HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EVOTAZ safely and effectively. See full prescribing information for EVOTAZ.

EVOTAZ™ (atazanavir and cobicistat) tablet, for oral use
Initial U.S. Approval: 2015

----------RECENT MAJOR CHANGES----------
Contraindications (4) 7/2016

----------INDICATIONS AND USAGE----------
EVOTAZ is a combination human immunodeficiency virus (HIV-1) protease inhibitor and CYP3A inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dosage in adults: One tablet once daily, taken orally with food. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 300 mg of atazanavir and 150 mg of cobicistat. (3, 16)

----------CONTRAINDICATIONS----------
- EVOTAZ is contraindicated in patients with previously demonstrated hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product. (4)
- Coadministration with certain drugs for which altered plasma concentrations are associated with serious and/or life-threatening events or loss of therapeutic effect. (4)

----------WARNINGS AND PRECAUTIONS----------
- *Cardiac conduction abnormalities:* PR interval prolongation may occur in some patients. Consider ECG monitoring in patients with preexisting conduction system disease or when administered with other drugs that may prolong the PR interval. (5.1, 6.2, 7.3, 12.2, 17)
- *Severe Skin Reactions:* Discontinue if severe rash develops. (5.2, 6.2, 17)
- Assess creatinine clearance (CLcr) before initiating treatment. Consider alternative medications that do not require dosage adjustments in patients with renal impairment. (5.3)
- When cobicistat, a component of EVOTAZ, is used in combination with a tenofovir disoproxil fumarate (tenofovir DF)-containing regimen, cases of acute renal failure and Fanconi syndrome have been reported. (5.4)
- When used with tenofovir DF, assess urine glucose and urine protein at baseline and monitor CLcr, urine glucose, and urine protein. Monitor serum phosphorus in patients with or at risk for renal impairment. Coadministration with tenofovir DF is not recommended in patients with CLcr below 70 mL/min or in patients also receiving a nephrotoxic agent. (5.4)
- *Nephrolithiasis and cholelithiasis* have been reported. Consider temporary interruption or discontinuation. (5.5, 6.2)
- *Hepatotoxicity:* Patients with hepatitis B or C coinfection are at risk of increased transaminases or hepatic decompensation. Monitor hepatic laboratory tests prior to therapy and during treatment. (2.4, 5.6, 8.7)
- The concomitant use of EVOTAZ and certain other medications may result in known or potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.7, 7.3)
- *Antiretrovirals that are not recommended:* EVOTAZ is not recommended for use with atazanavir or cobicistat, with ritonavir or products containing ritonavir, or in combination with other antiretroviral drugs that require CYP3A inhibition to achieve adequate exposures (e.g., other protease inhibitors and elvitegravir). (5.8)
- *Hyperbilirubinemia:* Most patients experience asymptomatic increases in indirect bilirubin, which is reversible upon discontinuation. If a concomitant transaminase increase occurs, evaluate for alternative etiologies. (5.9, 6.1)
- Patients receiving EVOTAZ may develop immune reconstitution syndrome (5.10), new onset or exacerbations of diabetes mellitus/hyperglycemia (5.11, 6.2), and redistribution/accumulation of body fat (5.12).
- *Hemophilia:* Spontaneous bleeding may occur and additional factor VIII may be required. (5.13)

----------ADVERSE REACTIONS----------
Most common adverse reactions seen with atazanavir coadministered with cobicistat (greater than 2%, Grades 2-4) are jaundice, ocular icterus, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
Coadministration of EVOTAZ can alter the concentration of other drugs and other drugs may alter the concentration of EVOTAZ. The potential drug-drug interactions must be considered prior to and during therapy. (4, 7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy:* Use only if the potential benefit justifies the potential risk. (8.1)
- *Nursing mothers* should be instructed not to breastfeed due to the potential for postnatal HIV transmission. (8.3)
- *Renal impairment:* EVOTAZ is not recommended for use in treatment-experienced patients with end-stage renal disease managed with hemodialysis. (2.3, 8.6)
- *Hepatic impairment:* EVOTAZ is not recommended in patients with hepatic impairment. (2.4, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 7/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Limitation of Use:

- Use of EVOTAZ in treatment-experienced patients should be guided by the number of baseline primary protease inhibitor resistance substitutions *[see Microbiology (12.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

EVOTAZ is a fixed-dose combination product containing 300 mg of atazanavir and 150 mg of cobicistat. In treatment-naive and -experienced adults, the recommended dosage of EVOTAZ is one tablet taken once daily orally with food. Administer EVOTAZ in conjunction with other antiretroviral agents *[see Drug Interactions (7)]*.

When coadministered with H_2-receptor antagonists or proton-pump inhibitors, dose separation may be required *[see Drug Interactions (7)]*.

2.2 Laboratory Testing Prior to Initiation of EVOTAZ

Prior to starting EVOTAZ, assess estimated creatinine clearance because cobicistat decreases estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function *[see Warnings and Precautions (5.3)]*. When coadministering EVOTAZ with tenofovir disoproxil fumarate (tenofovir DF) assess estimated creatinine clearance, urine glucose, and urine protein at baseline *[see Warnings and Precautions 5.4]*.

2.3 Dosage in Patients with Renal Impairment

EVOTAZ is not recommended in HIV-1 treatment-experienced patients with end-stage renal disease managed with hemodialysis *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

EVOTAZ coadministered with tenofovir DF is not recommended in patients who have an estimated creatinine clearance below 70 mL/min *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)]*.

2.4 Dosage in Patients with Hepatic Impairment

EVOTAZ is not recommended in patients with hepatic impairment. *[See Warnings and Precautions (5.6), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3).]*

3 DOSAGE FORMS AND STRENGTHS

EVOTAZ Tablets contain 342 mg atazanavir sulfate, equivalent to 300 mg of atazanavir, and 150 mg of cobicistat and are oval, biconvex, pink, film-coated, and debossed with "3641" on one side and plain on the other side.

4 CONTRAINDICATIONS

EVOTAZ is contraindicated:

- in patients with previously demonstrated clinically significant hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product *[see Warnings and Precautions (5.2)]*.
- when coadministered with drugs that are highly dependent on CYP3A or UGT1A1 for clearance, and for which elevated plasma concentrations of the interacting drugs are associated with serious and/or life-threatening events (see Table 1).
- when coadministered with drugs that strongly induce CYP3A and may lead to lower exposure and loss of efficacy of EVOTAZ (see Table 1).

Table 1 displays drugs that are contraindicated with EVOTAZ.

Table 1: Drugs that are Contraindicated with EVOTAZ

Drug Class	Drugs within class that are contraindicated with EVOTAZ	Clinical Comment
Alpha 1-Adrenoreceptor Antagonist	Alfuzosin	Potential for increased alfuzosin concentrations, which can result in hypotension.
Antianginal	Ranolazine	Potential for serious and/or life-threatening reactions.
Antiarrhythmics	Dronedarone	Potential for increased dronedarone concentrations.
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	Potential for decreased atazanavir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.
Antigout	Colchicine	Contraindicated in patients with renal and/or hepatic impairment due to the potential for serious and/or life-threatening reactions.

Table 1: Drugs that are Contraindicated with EVOTAZ

Drug Class	Drugs within class that are contraindicated with EVOTAZ	Clinical Comment
Antimycobacterials	Rifampin	Rifampin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect and development of resistance.
Antineoplastics	Irinotecan	Atazanavir inhibits UGT1A1 and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.
Antipsychotic	Lurasidone	Potential for serious and/or life-threatening reactions.
Benzodiazepines	Triazolam, orally administered midazolam[a]	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with atazanavir may cause large increases in the concentration of these benzodiazepines. Potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
Ergot Derivatives	Dihydroergotamine, ergotamine, methylergonovine	Potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	Cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products	St. John's wort (*Hypericum perforatum*)	Coadministration of products containing St. John's wort and EVOTAZ may result in loss of therapeutic effect and development of resistance.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for serious reactions such as myopathy including rhabdomyolysis.
Neuroleptic	Pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Non-nucleoside Reverse Transcriptase Inhibitors	Nevirapine	Nevirapine substantially decreases atazanavir exposure which may result in loss of therapeutic effect and development of resistance. Potential risk for nevirapine-associated adverse reactions due to increased nevirapine exposures.
Phosphodiesterase-5 (PDE-5) Inhibitors	Sildenafil[b] when administered for the treatment of pulmonary arterial hypertension	Potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, priapism, and syncope).
Protease Inhibitors	Indinavir	Both atazanavir and indinavir are associated with indirect (unconjugated) hyperbilirubinemia.

[a] See *Drug Interactions, Table 5 (7)* for parenterally administered midazolam.

[b] See *Drug Interactions, Table 5 (7)* for sildenafil when administered for erectile dysfunction.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiac Conduction Abnormalities

Atazanavir prolongs the PR interval of the electrocardiogram in some patients. In healthy volunteers and in patients, abnormalities in atrioventricular (AV) conduction were asymptomatic and generally limited to first-degree AV block. There have been reports of second-degree AV block and other conduction abnormalities *[see Adverse Reactions (6.2) and Overdosage (10)]*. In clinical trials of atazanavir that included electrocardiograms, asymptomatic first-degree AV block was observed in 6% of atazanavir-treated patients (n=920) and 5% of patients (n=118) treated with atazanavir coadministered with ritonavir. Because of limited clinical experience in patients with preexisting conduction system disease (e.g., marked first-degree AV block or second- or third-degree AV block), consider ECG monitoring in these patients. *[See Clinical Pharmacology (12.2).]*

5.2 Severe Skin Reactions

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 (4) and Adverse Reactions (6.1).]* EVOTAZ should be discontinued if severe rash develops.

Mild-to-moderate maculopapular skin eruptions have also been reported in atazanavir clinical trials. These reactions had a median time to onset of 7.3 weeks and median duration of 1.4 weeks and generally did not result in treatment discontinuation.

5.3 Effects on Serum Creatinine

Cobicistat decreases 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.

Prior to initiating therapy with EVOTAZ, assess estimated creatinine clearance *[see Dosage and Administration (2.2)]*. Dosage recommendations are not available for drugs that require dosage adjustments in cobicistat-treated patients with renal impairment *[see Adverse Reactions (6.1), Drug Interactions (7.3), and Clinical Pharmacology (12.2)]*. Consider alternative medications that do not require dosage adjustments in patients with renal impairment.

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/dL from baseline should be closely monitored for renal safety.

5.4 New Onset or Worsening Renal Impairment When Used with Tenofovir DF

Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported when cobicistat was used in an antiretroviral regimen that contained tenofovir DF. Therefore, coadministration of EVOTAZ and tenofovir DF is not recommended in patients who have an estimated creatinine clearance below 70 mL/min *[see Dosage and Administration (2.3)]*.

- When EVOTAZ is used with tenofovir DF, document urine glucose and urine protein at baseline and perform routine monitoring of estimated creatinine clearance, urine glucose, and urine protein during treatment.
- Measure serum phosphorus in patients at risk for renal impairment.
- Coadministration of EVOTAZ and tenofovir DF in combination with concomitant or recent use of a nephrotoxic agent is not recommended.

In the clinical trials over 48 weeks (N=771), six (1.5%) subjects treated with atazanavir coadministered with cobicistat and tenofovir DF discontinued study drug due to a renal adverse event, five of which had laboratory findings consistent with proximal renal tubulopathy. None of the five subjects had renal impairment at baseline (e.g., estimated creatinine clearance less than 70 mL/min). The laboratory findings in these five subjects with evidence of proximal tubulopathy improved but did not completely resolve in all subjects upon discontinuation of cobicistat coadministered with atazanavir and tenofovir DF. Renal replacement therapy was not required in any subject.

5.5 Nephrolithiasis and Cholelithiasis

Cases of nephrolithiasis and/or cholelithiasis have been reported during postmarketing surveillance in HIV-infected patients receiving atazanavir therapy. Some patients required hospitalization for additional management and some had complications. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made. If signs or symptoms of nephrolithiasis and/or cholelithiasis occur, temporary interruption or discontinuation of therapy may be considered. *[See Adverse Reactions (6.1, 6.2).]*

5.6 Hepatotoxicity

Patients with underlying hepatitis B or C viral infections or marked elevations in transaminases may be at increased risk for developing further transaminase elevations or hepatic decompensation. In these patients, hepatic laboratory testing should be conducted prior to initiating therapy with EVOTAZ and during treatment. *[See Dosage and Administration (2.4) and Use in Specific Populations (8.7).]*

5.7 Risk of Serious Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

Initiation of EVOTAZ, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving EVOTAZ, may increase plasma concentrations of medications metabolized by CYP3A.

Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of EVOTAZ, respectively. These interactions may lead to:

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

See Table 5 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions (7)]*. Consider the potential for drug interactions prior to and during EVOTAZ therapy; review concomitant medications during EVOTAZ therapy; and monitor for the adverse reactions associated with the concomitant medications *[see Contraindications (4) and Drug Interactions (7)]*.

When used with concomitant medications, EVOTAZ may result in different drug interactions than those observed or expected with atazanavir coadministered with ritonavir. Complex or unknown mechanisms of drug interactions preclude extrapolation of drug interactions with atazanavir coadministered with ritonavir to certain EVOTAZ interactions *[see Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

5.8 Antiretrovirals that are Not Recommended

EVOTAZ is not recommended in combination with other antiretroviral drugs that require CYP3A inhibition to achieve adequate exposures (e.g., other HIV protease inhibitors or elvitegravir) because dosing recommendations for such combinations have not been established

and coadministration may result in decreased plasma concentrations of the antiretroviral agents, leading to loss of therapeutic effect and development of resistance.

EVOTAZ is not recommended in combination with products containing the individual components of EVOTAZ (atazanavir or cobicistat).

EVOTAZ is not recommended in combination with ritonavir or products containing ritonavir due to similar effects of cobicistat and ritonavir on CYP3A.

See *Drug Interactions (7)* for additional recommendations on use with other antiretroviral agents.

5.9 Hyperbilirubinemia

Most patients taking atazanavir experience asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyltransferase (UGT). This hyperbilirubinemia is reversible upon discontinuation of atazanavir. Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies. No long-term safety data are available for patients experiencing persistent elevations in total bilirubin greater than 5 times the upper limit of normal (ULN). Alternative antiretroviral therapy to EVOTAZ may be considered if jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for patients. *[See Adverse Reactions (6.2).]*

5.10 Immune Reconstitution Syndrome

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

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

5.11 Diabetes Mellitus/Hyperglycemia

New-onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin

or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

5.12 Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.13 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.

6 ADVERSE REACTIONS

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

- cardiac conduction abnormalities *[see Warnings and Precautions (5.1)]*
- rash *[see Warnings and Precautions (5.2)]*
- effects on serum creatinine *[see Warnings and Precautions (5.3)]*
- new onset or worsening renal impairment when used with tenofovir DF *[see Warnings and Precautions (5.4)]*
- nephrolithiasis and cholelithiasis *[see Warnings and Precautions (5.5)]*
- hepatotoxicity *[see Warnings and Precautions (5.6)]*
- hyperbilirubinemia *[see Warnings and Precautions (5.9)]*

For additional safety information about atazanavir and cobicistat consult the full prescribing information for these individual products.

6.1 Clinical Trial Experience in Adults

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

The safety of atazanavir and cobicistat coadministered as single agents has been established from a Phase 2 trial, Study 105, and a Phase 3 trial, Study 114. In the pooled analysis, 771 HIV-1 infected, antiretroviral treatment-naive adults received for at least 48 weeks:

- atazanavir coadministered with cobicistat and emtricitabine/tenofovir DF (N=394) or
- atazanavir coadministered with ritonavir and emtricitabine/tenofovir DF (N=377).

The most common adverse reactions (all Grades) and reported in >10% of subjects in the atazanavir coadministered with cobicistat group were jaundice (13%), ocular icterus (15%), and nausea (12%); the most common adverse reactions in the atazanavir coadministered with ritonavir group were jaundice (11%), ocular icterus (17%), nausea (11%), and diarrhea (11%).

The proportion of subjects who discontinued study treatment due to adverse events, regardless of severity, was 7% in both the atazanavir coadministered with cobicistat and atazanavir coadministered with ritonavir groups. Table 2 lists the frequency of adverse reactions (Grades 2-4) occurring in at least 2% of subjects in the atazanavir coadministered with cobicistat group in pooled Studies 105 and 114.

Table 2: Selected Adverse Reactions[a] (Grades 2-4) Reported in ≥2% of HIV-1 Infected Treatment-Naive Adults in the Atazanavir Coadministered with Cobicistat Group in Studies 105 and 114 (Week 48 pooled analysis)

	Atazanavir coadministered with cobicistat and emtricitabine/tenofovir DF (n=394)	Atazanavir coadministered with ritonavir and emtricitabine/tenofovir DF (n=377)
Jaundice	5%	3%
Rash[b]	5%	4%
Ocular icterus	3%	1%
Nausea	2%	2%

[a] Frequencies of adverse reactions are based on Grades 2-4 adverse events attributed to study drugs.

[b] Rash events include dermatitis allergic, drug hypersensitivity, pruritus generalized, eosinophilic pustular folliculitis, rash, rash generalized, rash macular, rash maculopapular, rash morbilliform, rash papular, and urticaria.

Nephrolithiasis: Nephrolithiasis has previously been identified in patients receiving atazanavir *[see Warnings and Precautions (5.5)]*. In the pooled analysis of Studies 105 and 114 through 48 weeks, 8 subjects (2%) receiving atazanavir coadministered with cobicistat developed nephrolithiasis compared with no subjects in the atazanavir coadministered with ritonavir group. Median time to onset of nephrolithiasis in the atazanavir coadministered with cobicistat group was 24 weeks. Causality in these cases could not be determined with certainty, but the majority of renal stone events were not serious and no subject discontinued study drug.

Less Common Adverse Reactions

Selected adverse reactions of at least moderate severity (≥ Grade 2) occurring in less than 2% of subjects receiving atazanavir coadministered with cobicistat and emtricitabine/tenofovir DF are listed below. These events have been included because of investigator's assessment of potential causal relationship and were considered serious or have been reported in more than one subject treated with atazanavir coadministered with cobicistat, and reported with greater frequency compared with the atazanavir coadministered with ritonavir group.

Gastrointestinal Disorders: diarrhea, vomiting, upper abdominal pain

General Disorders and Administration Site Conditions: fatigue

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis

Nervous System Disorders: headache

Psychiatric Disorders: depression, abnormal dreams, insomnia

Renal and Urinary Disorders: nephropathy, Fanconi syndrome

Laboratory Abnormalities

The frequency of laboratory abnormalities (Grades 3-4) occurring in at least 2% of subjects in the atazanavir coadministered with cobicistat group in Studies 105 and 114 is presented in Table 3.

Table 3: Laboratory Abnormalities (Grades 3-4) Reported in ≥2% of HIV-1 Infected Treatment-Naive Adults in the Atazanavir Coadministered with Cobicistat Group in Studies 105 and 114 (Week 48 pooled analysis)

Laboratory Parameter Abnormality	48 weeks Atazanavir coadministered with cobicistat and emtricitabine/tenofovir DF (n=394)	48 weeks Atazanavir coadministered with ritonavir and emtricitabine/tenofovir DF (n=377)
Total Bilirubin (>2.5 × ULN)	65%	56%
Creatine Kinase (≥10.0 × ULN)	5%	6%
Serum Amylase[a] (>2.0 × ULN)	4%	2%
ALT (>5.0 × ULN)	3%	2%
AST (>5.0 × ULN)	3%	2%
GGT (>5.0 × ULN)	2%	1%
Urine Glucose (Glycosuria ≥1000 mg/dL)	3%	1%
Urine RBC (Hematuria) (>75 RBC/HPF)	3%	2%

[a] For subjects with serum amylase >1.5 × upper limit of normal, lipase test was also performed. The frequency of increased lipase (Grades 3-4) occurring in the atazanavir coadministered with cobicistat group (N=44) and atazanavir coadministered with ritonavir group (N=34) was 9% and 6%, respectively.

Increase in Serum Creatinine: Cobicistat, a component of EVOTAZ, has been shown to increase serum creatinine and decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.2)]*. In Studies 105 and 114, increases in serum creatinine and decreases in estimated creatinine clearance occurred early in treatment in the atazanavir coadministered with cobicistat group 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 coadministered with cobicistat group and −9.1 ± 14.7 mL/min in the atazanavir coadministered with ritonavir group.

Serum Lipids

Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides are presented in Table 4. In both groups, mean values for serum lipids remained within the normal range for each laboratory test. The clinical significance of these changes is unknown.

Table 4: Lipid Values, Mean Change from Baseline, Reported in HIV-1 Infected Treatment-Naive Adults Receiving Atazanavir Coadministered with Cobicistat and Emtricitabine/Tenofovir DF or Atazanavir Coadministered with Ritonavir and Emtricitabine/Tenofovir DF in Studies 105 and 114 (Week 48 pooled analysis)

	Atazanavir coadministered with cobicistat and emtricitabine/tenofovir DF		Atazanavir coadministered with ritonavir and 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=307]	+4 [N=307]	165 [N=299]	+8 [N=299]
HDL-cholesterol (fasted)	44 [N=306]	+3 [N=306]	43 [N=299]	+3 [N=299]
LDL-cholesterol (fasted)	102 [N=307]	+5 [N=307]	103 [N=300]	+7 [N=300]
Triglycerides (fasted)	128 [N=307]	+15 [N=307]	131 [N=299]	+29 [N=299]

[a] The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values and excludes subjects receiving an HMG-CoA reductase inhibitor drug.

6.2 Postmarketing Experience

See the full prescribing information for atazanavir for postmarketing information on atazanavir.

7 DRUG INTERACTIONS

See also *Contraindications (4), Warnings and Precautions (5.7), and Clinical Pharmacology (12.3)*.

7.1 Potential for EVOTAZ to Affect Other Drugs

Atazanavir is an inhibitor of CYP3A and UGT1A1 and a weak inhibitor of CYP2C8. Cobicistat is an inhibitor of CYP3A and CYP2D6. The transporters that cobicistat inhibits include P-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3.

Coadministration of EVOTAZ with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated *[see Contraindications (4)]*. Coadministration of EVOTAZ and drugs primarily metabolized by CYP3A, UGT1A1 and/or CYP2D6 or drugs that are substrates of P-gp,

BCRP, OATP1B1 and/or OATP1B3 may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic effects and adverse reactions which may require dose adjustments and/or additional monitoring as shown in Table 5. Use of EVOTAZ is not recommended when coadministered with drugs highly dependent on CYP2C8 for clearance with narrow therapeutic indices (e.g., paclitaxel, repaglinide). *[See Clinical Pharmacology, Table 7 (12.3).]*

7.2 Potential for Other Drugs to Affect EVOTAZ

Atazanavir and cobicistat are CYP3A4 substrates; therefore, drugs that induce CYP3A4 may decrease atazanavir and cobicistat plasma concentrations and reduce the therapeutic effect of EVOTAZ, leading to development of resistance to atazanavir (see Table 5). Cobicistat is also metabolized by CYP2D6 to a minor extent.

Coadministration of EVOTAZ with other drugs that inhibit CYP3A4 may increase the plasma concentrations of cobicistat and atazanavir (see Table 5).

Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir are expected if proton-pump inhibitors, antacids, buffered medications, or H_2-receptor antagonists are administered with EVOTAZ. *[See Dosage and Administration (2.1).]*

7.3 Established and Other Potentially Significant Drug Interactions

Drug interaction trials were not conducted for EVOTAZ. Drug interaction trials were conducted with cobicistat in combination with desipramine, digoxin, or efavirenz and with cobicistat coadministered with elvitegravir in combination with other drugs including rosuvastatin and rifabutin.

Table 5 provides dosing recommendations as a result of drug interactions with the components of EVOTAZ. These recommendations are based either on observed drug interactions in studies of cobicistat, atazanavir, or atazanavir coadministered with ritonavir or predicted drug interactions based on 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 May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
HIV Antiretroviral Agents: Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs and NtRTIs)		
didanosine buffered formulations enteric-coated (EC) capsules	↓ atazanavir ↓ didanosine	Coadministration of atazanavir with didanosine buffered tablets resulted in a marked decrease in atazanavir exposure (presumably due to the increase in gastric pH caused by buffers in the didanosine tablets). 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.
tenofovir disoproxil fumarate	↓ atazanavir ↑ tenofovir	Patients receiving EVOTAZ and tenofovir should be monitored for tenofovir-associated adverse reactions *[see Warnings and Precautions (5.4)]*.
HIV Antiretroviral Agents: Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) ***For contraindicated NNRTIs, see Contraindications (4).***		
efavirenz	↓ atazanavir ↓ cobicistat ↔ efavirenz	Coadministration of EVOTAZ with efavirenz is not recommended because it may result in a loss of therapeutic effect and development of resistance to atazanavir.
etravirine	↓ atazanavir ↓ cobicistat	Coadministration of EVOTAZ with etravirine is not recommended because it may result in the loss of therapeutic effect and development of resistance to atazanavir.
HIV Antiretroviral Agents: CCR5 Antagonist		
maraviroc	↑ maraviroc	When coadministering maraviroc and EVOTAZ, patients should receive maraviroc 150 mg twice daily.
HIV Antiretroviral Agents: Protease Inhibitors ***For contraindicated protease inhibitors, see Contraindications (4).***		
ritonavir or products containing ritonavir	↑ atazanavir	Coadministration of EVOTAZ and ritonavir or ritonavir-containing regimens is not recommended due to similar effects of cobicistat and ritonavir on CYP3A *[see Warnings and Precautions (5)]*.
HCV Antiviral Agents: Protease Inhibitors		
boceprevir telaprevir simeprevir	atazanavir: effects unknown boceprevir: effects unknown telaprevir: effects unknown ↑ simeprevir	No drug interaction data are available. Coadministration of EVOTAZ with boceprevir, telaprevir, or simeprevir is not recommended.
Other Agents		
Antacids (please also see H_2-receptor antagonists and proton-pump inhibitors below)	↓ atazanavir	With concomitant use, administer a minimum of 2 hours apart.

Table 5: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
Antiarrhythmics:		***For contraindicated antiarrhythmics, see Contraindications (4).***
amiodarone, quinidine lidocaine (systemic), disopyramide, flecainide mexiletine, propafenone	↑ antiarrhythmics	Clinical monitoring is recommended upon coadministration with antiarrhythmics.
digoxin	↑ digoxin	When coadministering EVOTAZ with digoxin, titrate the digoxin dose and monitor digoxin concentrations.
Antibacterials (macrolide or ketolide antibiotics):	↑ atazanavir ↑ cobicistat	Consider alternative antibiotics.
clarithromycin	↑ clarithromycin	
erythromycin	↑ erythromycin	
telithromycin	↑ telithromycin	
Anticancer Agents: (e.g., dasatinib, nilotinib, vinblastine, vincristine)	↑ anticancer agents	A decrease in the dosage or an adjustment of the dosing interval of dasatinib or nilotinib may be necessary upon coadministration with EVOTAZ. Consult the dasatinib and nilotinib full prescribing information for dosing instructions. For vincristine and vinblastine, monitor for hematologic or gastrointestinal side effects.
Anticoagulant:		
apixaban, rivaroxaban	↑ apixaban ↑ rivaroxaban	Concomitant use of apixaban or rivaroxaban and EVOTAZ is not recommended.
dabigatran etexilate	↑ dabigatran	Concomitant use of dabigatran etexilate and EVOTAZ is not recommended in specific renal impairment groups for certain indications. Refer to the dabigatran prescribing information for dosing recommendations for dabigatran etexilate when coadministered with P-gp inhibitors.
warfarin	warfarin: effect unknown	Monitor the International Normalized Ratio (INR) when coadministered with warfarin.
Anticonvulsants:		***For contraindicated anticonvulsants, see Contraindications (4).***
Anticonvulsants with CYP3A induction effects that are NOT contraindicated (e.g., eslicarbazepine, oxcarbazepine)	↓ atazanavir ↓ cobicistat	Consider alternative anticonvulsant or antiretroviral therapy to avoid potential changes in exposures. If coadministration is necessary, monitor for lack or loss of virologic response.
Anticonvulsants that are metabolized by CYP3A (e.g., clonazepam)	↑ clonazepam	Clinical monitoring of anticonvulsants is recommended with EVOTAZ coadministration.
Other anticonvulsants (e.g., lamotrigine)	lamotrigine: effects unknown	Monitoring of lamotrigine concentrations is recommended with EVOTAZ coadministration.

Table 5: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
Antidepressants:		
Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g., paroxetine)	SSRIs: effects unknown	When coadministering with SSRIs, TCAs, or trazodone, careful dose titration of the antidepressant to the desired effect, using the lowest feasible initial or maintenance dose, and monitoring for antidepressant response are recommended.
Tricyclic Antidepressants (TCAs) (e.g., amitriptyline, desipramine, imipramine, nortriptyline)	↑ TCAs	
Other Antidepressants (e.g., trazodone)	↑ trazodone	
Antifungals:		
ketoconazole, itraconazole	↑ atazanavir ↑ cobicistat ↑ ketoconazole ↑ itraconazole	Specific dosing recommendations are not available for coadministration of EVOTAZ with either itraconazole or ketoconazole.
voriconazole	effects unknown	Coadministration with voriconazole is not recommended unless the benefit/risk assessment justifies the use of voriconazole.
Antigout:		
colchicine	↑ colchicine	***The coadministration of EVOTAZ with colchicine in patients with renal or hepatic impairment is contraindicated [see Contraindications (4)].*** **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. Treatment course should be repeated no earlier than 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	atazanavir: effect unknown cobicistat: effect unknown ↑ rifabutin	***For contraindicated antimycobacterials, see Contraindications (4).*** A rifabutin dose reduction of up to 75% (e.g., 150 mg every other day or 3 times per week) is recommended. Increased monitoring for rifabutin-associated adverse reactions, including neutropenia and uveitis, is warranted.
Antipsychotics:		***For contraindicated antipsychotics, see Contraindications (4).***
quetiapine	↑ quetiapine	Initiation of EVOTAZ in patients taking quetiapine: Consider alternative antiretroviral therapy to avoid increases in quetiapine exposures. If coadministration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring. Initiation of quetiapine in patients taking EVOTAZ: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.

Table 5: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
Beta-Blockers: (e.g., metoprolol, carvedilol, timolol)	↔ atazanavir ↑ beta-blockers	Clinical monitoring is recommended when beta-blockers that are metabolized by CYP2D6 are coadministered with EVOTAZ.
Calcium channel blockers: (e.g., amlodipine, diltiazem, felodipine, nifedipine, and verapamil)	↑ calcium channel blocker	Clinical monitoring is recommended for coadministration with calcium channel blockers metabolized by CYP3A. ECG monitoring is recommended.
Corticosteroids (systemic): dexamethasone and other corticosteroids	↓ atazanavir ↓ cobicistat ↑ corticosteroids	Concomitant use 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.
Endothelin receptor antagonists: bosentan	↓ atazanavir ↓ cobicistat ↑ bosentan	***Initiation of bosentan in patients taking 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. ***Initiation of EVOTAZ in patients taking bosentan:*** Discontinue bosentan at least 36 hours before starting EVOTAZ. After at least 10 days following initiation of EVOTAZ, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability. ***Switching from atazanavir coadministered with ritonavir to EVOTAZ:*** Maintain bosentan dose.
H_2-Receptor antagonists (H_2RA): (e.g., famotidine)	↓ atazanavir	Coadministration of EVOTAZ with tenofovir DF and an H_2RA in treatment-experienced patients is not recommended. Administer EVOTAZ either at the same time or at a minimum of 10 hours after a dose of the H_2RA. The dose of the H_2RA should not exceed a dose comparable to famotidine 40 mg twice daily in treatment-naive patients or 20 mg twice daily in treatment-experienced patients.
HMG-CoA reductase inhibitors: atorvastatin, fluvastatin, pravastatin, rosuvastatin	↑ HMG-CoA reductase inhibitors	***For contraindicated HMG-CoA reductase inhibitors, see Contraindications (4).*** For HMG-CoA reductase inhibitors that are not contraindicated with EVOTAZ, start with the lowest recommended dose and titrate while monitoring for safety. Rosuvastatin dose should not exceed 10 mg/day.
Hormonal contraceptives: (e.g., progestin/estrogen)	progestin and estrogen: effects unknown	No data are available to make recommendations on the coadministration of EVOTAZ and oral or other hormonal contraceptives. Alternative nonhormonal forms of contraception should be considered.
Immunosuppressants: (e.g., cyclosporine, everolimus, sirolimus, tacrolimus)	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for these immunosuppressants when coadministered with EVOTAZ.

Table 5: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
Inhaled beta-agonist: salmeterol	↑ salmeterol	Coadministration with salmeterol is not recommended due to an increased risk of cardiovascular adverse reactions associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Inhaled/nasal steroids: budesonide, fluticasone and other inhaled or nasal steroids	↑ corticosteroids	Coadministration with inhaled or nasal corticosteroids that are metabolized by CYP3A is not recommended unless the potential benefit to the patient outweighs the risks. Consider alternative corticosteroids, particularly for long-term use.
Narcotic analgesics: For treatment of opioid dependence: buprenorphine, naloxone, methadone	buprenorphine or buprenorphine/ naloxone: effects unknown methadone: effects unknown	***Initiation of buprenorphine, buprenorphine/naloxone or methadone in patients taking EVOTAZ:*** Carefully titrate the dose of buprenorphine, buprenorphine/naloxone or methadone to the desired effect; use the lowest feasible initial or maintenance dose. ***Initiation of EVOTAZ in patients taking buprenorphine, buprenorphine/naloxone or methadone:*** A dose adjustment for buprenorphine, buprenorphine/naloxone or methadone may be needed. Monitor clinical signs and symptoms.
fentanyl	↑ fentanyl	When EVOTAZ is coadministered with fentanyl, careful monitoring of therapeutic and adverse effects of fentanyl (including potentially fatal respiratory depression) is recommended.
tramadol	↑ tramadol	When EVOTAZ is coadministered with tramadol, a decreased dose of tramadol may be needed.
Neuroleptics: (e.g., perphenazine, risperidone, thioridazine)	↑ neuroleptics	***For contraindicated neuroleptics, see Contraindications (4).*** A decrease in the dose of neuroleptics that are metabolized by CYP3A or CYP2D6 may be needed when coadministered with EVOTAZ.

Table 5: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
Phosphodiesterase-5 (PDE-5) inhibitors: avanafil, sildenafil, tadalafil, vardenafil	↑ PDE-5 inhibitors	***For contraindicated PDE-5 inhibitors, see Contraindications (4).*** Coadministration with avanafil is not recommended because a safe and effective avanafil dosage regimen has not been established. Coadministration with EVOTAZ may result in an increase in PDE-5 inhibitor-associated adverse reactions, including hypotension, syncope, visual disturbances, and priapism. **Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH):** Sildenafil when used for the treatment of pulmonary hypertension (PAH) is contraindicated with EVOTAZ *[see Contraindications (4)]*. Tadalafil: The following dose adjustments are recommended for the use of tadalafil with EVOTAZ: Initiation of tadalafil in patients taking EVOTAZ: o For patients receiving EVOTAZ for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability. Initiation of EVOTAZ in patients taking tadalafil: o Avoid the use of tadalafil when starting EVOTAZ. Stop tadalafil at least 24 hours before starting EVOTAZ. At least one week after starting EVOTAZ, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability. Patients switching from atazanavir coadministered with ritonavir to EVOTAZ: o Maintain tadalafil dose. **Use of PDE-5 inhibitors for erectile dysfunction:** Sildenafil: Reduced dosage to 25 mg every 48 hours with increased monitoring for adverse reactions. Tadalafil: Reduced dosage to 10 mg every 72 hours with increased monitoring for adverse reactions. Vardenafil: Reduced dosage to no more than 2.5 mg every 72 hours with increased monitoring for adverse reactions.
Proton-pump inhibitors (PPI): (e.g., omeprazole)	↓ atazanavir	In treatment-naive patients, administer EVOTAZ a minimum of 12 hours after administration of the PPI. The dose of the PPI should not exceed a dose comparable to omeprazole 20 mg daily. In treatment-experienced patients, coadministration of EVOTAZ with PPI is not recommended.
Sedatives/hypnotics: buspirone, diazepam, zolpidem, and parenterally administered midazolam	↑ sedatives/hypnotics	***For contraindicated sedatives/hypnotics, see Contraindications (4).*** **Parenterally administered midazolam:** Coadministration should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. ***Concomitant use with oral midazolam and triazolam is contraindicated [see Contraindications (4)].*** With other sedatives/hypnotics that are CYP3A metabolized, a dose reduction may be necessary and clinical monitoring is recommended.

[a] For magnitude of interactions see *Clinical Pharmacology, Table 7 (12.3)*.

7.4 Drugs with No Observed or Predicted Interactions with the Components of EVOTAZ

Based on known metabolic profiles, clinically significant drug interactions are not expected between EVOTAZ and acetaminophen, atenolol, dapsone, fluconazole, trimethoprim/sulfamethoxazole, or azithromycin. *[See Clinical Pharmacology, Table 7 (12.3).]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of EVOTAZ in pregnant women. Because animal reproduction studies are not always predictive of human response, EVOTAZ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Do not give EVOTAZ to treatment-experienced pregnant patients taking an H_2-receptor antagonist ***and/or*** tenofovir DF during the second or third trimester. See atazanavir prescribing information for clinical trial data on use of atazanavir coadministered with ritonavir in pregnancy.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to EVOTAZ, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263. See atazanavir prescribing information for antiretroviral pregnancy registry data on atazanavir-containing regimens.

Risk Summary

Atazanavir coadministered with ritonavir has been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate.

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

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

Animal Data

Atazanavir: In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals at systemic drug exposure levels (AUC) 0.7 (in rabbits) to 1.2 (in rats) times those observed at the human clinical dose (300 mg/day atazanavir coadministered with 100 mg/day ritonavir). In pre- and postnatal development studies in the rat, atazanavir caused body weight loss or weight gain suppression in the animal offspring with maternal drug exposure (AUC) 1.3 times the human exposure at this clinical dose. However, maternal toxicity also occurred at this exposure level.

Cobicistat: 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 No Observed Adverse Effects Levels (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.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. It is not known whether atazanavir or cobicistat is present in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **instruct mothers not to breastfeed**.

8.4 Pediatric Use

The safety and efficacy of EVOTAZ in pediatric patients less than 18 years of age have not been established. Atazanavir, and thus EVOTAZ, is not recommended for use in patients below the age of 3 months due to the risk of kernicterus.

8.5 Geriatric Use

Clinical studies with 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, 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 *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

EVOTAZ is not recommended for use in HIV-treatment-experienced patients with end-stage renal disease managed with hemodialysis *[see Dosage and Administration (2.3), Warnings and Precautions (5.3), and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

EVOTAZ is not recommended for use in patients with hepatic impairment *[see Dosage and Administration (2.4), Warnings and Precautions (5.6), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

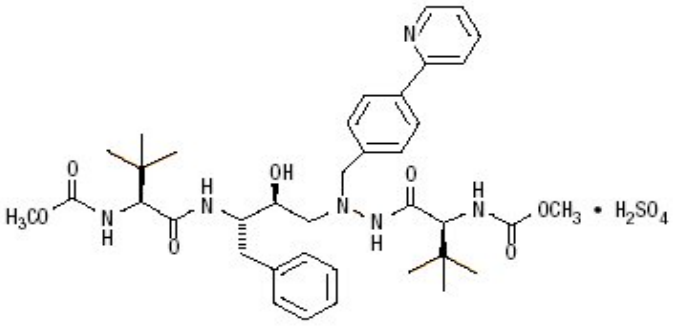
Treatment for overdosage with EVOTAZ should consist of general supportive measures, including monitoring of vital signs and ECG, and observations of the patient's clinical status. There is no specific antidote for overdose with EVOTAZ. Since atazanavir is extensively metabolized by the liver and both atazanavir and cobicistat are highly bound plasma proteins, it is unlikely that EVOTAZ will be significantly removed by hemodialysis or peritoneal dialysis.

Atazanavir: Human experience of acute overdose with atazanavir is limited. A single self-administered overdose of 29.2 g of atazanavir in an HIV-infected patient (73 times the 400-mg recommended dose of atazanavir administered without a CYP3A inhibitor) was associated with asymptomatic bifascicular block and PR interval prolongation. These events resolved spontaneously. At atazanavir doses resulting in high atazanavir exposures, jaundice due to indirect (unconjugated) hyperbilirubinemia (without associated liver function test changes) or PR interval prolongation may be observed. *[See Warnings and Precautions (5.1, 5.9) and Clinical Pharmacology (12.2).]*

11 DESCRIPTION

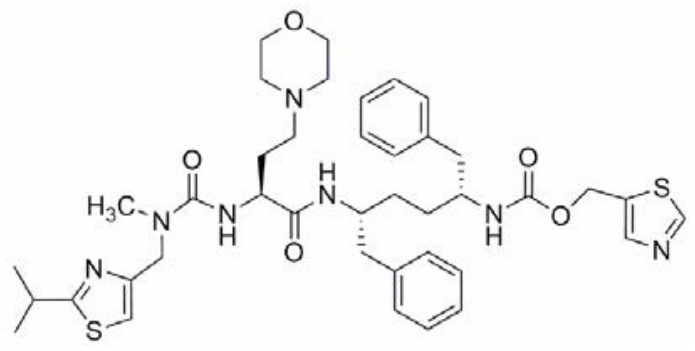
EVOTAZ™ is a fixed-dose combination tablet for oral administration containing the active ingredients atazanavir and cobicistat. Atazanavir is an HIV-1 protease inhibitor. Cobicistat is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family. EVOTAZ tablets contain 342 mg of atazanavir sulfate, equivalent to 300 mg of atazanavir, and 150 mg of cobicistat, as well as the following inactive ingredients in the tablet core: croscarmellose sodium, crospovidone, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, silicon dioxide, sodium starch glycolate, and stearic acid. The tablets are film-coated with a coating material containing the following inactive ingredients: hypromellose, red iron oxide, talc, titanium dioxide, triacetin.

Atazanavir: Atazanavir is present as the sulfate salt. The chemical name for atazanavir sulfate is (3*S*,8*S*,9*S*,12*S*)-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). Its molecular formula is $C_{38}H_{52}N_6O_7 \bullet H_2SO_4$, which corresponds to a molecular weight of 802.9 (sulfuric acid salt). The free base molecular weight is 704.9. Atazanavir sulfate has the following structural formula:



Atazanavir sulfate is a white to pale-yellow crystalline powder. It is slightly soluble in water (4-5 mg/mL, free base equivalent) with the pH of a saturated solution in water being about 1.9 at 24 ± 3°C.

Cobicistat: The chemical name for cobicistat is 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. It has a molecular formula of $C_{40}H_{53}N_7O_5S_2$ and a molecular weight of 776.0. It has the following structural formula:



Cobicistat is adsorbed onto silicon dioxide. Cobicistat on silicon dioxide is a white to pale yellow solid with a solubility of 0.1 mg/mL in water at 20°C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

EVOTAZ is a fixed-dose combination of the HIV-1 antiretroviral drug, atazanavir and the CYP3A inhibitor, cobicistat. *[See Microbiology (12.4).]*

12.2 Pharmacodynamics

Cardiac Electrophysiology

Atazanavir: The effect of atazanavir 400 mg and 800 mg without a CYP3A inhibitor on QTc interval was evaluated in a randomized, multiple-dose, placebo-controlled three-period crossover QT study in 72 healthy subjects. At a dose of 800 mg, atazanavir did not prolong the QTc interval to any clinically relevant extent. Prolongation of the PR interval was noted in subjects receiving atazanavir in the same study. The mean (±SD) maximum change in PR interval from the predose value was 24 (±15) msec for atazanavir 400 mg (n=65) compared to 13 (±11) msec for placebo (n=67). The PR interval prolongations in this study were asymptomatic. Steady state atazanavir exposures (C_{max} and AUC_{tau}) observed in this healthy volunteer study exceeded those observed in patients treated with atazanavir coadministered with cobicistat. There is limited information on the potential for a pharmacodynamic interaction in humans between atazanavir and other drugs that prolong the PR interval of the electrocardiogram. *[See Warnings and Precautions (5.1).]*

In 1793 HIV-infected patients receiving antiretroviral regimens, QTc prolongation was comparable in the atazanavir and comparator regimens. No atazanavir-treated healthy subject or HIV-infected patient in clinical trials had a QTc interval >500 msec. *[See Warnings and Precautions (5.1).]*

Cobicistat: The effect of cobicistat 250 mg (1.7 times the dose in EVOTAZ) and 400 mg (2.7 times the dose in EVOTAZ) on QTc interval was evaluated in a randomized, single-dose, placebo- and active-controlled (moxifloxacin 400 mg) four-period crossover thorough QT study in 48 healthy subjects. At a dose 2.7 times the dose in EVOTAZ, cobicistat did not prolong QTc interval to any clinically relevant extent. 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) msec for 250 mg and 20.2 (22.8) msec for 400 mg dose of cobicistat.

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 in 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 *[see Warnings and Precautions (5.3)]*.

12.3 Pharmacokinetics

One EVOTAZ tablet provided comparable atazanavir exposures (90% confidence intervals within 80%-125%) to one atazanavir capsule (300 mg) plus one cobicistat tablet (150 mg) following single-dose administration with a light meal to healthy subjects (N=62).

The activity of cobicistat as a CYP3A inhibitor to increase the systemic exposures of atazanavir 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 coadministered with cobicistat were comparable to those observed with ritonavir as shown in Table 6 *[see Clinical Studies (14)]*.

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

Parameter	Atazanavir coadministered with cobicistat and emtricitabine/tenofovir DF (n=22)	Atazanavir coadministered with ritonavir and emtricitabine/tenofovir DF (n=26)
AUC (µg•h/mL)	46.13 ± 26.18	47.59 ± 24.38
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 median T_{max} of approximately 3.5 hours following multiple daily doses of atazanavir 300 mg with cobicistat 150 mg in HIV-infected subjects.

Cobicistat: In a trial where subjects were instructed to take coadministered atazanavir and cobicistat with food, the median cobicistat T_{max} was approximately 3.0 hours post-dose. Steady-state cobicistat C_{max}, AUC_{tau}, and C_{tau} (mean ± SD), values were 1.5 ± 0.5 µg/mL, 11.1 ± 4.5 µg•hr/mL, and 0.05 ± 0.07 µg/mL, respectively (n=22).

Food Effect

Administration of a single dose of EVOTAZ with a light meal (336 kcal, 5.1 g fat, 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 (1,038 kcal, 59 g fat, 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.

Cobicistat: Cobicistat is 97% to 98% bound to human plasma proteins and the mean blood-to-plasma ratio was approximately 0.5.

Metabolism

Atazanavir: Atazanavir is extensively metabolized in humans by CYP3A. Other minor biotransformation pathways for atazanavir or its metabolites consisted of glucuronidation, N-dealkylation, hydrolysis, and oxygenation with dehydrogenation.

Cobicistat: Cobicistat is metabolized by CYP3A and to a minor extent by CYP2D6 enzymes and does not undergo glucuronidation.

Elimination

Atazanavir: The mean elimination half-life of atazanavir in healthy volunteers (n=62) and HIV-infected adult patients (n=13) was approximately 7.5 hours at steady state following a single dose of EVOTAZ with a light meal.

Cobicistat: The median terminal plasma half-life of cobicistat following administration is approximately 3 to 4 hours. With single dose administration of [^{14}C] cobicistat after multiple dosing of cobicistat for six days, 86.2% and 8.2% of the administered dose was excreted in feces and urine, respectively.

Specific Populations

Renal Impairment

EVOTAZ is not recommended for use in HIV-treatment-experienced adults with end-stage renal disease managed with hemodialysis. *[See Dosage and Administration (2.3).]*

Atazanavir: In healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. Atazanavir has been studied in adult subjects with severe renal impairment (n=20), including those on hemodialysis, at multiple doses of 400 mg once daily. The mean atazanavir C_{max} was 9% lower, AUC was 19% higher, and C_{min} 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. In a 4-hour dialysis session, 2.1% of the administered dose was removed. When atazanavir was administered either prior to, or following hemodialysis (n=10), the geometric means for C_{max}, AUC, and C_{min} were approximately 25% to 43% lower compared to subjects with normal renal function. The mechanism of this decrease is unknown.

Cobicistat: A study of the pharmacokinetics of cobicistat was performed in non–HIV-1 infected subjects with severe renal impairment (estimated creatinine clearance below 30 mL/min). No clinically relevant differences in cobicistat pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects. *[See Use in Specific Populations (8.6).]*

Hepatic Impairment

EVOTAZ has not been studied in patients with hepatic impairment and is not recommended for use in patients with hepatic impairment. *[See Dosage and Administration (2.4).]*

Atazanavir: Atazanavir is primarily metabolized and eliminated by the liver. 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. No clinically relevant differences in cobicistat pharmacokinetics were observed between subjects with moderate hepatic impairment (Child-Pugh Class B) and healthy subjects. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of cobicistat has not been studied. *[See Use in Specific Populations (8.7).]*

Gender and Age

Atazanavir: There were no clinically important pharmacokinetic differences observed due to age or gender.

Cobicistat: No clinically relevant pharmacokinetic differences have been observed between men and women for cobicistat.

Assessment of Drug Interactions

Atazanavir has been shown *in vivo* not to induce its own metabolism, nor to increase the biotransformation of some drugs metabolized by CYP3A. In a multiple-dose study, atazanavir decreased the urinary ratio of endogenous 6β-OH cortisol to cortisol versus baseline, indicating that CYP3A production was not induced.

Drug interaction studies were not conducted for EVOTAZ or for atazanavir coadministered with cobicistat. Drug interaction studies of cobicistat were conducted with desipramine, digoxin, and efavirenz. Drug interaction studies of cobicistat coadministered with elvitegravir included rosuvastatin and rifabutin. The effects of cobicistat on the exposure of coadministered drugs are summarized in Table 7. For information regarding clinical recommendations, see *Drug Interactions (7).*

Table 7: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Cobicistat[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	Cobicistat Dose/Schedule	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without cobicistat; No Effect = 1.00		
			C_{max}	AUC	C_{min}
desipramine	50 mg single dose (n=8)	150 mg QD (n=8)	1.24 (1.08, 1.44)	1.65 (1.36, 2.02)	NC
digoxin	0.5 mg single dose (n=22)	150 mg QD (n=22)	1.41 (1.29, 1.55)	1.08 (1.00, 1.17)	NC
efavirenz	600 mg single dose (n=17)	150 mg QD (n=17)	0.87 (0.80, 0.94)	0.93 (0.89, 0.97)	NC
rifabutin	150 mg once every other day (n=12)	150 mg QD[b] (n=12)	1.09 (0.98, 1.20)[c] 25-O-desacetyl-rifabutin 4.84[c] (4.09, 5.74)	0.92 (0.83, 1.03)[c] 25-O-desacetyl-rifabutin 6.25[c] (5.08, 7.69)	0.94 (0.85, 1.04)[c] 25-O-desacetyl-rifabutin 4.94[c] (4.04, 6.04)
rosuvastatin	10 mg single dose (n=10)	150 mg single dose[b] (n=10)	1.89 (1.48, 2.42)	1.38 (1.14, 1.67)	1.43[d] (1.08, 1.89)

[a] All interaction studies conducted in healthy volunteers.
[b] Study was conducted in the presence of 150 mg elvitegravir.
[c] Comparison based on rifabutin 300 mg QD.
[d] parameter is C_{last}
NC = not calculated

12.4 Microbiology

Mechanism of Action

EVOTAZ is a fixed-dose combination of atazanavir (ATV) and the CYP3A inhibitor 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 the CYP3A substrate atazanavir.

Antiviral Activity in Cell Culture

Atazanavir exhibits anti–HIV-1 activity with a mean 50% effective concentration (EC_{50} value) 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 (1.9-32 nM), with EC_{50}

values above the EC_{50} values of failure isolates. Two-drug combination antiviral activity studies with ATV showed no antagonism in cell culture with NNRTIs (delavirdine, efavirenz, and nevirapine), PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine), the HIV-1 fusion inhibitor enfuvirtide, and two compounds used in the treatment of viral hepatitis, adefovir and ribavirin, without enhanced cytotoxicity.

Cobicistat does not inhibit recombinant HIV-1 protease in a biochemical assay and has no detectable antiviral activity in cell culture against HIV-1, HBV, or HCV. The antiviral activity in cell culture of selected HIV-1 antiretroviral drugs was not antagonized by cobicistat.

Resistance

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

Clinical Studies: Resistance to EVOTAZ is driven by atazanavir as cobicistat lacks antiviral activity. For the complete atazanavir resistance-associated substitutions, refer to the atazanavir full prescribing information.

Clinical Studies of Treatment-Naive Patients Receiving Atazanavir 300 mg Coadministered with Cobicistat 150 mg: In an analysis of treatment-failure subjects who received atazanavir coadministered with cobicistat 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 this group (3%, 11/344). Among the 11 subjects, 2 developed the emtricitabine-associated resistance substitution M184V. No subject developed the tenofovir-associated resistance substitution K65R or any primary resistance substitution associated with protease inhibitors. In the ritonavir group, evaluable genotypic data was available for all 12 virologic failures (3%, 12/348) and no subject had emergent resistance to any component of the regimen.

Cross-Resistance

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

International AIDS Society (IAS)-defined PI resistance substitutions, depending on the number and type, may confer a reduced virologic response to atazanavir. Please refer to the "Baseline Genotype/Phenotype and Virologic Outcome Analyses" section in the atazanavir full prescribing information.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

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 rat-specific, 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.

Mutagenesis

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

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

Impairment of Fertility

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

Cobicistat: Cobicistat did not affect fertility in male or female rats at daily exposures (AUC) approximately 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) of approximately similar human exposures at the recommended 150 mg daily dose.

14 CLINICAL STUDIES

The safety and efficacy of atazanavir coadministered with cobicistat were evaluated in a randomized, double-blind, active-controlled trial (Study 114) in HIV-1 infected treatment-naive subjects with baseline estimated creatinine clearance above 70 mL/min (N=692). In Study 114, subjects were randomized in a 1:1 ratio to receive either atazanavir 300 mg coadministered with cobicistat 150 mg once daily or atazanavir 300 mg coadministered with ritonavir 100 mg once daily. All subjects received concomitant treatment with 300 mg of tenofovir DF and 200 mg of emtricitabine once a day administered as a single tablet. Randomization was stratified by screening HIV-1 RNA level (≤100,000 copies/mL or >100,000 copies/mL).

The mean age of subjects was 37 years (range: 19-70); 83% were male, 60% were White, 18% were Black, and 12% were Asian. The mean baseline plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL (range: 3.2-6.4). The mean baseline CD4+ cell count was 352 cells/mm^3 (range: 1-1455) and 17% had CD4+ cell counts ≤200 cells/mm^3. Forty percent (40%) of patients had baseline viral loads >100,000 copies/mL.

Virologic outcomes in Study 114 through Week 48 are presented in Table 8. In Study 114, the mean increase from baseline in CD4+ cell count at Week 48 was 213 cells/mm^3 in patients receiving atazanavir coadministered with cobicistat and 219 cells/mm^3 in patients receiving atazanavir coadministered with ritonavir.

Table 8: Virologic Outcomes of Randomized Treatment of Study 114 in HIV-1 Infected Treatment-Naive Adults at Week 48[a]

	Atazanavir 300 mg coadministered with cobicistat 150 mg (once daily) + emtricitabine/tenofovir disoproxil fumarate (n=344)	**Atazanavir 300 mg coadministered with ritonavir 100 mg + emtricitabine/tenofovir disoproxil fumarate (n=348)**
HIV-1 RNA <50 copies/mL	85%	87%
Treatment Difference	−2.2% (95% CI = −7.4%, 3.0%)	
HIV-1 RNA ≥50 copies/mL[b]	6%	4%
No Virologic Data at Week 48 Window	9%	9%
Discontinued Study Drug Due to AE or Death[c]	6%	7%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL[d]	3%	2%

[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 time window if this resulted in no virologic data on treatment during the specified window. There were no deaths reported in Study 114.

[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).

16 HOW SUPPLIED/STORAGE AND HANDLING

EVOTAZ™ tablets, 300 mg atazanavir and 150 mg cobicistat, are oval, biconvex, pink, film-coated, debossed with "3641" on one side and plain on the other side. Each bottle contains 30 tablets (NDC-0003-3641-11), a silica gel desiccant and is closed with a child-resistant closure.

Store EVOTAZ tablets at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Keep container tightly closed.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

A statement to patients and healthcare providers is included on the product's label: **ALERT: Find out about medicines that should NOT be taken with EVOTAZ.**

Inform patients that EVOTAZ is not a cure for HIV infection and they may continue to experience illnesses associated with HIV infection, including opportunistic infections. Inform patients that sustained decreases in plasma HIV RNA are associated with a reduced risk of progression to AIDS and death. Advise patients they should remain under the care of a healthcare provider when using EVOTAZ.

Advise patients to avoid doing things that can spread HIV infection to others.

- **Do not share or reuse needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** It is not known if EVOTAZ can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in breast milk.

Dosing Instructions

Advise patients to take EVOTAZ with food every day and take other concomitant antiretroviral therapy as prescribed.

Inform patients that EVOTAZ must always be used in combination with other antiretroviral drugs. Tell patients not to discontinue therapy without consulting with their healthcare provider.

Advise patients not to miss a dose of EVOTAZ, but if they do miss a dose they should follow the guidelines below.

- If a dose of EVOTAZ is missed by 12 hours or less, take the missed dose of EVOTAZ right away. Take the next dose of EVOTAZ at the usual time.
- If a dose of EVOTAZ is missed by more than 12 hours, wait and take the next dose at the usual time. If a dose of EVOTAZ is missed, do not double the next dose.

Advise patients or caregivers to call their healthcare provider or pharmacist if they have any questions.

Drug Interactions

EVOTAZ may interact with some drugs; therefore, inform patients of the potential for serious drug interactions with EVOTAZ, and that some drugs should not be taken with EVOTAZ, or some drugs may need a change in dose. Advise patients to report to their healthcare provider the use of any other prescription, nonprescription medication, or herbal products, particularly St. John's wort.

Advise patients receiving a PDE5 inhibitor and EVOTAZ that they may be at an increased risk of PDE5 inhibitor-associated adverse events including hypotension, syncope, visual disturbances, and priapism, and to promptly report any symptoms to their doctor.

Inform patients that REVATIO® (used to treat pulmonary arterial hypertension) is contraindicated with EVOTAZ and that dose adjustments are necessary when EVOTAZ is used with CIALIS®, LEVITRA®, or VIAGRA® (used to treat erectile dysfunction), or ADCIRCA® (used to treat pulmonary arterial hypertension).

Instruct patients receiving hormonal contraceptives to use additional or alternative non-hormonal contraceptive measures during therapy with EVOTAZ because no data are available to make recommendations regarding use of hormonal contraceptives and atazanavir coadministered with cobicistat.

Cardiac Conduction Abnormalities

Inform patients that EVOTAZ may produce changes in the electrocardiogram (e.g., PR prolongation). Advise patients to consult their healthcare provider if they are experiencing symptoms such as dizziness or lightheadedness.

Severe Skin Reactions

Inform patients that mild rashes without other symptoms have been reported with atazanavir use. These rashes go away within two weeks with no change in treatment. However, inform patients there have been reports of severe skin reactions (e.g., Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions) with atazanavir use. Advise patients to seek medical evaluation immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, muscle or joint aches, blisters, oral lesions, conjunctivitis, or facial edema).

Nephrolithiasis and Cholelithiasis

Inform patients that kidney stones and/or gallstones have been reported with atazanavir use. Some patients with kidney stones and/or gallstones required hospitalization for additional management and some had complications.

Hyperbilirubinemia

Inform patients that asymptomatic elevations in indirect bilirubin have occurred in patients receiving atazanavir, a component of EVOTAZ. Tell patients this may be accompanied by yellowing of the skin or whites of the eyes and alternative antiretroviral therapy may be considered if they have cosmetic concerns.

Fat Redistribution

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy including protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time.

PATIENT INFORMATION

EVOTAZ™ (EV-oh-taz)
(atazanavir and cobicistat)
tablet

Read this Patient Information before you start taking EVOTAZ and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is EVOTAZ?

EVOTAZ is a prescription HIV-1 (Human Immunodeficiency Virus) medicine used with other antiretroviral medicines to treat HIV-1 infection in adults. HIV is the virus that causes AIDS (Acquired Immunodeficiency Syndrome).

EVOTAZ contains the prescription medicines REYATAZ® (atazanavir) and TYBOST® (cobicistat).

It is not known if EVOTAZ is safe and effective in children under 18 years of age.

When used with other antiretroviral medicines to treat HIV-1 infection, EVOTAZ may help:

- reduce the amount of HIV-1 in your blood. This is called “viral load.”
- increase the number of CD4+ (T) cells in your blood that help to fight off other infections.

Reducing the amount of HIV-1 and increasing the CD4+ (T) cells in your blood may help improve your immune system. This may reduce your risk of death or getting infections that can happen when your immune system is weak (opportunistic infections).

EVOTAZ does not cure HIV-1 infection or AIDS. You must keep taking HIV-1 medicines to control HIV-1 infection and decrease HIV-related illnesses.

Avoid doing things that can spread HIV-1 infection to others:

- Do not share or reuse needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
- Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.

Ask your healthcare provider if you have any questions about how to prevent passing HIV to other people.

Who should not take EVOTAZ?

Do not take EVOTAZ if you:

- are allergic to any of the ingredients in EVOTAZ. See the end of this leaflet for a complete list of ingredients in EVOTAZ.
- are taking any of the following medicines. EVOTAZ may cause serious life-threatening side effects or death when used with these medicines:
  - alfuzosin (UROXATRAL®)
  - carbamazepine (CARBATROL®, EPITOL®, EQUETRO®, TEGRETOL®)
  - cisapride (PROPULSID®, PROPULSID® QUICKSOLV®)
  - colchicine (COLCRYS®, MITIGARE™), if you have liver or kidney problems
  - dronedarone hydrochloride (MULTAQ®)
  - ergot-containing medicines:
    - dihydroergotamine mesylate (D.H.E. 45®, EMBOLEX®, MIGRANAL®)
    - ergotamine tartrate (CAFERGOT®, MIGERGOT®, ERGOMAR®, ERGOSTAT®, MEDIHALER®, WIGRAINE®, WIGRETTES®)
    - methylergonovine (METHERGINE®)
  - indinavir (CRIXIVAN®)
  - irinotecan (CAMPTOSAR®)
  - lovastatin (ADVICOR®, ALTOPREV®, MEVACOR®)
  - lurasidone (LATUDA®)
  - midazolam (VERSED®), when taken by mouth for sedation
  - nevirapine (VIRAMUNE®, VIRAMUNE XR®)
  - phenobarbital (LUMINAL®)
  - phenytoin (DILANTIN®, PHENYTEX®)
  - pimozide (ORAP®)
  - ranolazine (RANEXA®)
  - rifampin (RIMACTANE®, RIFADIN®, RIFATER®, RIFAMATE®)
  - sildenafil (REVATIO®), when used for the treatment of pulmonary arterial hypertension (PAH)
  - simvastatin (ZOCOR®, VYTORIN®, SIMCOR®)
  - St. John's wort (*Hypericum perforatum*), or a product that contains St. John's wort
  - triazolam (HALCION®)

What should I tell my healthcare provider before taking EVOTAZ?

Before taking EVOTAZ, tell your healthcare provider if you:

- have heart problems
- have liver problems, including hepatitis B or C virus infection
- have kidney problems
- have diabetes
- have hemophilia
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if EVOTAZ will harm your unborn baby. Pregnant women have developed a serious condition called lactic acidosis (a build-up of lactic acid in the blood) when taking EVOTAZ with other HIV medicines called nucleoside analogues.
  - **Hormonal forms of birth control, such as injections, vaginal rings or implants, contraceptive patch, and some birth control pills may not work during treatment with EVOTAZ.** Talk to your healthcare provider about forms of birth control that may be used during treatment with EVOTAZ.
  - **Pregnancy Registry.** There is a pregnancy registry for women who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
  - **After your baby is born**, tell your healthcare provider if your baby's skin or the white part of his/her eyes turns yellow.
- are breastfeeding or plan to breastfeed. Do not breastfeed if you take EVOTAZ.
  - You should not breastfeed if you have HIV because of the risk of passing HIV to your baby.
  - It is not known if EVOTAZ passes into your breast milk.
  - Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines interact with EVOTAZ. **Keep a list of your medicines to show your healthcare provider and pharmacist.**

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with EVOTAZ.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take EVOTAZ with other medicines.

How should I take EVOTAZ?

- Take EVOTAZ exactly as your healthcare provider tells you.

- Do not change your dose or stop taking EVOTAZ without talking to your healthcare provider.
- EVOTAZ must be used with other antiretroviral medicines.
- Take EVOTAZ 1 time a day with food.
- If you miss a dose of EVOTAZ by 12 hours or less, take your missed dose of EVOTAZ right away. Then take your next dose of EVOTAZ at your regularly scheduled time.
- If you miss a dose of EVOTAZ by more than 12 hours, wait and then take the next dose of EVOTAZ at your regularly scheduled time.
- If a dose of EVOTAZ is missed, do not double the next dose.
- If you take too much EVOTAZ, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of EVOTAZ?

EVOTAZ can cause serious side effects, including:

- **A change in the way your heart beats (heart rhythm change).** Tell your healthcare provider right away if you get dizzy or lightheaded. These could be symptoms of a heart problem.
- **Skin rash.** Skin rash is common with EVOTAZ but can sometimes be severe. Skin rash usually goes away within 2 weeks without any change in treatment. Severe rash may develop with other symptoms which could be serious. If you develop a severe rash or a rash with any of the following symptoms, call your healthcare provider or go to the nearest hospital emergency room right away:
  - general feeling of discomfort or "flu-like" symptoms
  - fever
  - muscle or joint aches
  - swelling of your face
  - red or inflamed eyes, like "pink eye" (conjunctivitis)
  - blisters
  - mouth sores
  - painful, warm, or red lump under your skin
- **Kidney problems.** EVOTAZ, when taken with certain other medicines, can cause new or worse kidney problems, including kidney failure. Your healthcare provider should check your kidneys before you start and while you are taking EVOTAZ.
- **Kidney stones** have happened in some people who take atazanavir, one of the medicines in EVOTAZ. Tell your healthcare provider right away if you get symptoms of kidney stones, which may include pain in your low back or low stomach area, blood in your urine, or pain when you urinate.
- **Gallbladder disorders** have happened in some people who take atazanavir, one of the medicines in EVOTAZ. Tell your healthcare provider right away if you get symptoms of gallbladder problems, which may include:
  - pain in the right or middle upper stomach area

- fever
- nausea and vomiting
- your skin or the white part of your eyes turns yellow

- **Liver problems.** If you have liver problems, including hepatitis B or C infection, your liver problems may get worse when you take EVOTAZ. Your healthcare provider will do blood tests to check your liver before you start EVOTAZ and during treatment. Tell your healthcare provider right away if you get any of the following symptoms:
  - your skin or the white part of your eyes turns yellow
  - dark (tea-colored) urine
  - light colored stools
  - nausea
  - itching
  - stomach-area pain
- **Yellowing of the skin or the white part of your eyes** is common with EVOTAZ but may be a symptom of a serious problem. These effects may be due to increases in bilirubin levels in the blood (bilirubin is made by the liver). Although these effects may not be damaging to your liver, skin, or eyes, tell your healthcare provider right away if your skin or the white part of your eyes turns yellow.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider if you start having new symptoms after starting your HIV-1 medicine.
- **Diabetes and high blood sugar (hyperglycemia)** have happened and worsened in some people who take protease inhibitor medicines like EVOTAZ. Some people have had to start taking medicine to treat diabetes or have had to change their diabetes medicine.
- **Changes in body fat** can happen in people taking HIV-1 medicines. These changes may include increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- **Increased bleeding problems in people with hemophilia** have happened when taking protease inhibitors including EVOTAZ.

The most common side effects of EVOTAZ were yellowing of the skin or whites of the eyes, and nausea.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of EVOTAZ. For more information ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store EVOTAZ?

- Store EVOTAZ tablets at room temperature between 68°F and 77°F (20°C and 25°C).
- Keep tablets in a tightly closed container.

Keep EVOTAZ and all medicines out of the reach of children.

General information about EVOTAZ

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EVOTAZ for a condition for which it was not prescribed. Do not give EVOTAZ to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about EVOTAZ that is written for health professionals.

For more information, call 1-800-321-1335.

What are the ingredients in EVOTAZ?

Active ingredients: atazanavir and cobicistat

Inactive ingredients: croscarmellose sodium, crospovidone, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, silicon dioxide, sodium starch glycolate, and stearic acid. The film-coating contains hypromellose, red iron oxide, talc, titanium dioxide, triacetin.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Product of Canada

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