazanavir was separated by 12 hours.

The effects of coadministered drugs on the exposure of cobicistat are shown in Table 13. The effects of cobicistat on the exposure of coadministered drugs are shown in Table 14.

In drug interaction studies conducted with cobicistat, there was no clinically significant interaction observed between cobicistat and famotidine or omeprazole.

Table 13: Pharmacokinetic Parameters for Cobicistat in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose (mg)	Cobicistat Dose (mg)	N	% Change of Cobicistat Pharmacokinetic Parameters[b, d] Coadministered (90% CI)		
				C_{max}	AUC	C_{min}
famotidine	40 once daily given 12 hours after elvitegravir	150 once daily[c]	10	⇔	⇔	⇔
	40 once daily given simultaneously with elvitegravir		16	⇔	⇔	⇔
omeprazole	20 once daily given 2 hours before elvitegravir	150 once daily[c]	11	⇔	⇔	⇔
	20 once daily given 2 hours before elvitegravir		11	⇔	⇔	⇔
carbamazepine	200 twice daily	150 once daily[c]	12	↓72 (↓76 to ↓67)	↓84 (↓86 to ↓82)	↓90 (↓93 to ↓86)
rifabutin	150 once every other day	150 once daily[c]	12	⇔	⇔	↓66 (↓74 to ↓54)
rosuvastatin	10 single dose	150 once daily[c]	10	⇔	⇔	⇔

a. All interaction studies conducted in healthy volunteers
b. ↑ = Increase; ↓ = Decrease; ⇔= No Effect
c. Study was conducted in the presence of 150 mg elvitegravir
d. Comparison based on elvitegravir/cobicistat 150/150 mg once daily.

Table 14: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Cobicistat[a]

Coadministered Drug	Coadministered Drug Dose (mg)	Cobicistat Dose (mg)	N	% Change of Cobicistat Pharmacokinetic Parameters[b] Coadministered (90% CI)		
				C_{max}	AUC	C_{min}
buprenorphine	16 - 24 once daily	150 once daily[c]	17	↑12 (↓2 to ↑27)	↑35 (↑18 to↑55)	↑66 (↑43 to↑93)
norbuprenorphine				↑24 (↑3 to ↑49)	↑42 (↑22 to ↑67)	↑57 (↑31 to↑88)
carbamazepine	200 twice daily	150 once daily[c]	12	↑40 (↑32 to ↑49)	↑43 (↑36 to ↓52)	↑51 (↑41 to↑62)
carbamazepine-10,11-epoxide				↓27 (↓30 to ↓22)	↓35 (↓37 to ↓34)	↓41 (↓43 to↓39)
naloxone	4 - 6 once daily	150 once daily[c]	17	↓28 (↓39 to ↓15)	↓28 (↓41 to ↓13)	N/A
R-Methadone	80-120 daily	150 once daily[c]	11	⇔	⇔	⇔
S-Methadone				⇔	⇔	⇔
norgestimate/ (↑143 to ↑192) ethinyl estradiol	0.180/0.215/ 0.250 norgestimate once daily	150 once daily[c]	13	↑108 (↑100 to ↑117)	↑126 (↑115 to ↑137)	↑167 (↑143 to ↑192)
	0.025 ethinyl estradiol once daily			⇔	↓25 (↓31 to ↓19)	↓44 (↓48 to ↓39)
desipramine	50 single dose	150 once daily	8	↑24 (↑8 to ↑44)	↑65 (↑36 to ↑102)	NC
digoxin	0.5 single dose	150 once daily	22	↑41 (↑29 to ↑55)	⇔	NC
efavirenz	600 single dose	150 once daily	17	↓13 (↓20 to ↓6)	⇔	NC
rifabutin 25-O-desacetylrifabutin	150 once every other day	150 once daily[c]	12	⇔[d] ↑384d (↑309 to ↑474)	⇔[d] ↑525d (↑408 to ↑669)	⇔[d] ↑394d (↑304 to ↑504)
rosuvastatin	10 single dose	150 once daily[c]	10	↑89 (↑48 to ↑142)	↑38 (↑14 to ↑67)	↑43 (↑8 to ↑89)

a. All interaction studies conducted in healthy volunteers
b. ↑ = Increase; ↓ = Decrease; ⇔= No Effect
c. Study was conducted in the presence of 150 mg elvitegravir
d. Comparison based on elvitegravir/cobicistat 150/150 mg once daily.
NC = Not calculated

MICROBIOLOGY

EVOTAZ is a fixed-dose combination of atazanavir (ATV) boosted by the pharmacokinetic enhancer cobicistat. ATV is an azapeptide HIV-1 protease inhibitor (PI) that selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions. Cobicistat is a mechanism-based inhibitor of cytochrome P450 3A (CYP3A). Inhibition of CYP3A-mediated metabolism by cobicistat increases the systemic exposure of CYP3A substrates.

Antiviral activity *in vitro*

Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC50) in the absence of human serum of 2 to 5 nM against a variety of laboratory and clinical HIV-1 isolates grown in peripheral blood mononuclear cells, macrophages, CEM-SS cells, and MT-2 cells. ATV has activity against HIV-1 Group M subtype viruses A, B, C, D, AE, AG, F, G, and J isolates in cell culture. ATV has variable activity against HIV-2 isolates (1.9 to 32 nM), with EC50 values above the EC50 values of failure isolates. Two-drug combination studies with ATV showed additive to antagonistic antiviral activity *in vitro* with abacavir and the NNRTIs (delavirdine, efavirenz, and nevirapine) and additive antiviral activity *in vitro* with the PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir), NRTIs (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.

Cobicistat does not inhibit recombinant HIV-1 protease in a biochemical assay and has no detectable antiviral activity against HIV-1, HBV, or HCV and does not antagonize the antiviral effect of HIV inhibitors.

Resistance

Clinical Studies of Treatment-Naive Patients Receiving Atazanavir 300 mg With Cobicistat 150 mg: In an analysis of treatment-failure subjects in Study 114 through Week 48, evaluable genotypic data from paired baseline and treatment-failure isolates were available for 11 of the 12 virologic failures in the atazanavir + cobicistat group. Among the 11 subjects, 2 developed the emtricitabine-associated resistance substitution M184V. No subject developed the tenofovir associated resistance substitution or any primary resistance substitution associated with protease inhibitors. In the ritonavir group, evaluable genotypic data were available for all 12 virologic failures and no patient had emergent resistance to any component of the regimen (see CLINICAL TRIALS).

Clinical Studies of Treatment-Naive Patients Receiving Atazanavir300 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 ≥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 virologic failure isolate had a 56-fold decrease in ATV susceptibility emerge on therapy with the development of PI substitutions L10F, V32I, K43T,

M46I, A71I, G73S, I85I/V, and L90M. Five of the treatment failure isolates in the ATV/RTV arm developed emtricitabine resistance with the emergence of either the MI84I (1 patient) or the M184V (4 patients) substitution on therapy. In the LPV/RTV arm, one virologic failure isolate had a 69-fold decrease in LPV susceptibility emerge on therapy with the development of PI substitutions L10V and V11I in addition to baseline PI substitutions V32I, I54I/V, V82A, L90M, L10I, A71I, G73S and L89V. Six of the failure isolates in the LPV/RTV arm developed emtricitabine resistance with the emergence of the M184V substitution.

Clinical Studies of Treatment-Experienced Patients: In contrast, from studies of treatment-experienced patients treated with ATV or ATV/RTV, most ATV-resistant isolates from patients who experienced virologic failure developed mutations that were associated with resistance to multiple PIs and displayed decreased susceptibility to multiple PIs. The most common protease mutations 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 mutations 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 mutations were present in the HIV-1 of the patient at baseline, ATV resistance developed through mutations associated with resistance to other PIs and could include the development of the I50L mutation. The I50L mutation has been detected in treatment-experienced patients experiencing virologic failure after long-term treatment. Protease cleavage site changes also emerged on ATV treatment but their presence did not correlate with the level of ATV resistance.

Cross-Resistance

An association between virologic response at 48 weeks and the number and type of primary PI-resistance-associated mutations detected in baseline HIV-1 isolates from antiretroviral-experienced patients receiving ATV/RTV once daily or lopinavir (LPV)/RTV twice daily in Study AI424-045 is shown in Table 15.

Overall, both the number and type of baseline PI mutations affected response rates in treatment-experienced patients. In the ATV/RTV group, patients had lower response rates when 3 or more baseline PI mutations including a mutation at position 36, 71, 77, 82, or 90 were present compared to patients with 1-2 PI mutations including one of these mutations.

Table 15: HIV RNA Response by Number and Type of Baseline PI Mutation, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

	Virologic Response = HIV RNA <400 copies/mL[b]	
Number and Type of Baseline PI Mutations[a]	**ATV/RTV (n=110)**	**LPV/RTV (n=113)**
3 or more primary PI mutations 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)

Table 15: HIV RNA Response by Number and Type of Baseline PI Mutation, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

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 mutations[a]		
All patients, as-treated	58% (64/110)	59% (67/113)
0–2 PI mutations	75% (50/67)	75% (50/67)
3–4 PI mutations	41% (14/34)	43% (12/28)
5 or more PI mutations	0% (0/9)	28% (5/18)

[a] Primary mutations 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<3) for PI mutations V32I, I47V, G48V, I50V, and F53L.

The response rates of antiretroviral-experienced patients in Study AI424-045 were analyzed by baseline phenotype (shift in in vitro susceptibility relative to reference, Table 16). The analyses are based on a select patient population with 62% of patients receiving an NNRTI-based regimen before study entry compared to 35% receiving a PI-based regimen. Additional data are needed to determine clinically relevant break points for atazanavir.

Table 16: Baseline Phenotype by Outcome, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

Baseline Phenotype[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 in *in vitro* susceptibility relative to the wild-type reference.

[b] Results should be interpreted with caution because the subgroups were small.

TOXICOLOGY

Acute Toxicity

Atazanavir: The single-dose oral toxicity of atazanavir was evaluated in mice and rats at doses of 200 to 1600 mg/kg. In mice, doses of 800 and 1600 mg/kg produced death; clinical signs including tremors, hypoactivity, ptosis, scant stool, and/or urogenital staining; and transient group mean body weight loss (males). Additional clinical signs observed at 1600 mg/kg included loss of righting reflex, recumbency, and labored respiration. Clinical signs were generally first noted on Day 2 and resolved within 2 to 3 days. Doses up to 400 mg/kg were well tolerated in mice with only transient scant stool observed at 400 mg/kg. The no-effect dose in mice was 200 mg/kg. In rats, no atazanavir-related effects were observed after administration of single oral doses up to 1600 mg/kg.

Short- and Long-Term Toxicity

Atazanavir: Repeat-dose oral toxicity studies were conducted in rats for 2 weeks to 6 months, and in dogs for 2 weeks to 9 months to evaluate the short- and long-term toxicity of atazanavir. Atazanavir-related findings were generally confined to the liver and included increases in serum total bilirubin in both species and liver enzymes in dogs, and hepatocellular vacuolation and hypertrophy in rats. These liver changes were observed at systemic exposures (AUC) of atazanavir that were 0.4 to 4 times in rats and 0.2 to 20 times in dogs the exposure in humans given atazanavir at 400 mg once daily. Similar liver changes were also observed in a 3-month oral toxicity study in mice at exposures 0.4 to 12 times the exposure in humans given 400 mg once daily. Additionally in mice, cytotoxic liver changes were observed in males (increased transaminases) and females (increased transaminases and single-cell necrosis) at exposures equivalent to and 12 times, respectively, that observed in humans given 400 mg once daily, whereas no effects were observed at exposures of 0.4 and 4 times, respectively, human exposure. Serum cholesterol and glucose were minimally to mildly increased in rats but not in mice. Similar increases were observed in an initial 2-week oral toxicity study performed in dogs. Subsequent 2-week and 9-month oral toxicity studies in dogs showed no drug-related changes in serum cholesterol and glucose.

Cardiotoxicity

Atazanavir: Atazanavir minimally increased the duration of the rabbit Purkinje fiber action potential, weakly inhibited sodium and potassium IKr (HERG-encoded) and IKs currents (IC_{50} > 30 μM), and moderately inhibited calcium current (IC_{50} = 10.4 μM) *in vitro*. Electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prolongation of QT interval, and prolongation of QRS complex) were observed only in an initial 2-week oral toxicity study performed in dogs and were considered secondary to the marked clinical toxicity and not a direct drug effect. Subsequent 2-week and 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes.

Cobicistat: Ex vivo rabbit studies and *in vivo* dog studies suggest that cobicistat has a low potential for QT prolongation, and may slightly prolong the PR interval and decrease left

ventricular function at mean concentrations at least 10-fold higher than the human exposure at the recommended 150 mg daily dose (see ACTION AND CLINICAL PHARMACOLOGY: Effects on Electrocardiogram).

Reproduction and Teratology

Atazanavir: In a fertility and early embryonic development study in rats, atazanavir altered oestrus cycling with no effects on mating or fertility. No teratogenic effects were observed in rats or rabbits at maternally toxic doses. In the pre- and postnatal development assessment in rats, atazanavir produced a transient reduction in body weight in the offspring at a maternally toxic dose. Systemic exposure to atazanavir at doses that resulted in maternal toxicity was at least equal to or slightly greater than that observed in humans given 400 mg once daily.

Cobicistat: Reproductive studies were conducted in rats and rabbits. Animal studies do not indicate direct or indirect harmful effects of cobicistat with respect to pregnancy, fetal development, parturition or postnatal development. There were no effects on mating and fertility parameters.

Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with cobicistat during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-fetal NOAELs in rats and rabbits were respectively 1.4 and 3.3 times higher than the exposure in humans at the recommended daily dose of 150 mg.

Cobicistat did not affect fertility in male or female rats at daily exposures (AUC) approximately 3.3-fold higher than human exposures at the recommended 150 mg daily dose.

Fertility was normal in the offspring of rats exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) approximately 0.9-fold human exposures at the recommended 150 mg daily dose.

Carcinogenicity and Mutagenicity

Atazanavir: Carcinogenicity studies with atazanavir were conducted in mice and rats. Mice were administered doses of 20, 40, and 80 mg/kg/day in males and 40, 120, and 360 mg/kg/day in females. In female mice, there was an increase in the incidence of benign hepatocellular adenomas at the highest dose. The exposure in female mice at the high dose is approximately seven times exposure in humans given atazanavir 400 mg once daily. No increase in the incidence of tumors was observed in female mice at lower doses or male mice at any dose. Exposures in male and female mice at nontumorigenic doses are approximately four times human exposure at 400 mg/day. In rats administered doses of 100, 350, and 1200 mg/kg/day, there was no increased incidence of any tumor type. Exposures in rats at the high dose are approximately two (males) and six (females) times exposure in humans given atazanavir 400 mg once daily. The clinical significance of benign hepatocellular adenomas in high-dose female mice is unknown as these benign tumors occurred in mice only at exposures (approximately seven times human exposure at 400 mg/day) causing significant liver damage. 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).

Cobicistat: In a long-term carcinogenicity study in mice, no drug-related increases in tumor incidence were observed at doses up to 50 and 100 mg/kg/day (males and females, respectively). Cobicistat exposures at these doses were approximately 7 (male) and 16 (females) times, respectively, the human systemic exposure at the therapeutic daily dose. In a long-term carcinogenicity study of cobicistat in rats, an increased incidence of follicular cell adenomas and/or carcinomas in the thyroid gland was observed at doses of 25 and 50 mg/kg/day in males, and at 30 mg/kg/day in females. The follicular cell findings are considered to be ratspecific, secondary to hepatic microsomal enzyme induction and thyroid hormone imbalance, and are not relevant for humans. At the highest doses tested in the rat carcinogenicity study, systemic exposures were approximately 2 times the human systemic exposure at the therapeutic daily dose.

Cobicistat was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

REFERENCES

1. Gallant J, Koenig E, Andrade-Villanueva J, Chetchotisakd P, DeJesus E, Antunes F, et al. Cobicistat Versus Ritonavir as a Pharmacoenhancer of Atazanavir Plus Emtricitabine/Tenofovir DF in Treatment-Naïve HIV Type 1-Infected Patients: Week 48 Results. Journal of Infectious Diseases Advance Access published April 19, 2013, DOI: 10.1093/infid/jit122.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

^{Pr}EVOTAZ™
atazanavir and cobicistat tablets
(as atazanavir sulfate)

Read this carefully before you start taking **EVOTAZ** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **EVOTAZ**.

What is EVOTAZ used for?

EVOTAZ is a drug, used in combination with other antiviral drugs to treat HIV-1 infection in adults.

How does EVOTAZ work?

EVOTAZ contains two active substances:

- atazanavir, is a type of anti-HIV drug called a protease inhibitor. It blocks HIV protease, an enzyme needed for HIV to multiply.
- cobicistat, boosts the amount of atazanavir in the blood.

What are the ingredients in EVOTAZ?

Medicinal ingredients: **Atazanavir sulfate, cobicistat**

Non-medicinal ingredients: Croscarmellose sodium, crospovidone, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, red iron oxide, silicon dioxide, sodium starch glycolate, stearic acid, talc, titanium dioxide, and triacetin.

EVOTAZ comes in the following dosage forms:

EVOTAZ is supplied as tablets containing atazanavir 300 mg (as atazanavir sulfate) and cobicistat 150 mg.

Do not use EVOTAZ if you:

- are allergic to EVOTAZ or to any of the other ingredients of EVOTAZ. The active ingredients are atazanavir sulfate and cobicistat. (See "What are the ingredients in EVOTAZ?").
- have liver disease.
- take any of these medicines:

Type of Drug	Examples of Generic Names (Brand Names)
Alpha 1-Adrenoreceptor Antagonist (to treat enlarged prostate)	alfuzosin (Xatral*)
Antiarrhythmics (to treat abnormal heart rhythms)	quinidine (Biquin*)
Anticonvulsants (to treat epilepsy and prevent seizures)	carbamazepine (Tegretol*), phenytoin (Dilantin*), or phenobarbital
Antimycobacterials (to treat tuberculosis)	rifampin (Rifadin*, Rifater*, or Rofact*)
Antineoplastics (to treat cancer)	irinotecan (Camptosar*)
Beta 2- adrenoceptor Agonist (to treat asthma and/or chronic obstructive pulmonary disease)	salmeterol (Advair*)
Benzodiazepines (to treat trouble with sleeping and/or anxiety)	triazolam
Ergot Derivatives (to treat migraine and headaches)	dihydroergotamine (Migranal NS*)
Hepatitis C Direct-Acting Antivirals (to treat Hepatitis C Virus)	elbasvir / grazoprevir (ZEPATIER)
Herbal Products (to improve mood)	St. John's Wort
HMG-CoA Reductase Inhibitors also known as statins (to lower cholesterol)	lovastatin (Mevacor*), simvastatin (Zocor*)
Neuroleptic (to treat psychiatric conditions)	pimozide (Orap*)
PDE5 Inhibitor (to treat pulmonary arterial hypertension)	sildenafil (Revatio*)
Protease Inhibitors (used to HIV infection)	indinavir (Crixivan*) ritonavir (Norvir*)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take EVOTAZ. Talk about any health conditions or problems you may have, including:

- If you are pregnant or planning to become pregnant, or breast feeding.
- If you have a heart problem.
- If you have liver disease, kidney problems, hemophilia, diabetes.
- EVOTAZ should not be used in combination with quetiapine. Serious and/or life-threatening reactions, including severe sedation and coma, have been reported for use of HIV protease inhibitors together with quetiapine. If co-administration is necessary, your doctor may need to monitor and adjust the dose of quetiapine.

Talk to your doctor right away if the following occurs while taking EVOTAZ, as these have occurred with protease inhibitors such as EVOTAZ:

- You have changes in your heartbeat (irregular, fast, slow).
- You start bleeding (nose, gums, bruising in skin, dark urine).
- You have symptoms of kidney stones such as a pain in your side, blood in urine, pain when you urinate.
- Your diabetes worsens or blood sugar increases with symptoms such as increased thirst,

urination, fatigue, weakness, weight loss or gain.

- You suffer lactic acidosis (build up of acid in the blood). The symptoms that may be signs of lactic acidosis include: feeling very weak, tired or uncomfortable; unusual or unexpected stomach discomfort; feeling cold; feeling dizzy or lightheaded; suddenly developing a slow or irregular heartbeat. This rare but serious side effect has occasionally been fatal.
- You become pregnant.

Other warnings you should know about:

You may see changes in your body fat. You may have greater amounts of fat in your neck, back, breast and around your stomach. You may lose fat from your arms, legs and face. The long-term effects of these changes are unknown.

See section on SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM, for more information.

Can I take EVOTAZ during pregnancy and breast-feeding?

- Pregnancy: It is not known if EVOTAZ can harm your unborn baby. You and your doctor will need to decide if EVOTAZ is right for you. If you use EVOTAZ while you are pregnant, talk to your healthcare provider about the Antiretroviral Pregnancy Registry.
- Breast-feeding: You should not breast-feed if you have HIV because of the chance of passing HIV to your baby. Talk with your doctor about the best way to feed your baby.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

No drug interactions studies have been done for EVOTAZ. **The following may interact with EVOTAZ:**

EVOTAZ may interact with other drugs, including those you take without a prescription. You must tell your doctor or pharmacist about all drugs, including prescription and non-prescription drugs, herbal products and supplements and street drugs, you are taking or planning to take before you take EVOTAZ. EVOTAZ should be taken in combination with other drugs to treat HIV. Do not use EVOTAZ in combination with products containing the same components (atazanavir or cobicistat), or with fixed-dose products that contain cobicistat.

EVOTAZ should not be taken with indinavir (CRIXIVAN*) as both atazanavir and CRIXIVAN* sometimes cause increased levels of bilirubin in the blood (increased levels of bilirubin can cause yellowing of the skin and the white part of the eyes). Please see section "Do not use EVOTAZ if you:"

If you are taking didanosine (VIDEX*) buffered tablets or antacids, take EVOTAZ with a meal one hour after or more than two hours before you take these drugs. Taking them together causes less atazanavir in the blood making it less effective. Tell your doctor if you are taking any of the following drugs:

Type of Drug	Examples of Generic Names (Brand Names)
Antiarrhythmics (to treat abnormal heart rhythms)	lidocaine , quinidine (Biquin*), amiodarone (Cordarone*), flecainide, propefenone
Antibacterials (to treat bacterial infections)	clarithromycin (Biaxin*) erythromycin, telithromycin
Anticancer (to treat cancer)	dasatinib (Sprycel*), nilotinib (Tasigna*), vincristine
Anticoagulants (to prevent the clotting of red blood cells)	warfarin (Coumadin*)
Anticonvulsants (to treat epilepsy and prevent seizures)	lamotrigine (Lamictal*)
Antidepressants (to treat depression, anxiety, or panic disorder)	trazodone (Oleptro*), paroxetine (Paxil*), amitriptyline (Elavil*), desipramine, imipramine (Tofranil*)
Antifungals (to treat fungal infections)	voriconazole (Vfend*), ketoconazole (Nizoral*) and itraconazole (Sporanox*)
Antigout (to treat gout and familial Mediterranean fever)	colchicine
Antimycobacterials (to treat bacterial infections)	rifabutin (Mycobutin*)
Antipsychotics (used to treat schizophrenia and bipolar disorder)	quetiapine (Seroquel*)
Beta-Blockers (to treat heart disease)	timolol, metoprolol (Betaloc*)
Calcium Channel Blockers (to treat heart disease)	diltiazem (Cardizem*, Tiazac*), felodipine (Plendil*), verapamil (Covera-HS* or Isoptin SR*)
Corticosteroids (to treat inflammation or asthma)	fluticasone propionate (Flonase* or Flovent*), dexamethasone
Endothelin receptor antagonists (to treat pulmonary arterial hypertension)	bosentan (Tracleer*)
H2-Receptor antagonists	famotidine (Pepcid AC*)
HCV Antiviral Agents (to treat Hepatitis C Virus [HCV])	elbasvir / grazoprevir (ZEPATIER*)
HIV antivirals	delaviridine, etravirine, tenofovir DF, nevirapine, and efavirenz
HMG-CoA Reductase Inhibitors (to lower cholesterol levels)	atorvastatin (Lipitor*), rosuvastatin (Crestor*)
Hormonal contraceptives	progestin, estrogen
Immunosuppressants (to prevent organ transplant rejection)	cyclosporine (Sandimmune*, Neoral*), tacrolimus (Prograf*) and sirolimus (Rapamune*)
Inhaled Beta-Agonists (to treat asthma and/or chronic obstructive pulmonary disease)	salmeterol (Servent Diskus*), salmeterol with fluticasone (Advair*)
Opiods (to treat opioid dependence)	buprenorphine, fentanyl, tramadol
PDE5 Inhibitors (to treat erectile dysfunction)	sildenafil (Viagra*), or tadalafil (Cialis*)
PDE5 Inhibitors (to treat pulmonary arterial hypertension)	tadalafil (Cialis*)
Proton-pump inhibitors (to prevent or treat stomach ulcers, heartburn or acid reflux disease)	omeprazole (Losec*)

Type of Drug	Examples of Generic Names (Brand Names)
Sedatives/ hypnotics (to treat trouble with sleeping and/or anxiety)	midazolam (taken by injection), diazepam, flurazepam, zolpidem

How to take EVOTAZ:

The recommended adult dosage of EVOTAZ is one tablet once a day (1 tablet containing 300 mg atazanavir and 150 mg cobicistat).

- Always take EVOTAZ tablets with food (a meal or snack). Swallow the tablets whole. Do not break, cut, or crush the tablets. Take EVOTAZ at the same time each day.
- Do not change your dose or stop taking EVOTAZ without first talking with your healthcare provider. It is important to stay under a healthcare provider's care while taking EVOTAZ.
- Always keep EVOTAZ on hand so you don't run out. When you travel or need to stay in the hospital, make sure you will have enough EVOTAZ to last until you can get a new supply.

Overdose:

If you think you have taken too much EVOTAZ, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of EVOTAZ by 12 hours or less, take it right away and then take your next scheduled dose at the usual time. If you miss a dose and it is more than 12 hours from the time you should have taken EVOTAZ, do not take the missed dose. Wait and take the next dose at the usual time. Do not double the next dose. It is important that you do not miss any doses of EVOTAZ or your other anti-HIV drugs.

What are possible side effects from using EVOTAZ?

The following is not a complete list of side effects reported with EVOTAZ. If you experience any side effects not listed here, contact your doctor. Your doctor can discuss with you a more complete list of side effects.

- If you have liver disease including hepatitis B or C, your liver disease may get worse when you take anti-HIV drugs like EVOTAZ.
- Changes in your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time, or you could develop an autoimmune disease in which your immune system reacts against your own body (e.g. Graves' disease (which affects the thyroid gland), Guillain-Barre syndrome (which affects the nervous system) or polymyositis (which affects the muscles) and it may develop at any time, sometimes months later after the start of HIV therapy). Sometimes symptoms can

be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling, or fatigue or any new symptoms contact your doctor straight away.

Tell your doctor right away about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Rash (redness & itching)	✔		
Hyperbilirubinemia (high levels of bilirubin in the blood) with symptom such as yellowing of the skin or eyes		✔	
UNCOMMON			
Frequent nausea, vomiting & stomach pain (occurs more often in women, particularly if very overweight)		✔	
Kidney stones and symptoms such as a pain in the side, blood in the urine, and painful urination		✔	
Worsening diabetes or high blood sugar levels with symptoms such as unusual thirst, frequent urination, fatigue, weight gain or loss, or blurred vision		✔	
Gall bladder problems with symptoms such as abdominal pain, yellowing of the skin, nausea, vomiting, fever, and chills		✔	
Heart rhythm changes with symptoms such as fast or slow heartbeat, irregular heartbeat		✔	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html. for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store EVOTAZ Tablets at 25°C, with excursions permitted to 15°C - 30°C.

Keep out of reach and sight of children.

If you want more information about EVOTAZ:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website http://www.bmscanada.ca, or by calling 1-866-463-6267.

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