AUSTRALIAN PRODUCT INFORMATION - EVOTAZ® (ATAZANAVIR/COBICISTAT)

1 NAME OF THE MEDICINE

EVOTAZ (atazanavir/cobicistat)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

EVOTAZ tablets are oval, biconvex, pink film-coated, debossed with "3641" on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

EVOTAZ is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended adult dosage of EVOTAZ is one tablet once daily taken orally with food. Administer EVOTAZ in conjunction with other antiretroviral agents. When co-administered with H_2-receptor antagonists or proton-pump inhibitors, dose separation may be required (see 4.5 Interactions with other medicines and other forms of interactions).

EVOTAZ tablets should be taken whole and not broken, cut, or crushed.

If a dose of EVOTAZ is missed by 12 hours or less, the missed dose of EVOTAZ should be taken right away. The next dose of EVOTAZ should be taken at the usual time. If a dose of EVOTAZ is missed by more than 12 hours, the patient should wait and take the next dose at the usual time. If a dose of EVOTAZ is missed, the patient should not double the next dose.

Renal impairment

EVOTAZ should not be administered to HIV treatment-experienced patients with severe renal disease managed with haemodialysis. Cobicistat, a component of EVOTAZ, has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual glomerular function. Consider this effect when EVOTAZ is coadministered with a drug that has dosing adjustment recommendations guided by estimated creatinine clearance (see 4.4 Special warnings and precautions for use).

Laboratory Testing Prior to Initiation of EVOTAZ

Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. This effect should be considered when EVOTAZ is coadministered with a drug that has dosing adjustment recommendations guided by estimated creatinine clearance. For example, EVOTAZ should not be initiated as part of a regimen containing emtricitabine, lamivudine, tenofovir disoproxil fumarate or adefovir dipivoxil in patients who have an estimated creatinine clearance below 70 mL/min since dose adjustment of these

drugs is required below 50 mL/min and such dose adjustments have not been established in combination with EVOTAZ (see 4.4 Special warnings and precautions for use).

Hepatic impairment

EVOTAZ is not recommended in patients with hepatic impairment (see 4.4 Special warnings and precautions for use).

Pregnancy

EVOTAZ is not recommended during pregnancy nor should it be initiated in pregnant patients; an alternative regimen is recommended. This is due to substantially lower exposures of cobicistat and consequently, lower exposures of co-administered antiretroviral agents, including atazanavir, during the second and third trimesters, compared to postpartum (see 4.6 Fertility, pregnancy and lactation).

4.3 CONTRAINDICATIONS

EVOTAZ is contraindicated in patients with known hypersensitivity to any of its ingredients (see 6.1 List of excipients).

Patients taking EVOTAZ should not use medicinal products that are substrates of the CYP3A4 isoform of cytochrome P450 or are highly dependent on UGT1A1 for clearance and have narrow therapeutic windows. Co-administration may result in competitive inhibition of the metabolism of these medicinal products and create the potential for serious and/or life-threatening adverse events such as cardiac arrhythmia (e.g., cisapride, pimozide), prolonged sedation or respiratory depression (e.g., orally administered midazolam, triazolam), or other events (e.g., ergot derivatives).

EVOTAZ should not be used in combination with elbasvir/grazoprevir because of the potential increase in the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition.

EVOTAZ should not be used in combination with glecaprevir/pibrentasvir because of the increased risk of ALT elevations due to an increase in glecaprevir and pibrentasvir plasma concentrations.

Co-administration of EVOTAZ with the following is contraindicated due to the potential for serious and/or life-threatening events or loss of virologic response and possible resistance (see 4.5 Interactions with other medicines and other forms of interactions):

- Alpha 1-adrenoreceptor antagonists: alfuzosin
- Antiarryhthmics: dronedarone, quinidine
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifabutin, rifampicin, rifapentine
- Antipsychotics: lurasidone
- Antineoplastic: irinotecan
- Calcium channel blocker: bepridil
- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine
- GI motility agents: cisapride
- Hepatitis C Direct-Acting Antivirals: elbasvir/grazoprevir
- Herbal products: St. John's wort (*Hypericum perforatum*)
- Lipid-modifying agents: HMG-CoA reductase inhibitors lovastatin, simvastatin
- Other lipid-modifying agents: lomitapide

- Neuroleptics: pimozide
- Non-nucleoside reverse transcriptase inhibitors: nevirapine, efavirenz
- PDE-5 inhibitors: sildenafil and tadalafil for the treatment of pulmonary arterial hypertension
- Sedative/hypnotics: orally administered midazolam, triazolam
- Beta-agonist: salmeterol

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use with other Antiretroviral Products

Do not use EVOTAZ in combination with products containing the same components (atazanavir or cobicistat), or with fixed-dose products that contain cobicistat. Do not use EVOTAZ in combination with another antiretroviral that requires a pharmacokinetic enhancer (eg, elvitegravir) because dosing recommendations for such combinations have not been established and may result in decreased plasma concentrations of the antiretroviral agent, leading to loss of therapeutic effect and development of resistance. Do not use EVOTAZ with other HIV-protease inhibitors. Do not use EVOTAZ in combination with nevirapine or efavirenz. EVOTAZ should not be used concurrently with product containing ritonavir or regimens containing ritonavir due to similar effects of cobicistat or ritonavir on CYP3A. See 4.5 Interactions with other medicines and other forms of interactions.

Use in renal impairment

Effect on Serum Creatinine

Dosing recommendations are not available for use of EVOTAZ in combination with other drugs that require dosing adjustment for renal impairment. Consider alternative medications that do not require dosing adjustments. Cobicistat, a component of EVOTAZ, has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. This effect should be considered when interpreting changes in estimated creatinine clearance in patients initiating EVOTAZ particularly in patients with medical conditions or receiving drugs needing monitoring with estimated creatinine clearance, or when co-administered with drugs with dosing adjustment recommendations guided by estimated creatinine clearance.

Although cobicistat may cause modest increases in serum creatinine and modest declines in estimated creatinine clearance without affecting renal glomerular function, patients who experience a confirmed increase in serum creatinine of greater than 35 μmol/L f from baseline should be monitored and evaluated for evidence of tubulopathy. EVOTAZ should not be initiated in patients with creatinine clearance less than 70 ml/min if one or more co-administered agent requires dose adjustment based on creatinine clearance (e.g. emtricitabine, lamivudine, tenofovir DF or adefovir).

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 is used in an antiretroviral regimen that contains tenofovir disoproxil fumarate (tenofovir DF).

- Do not initiate EVOTAZ as part of a regimen containing tenofovir DF in patients who have an estimated creatinine clearance below 70 mL/min because dose adjustment of tenofovir DF is required below 50 mL/min and such dose adjustments have not been established for coadministration with EVOTAZ. Patients should be switched to an alternative antiretroviral regimen if estimated creatinine clearance decreases to less than 50 mL/min.
- Document estimated creatinine clearance, urine glucose and urine protein (ratio) at baseline and perform routine monitoring during treatment when EVOTAZ is used with tenofovir DF.
- Proteinuria, normoglycemic glycosuria and increased fractional excretion of phosphorous may represent the first signs of tubulopathy and precede any decline in renal function.

- Measure serum phosphorus in patients with or at risk for renal impairment.
- Avoid use of EVOTAZ with tenofovir DF in combination with concomitant or recent use of a nephrotoxic agent.

Diabetes Mellitus/Hyperglycaemia

Atazanavir:

New onset diabetes mellitus, hyperglycaemia, and exacerbation of existing diabetes mellitus have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitors. In some of these, the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions, some of which required therapy with agents that have been associated with development of diabetes or hyperglycaemia.

Haemophilia

Atazanavir: There have been reports of increased bleeding, including spontaneous skin hematomas and haemarthrosis, in patients with haemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In most reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship between protease inhibitor therapy and these events has not been established. Haemophiliac patients should be made aware of the possibility of increased bleeding.

Fat Redistribution

Atazanavir: 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.

Immune Reconstitution Syndrome

Atazanavir: 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 [PCP], or tuberculosis), which may necessitate further evaluation and treatment. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Cardiac effects

Atazanavir: Atazanavir, a component of EVOTAZ, has the potential to prolong the PR interval of the electrocardiogram in some patients. EVOTAZ should be used with caution in patients with pre-existing conduction system disease (eg, marked first-degree atrioventricular [AV] block or second- or third-degree AV block). Caution should be used when co-administering EVOTAZ with medicinal products known to induce PR interval prolongation especially those that are metabolized by CYP3A (eg, verapamil) or CYP2D6 (eg, beta-blockers other than atenolol). Caution should be used when prescribing EVOTAZ in association with medicinal products which have the potential to increase the QT interval and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances). See 4.5 Interactions with other medicines and other forms of interactions.

Hyperbilirubinemia and jaundice

Atazanavir: Most patients taking atazanavir experience asymptomatic elevations in indirect (unconjugated) bilirubin, and this may be associated with scleral icterus and jaundice in some patients. This isolated hyperbilirubinemia is reversible upon discontinuation of atazanavir. Hyperbilirubinemia

was related to atazanavir plasma concentrations and not generally associated with elevation of serum transaminases. Preclinical studies suggest that elevation in bilirubin was not associated with haemolysis and was related to inhibition of UDP-glucuronosyl transferase (UGT) by atazanavir. Hepatic transaminase elevations that occur with elevated bilirubin in patients receiving EVOTAZ should be evaluated for alternative etiologies. No long-term safety data are available for patients experiencing persistent elevations in bilirubin >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.

Rash

Atazanavir: In controlled clinical trials (n=1597), rash (all grades, regardless of causality) occurred in approximately 21% of patients treated with atazanavir. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 3 weeks of initiating therapy with atazanavir. In most patients, rash resolves within 2 weeks while continuing atazanavir therapy. The discontinuation rate for rash in clinical trials with atazanavir was 0.4%. EVOTAZ should be discontinued if severe rash develops. Cases of Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions including drug rash, eosinophilia, and systemic symptoms (DRESS) syndrome have been reported in patients receiving atazanavir. Patients should be advised of the signs and symptoms and monitored closely for skin reactions.

Use in hepatic impairment

Atazanavir and cobicistat are principally metabolized by the liver. EVOTAZ is not recommended in patients with hepatic impairment (see 4.2 Dose and method of administration). 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.

Chronic kidney disease

Chronic kidney disease in HIV-infected patients treated with atazanavir, with or without ritonavir, has been reported during postmarketing surveillance. EVOTAZ should be used with caution, particularly in those patients with other risk factors for chronic kidney disease.

Nephrolithiasis and Cholelithiasis

Atazanavir: Cases of nephrolithiasis and/or cholelithiasis have been reported during postmarketing surveillance in HIV-infected patients receiving atazanavir, a component of EVOTAZ (see 4.8 Adverse effects (Undesirable effects): Postmarketing experience). Some patients required hospitalization for additional management and some had complications. As 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.

Lactic acidosis

Atazanavir: Cases of lactic acidosis, sometimes fatal, and symptomatic hyperlactatemia have been reported in patients receiving atazanavir in combination with nucleoside analogues, which are known to be associated with increased risk of lactic acidosis. In studies where didanosine and stavudine were administered with atazanavir to patients without prior antiretroviral therapy, lactic acidosis/symptomatic hyperlactatemia was observed in 2.2% of subjects. Female gender and obesity are known risk factors for lactic acidosis. The contribution of atazanavir to the risk of development of lactic acidosis has not been established.

Paediatric Use

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

Use in the Elderly

There are no data available to make a dose recommendation for patients over the age of 65 years.

Effect on Laboratory Tests

The most frequently reported laboratory abnormality in patients receiving regimens containing EVOTAZ and one or more NRTIs was elevated total bilirubin reported predominantly as elevated indirect [unconjugated] bilirubin (87%, Grade 1, 2, 3, or 4). Grade 3 or 4 elevation of total bilirubin was noted in 37% (6% Grade 4). Discontinuation of treatment due to elevated bilirubin was < 1%. Other marked clinical laboratory abnormalities (Grade 3 or 4) reported in greater than or equal to 2% of patients receiving regimens containing EVOTAZ and one or more NRTIs included: elevated creatine kinase (CK) (7%), elevated ALT/SGPT (5%), low neutrophils (5%), elevated AST/SGOT (3%), and elevated lipase.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drug Interactions

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

Atazanavir: Atazanavir is metabolized in the liver by the cytochrome P450 enzyme system, and is an inhibitor of CYP3A4. Atazanavir has been shown *in vivo* not to induce its own metabolism, nor to increase the biotransformation of some drugs metabolized by CYP3A4. Atazanavir is a weak to moderate inhibitor of CYP2C8.Atazanavir is an inhibitor of CYP3A4 and UGT1A1. Co-administration of atazanavir and drugs primarily metabolized by CYP3A4 (eg, calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants, and phosphodiesterase inhibitors) or UGT1A1 (eg, irinotecan) may result in increased plasma concentrations of the other drug that could increase or prolong both its therapeutic and adverse effects. Atazanavir is metabolized in the liver by the cytochrome P450 enzyme system. Co-administration of atazanavir and drugs that induce CYP3A4, such as rifampicin, may decrease atazanavir plasma concentrations and reduce its therapeutic effect. Co-administration of atazanavir and drugs that inhibit CYP3A4 may increase atazanavir plasma concentrations.

Cobicistat: Cobicistat is a potent mechanism-based inhibitor of cytochrome P450 3A (CYP3A) and may increase plasma concentrations of agents that are primarily metabolised by CYP3A. Drugs that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in exposure when co-administered with cobicistat. Thus, co-administration of cobicistat with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring. Cobicistat is a weak inhibitor of CYP2D6. Cobicistat is not expected to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9 or CYP2C19. Cobicistat is not expected to induce CYP1A2, CYP3A4, CYP2C9, CYP2C19, UGT1A1, or MDR1.

EVOTAZ:

- Co-administration of EVOTAZ and drugs primarily metabolized by CYP3A4 (eg, calcium channel blockers, some HMG-CoA reductase inhibitors, immunosuppressants, and phosphodiesterase (PDE5) inhibitors), UGT1A1, and/or CYP2D6, or drugs that are substrates of P-gp, BCP, OATP1B1, and/or OATP1B3 (eg grazoprevir) may result in increased plasma concentrations of the other drug that could increase or prolong both the therapeutic and adverse effects of the other drug.

- Co-administration of EVOTAZ and drugs that induce CYP3A4 (eg, rifampicin) may decrease atazanavir and cobicistat plasma concentrations and reduce the therapeutic effect of EVOTAZ.
- Co-administration of EVOTAZ and drugs that inhibit CYP3A4 (eg, ketoconazole) may increase atazanavir and cobicistat plasma concentrations.
- Caution should be used with co-administration of EVOTAZ and drugs highly dependent on CYP2C8 with narrow therapeutic indices (eg, paclitaxel, repaglinide).

For drugs that are contraindicated with EVOTAZ, see 4.3 Contraindications. Established and potentially significant drug interactions are included in Table 1. These recommendations are based on either drug interaction studies with the components of EVOTAZ, or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of therapeutic effect of EVOTAZ.

Table 1: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
Antiretroviral Agents: *CCR5 Antagonist*		
maraviroc	↑ maraviroc	Maraviroc is a substrate of CYP3A and its plasma concentration increases when coadministered with potent CYP3A inhibitors. When co-administering maraviroc and EVOTAZ, patients should receive maraviroc 150 mg twice daily. For further details, see local prescribing information for maraviroc. Maraviroc is not expected to have an impact on concentrations of atazanavir and cobicistat.
HIV Antiretroviral Agents: *Protease Inhibitors*		
saquinavir (soft gelatin capsules)	↑ saquinavir	Appropriate dosing recommendations for the co-administration of EVOTAZ and saquinavir with respect to efficacy and safety have not been established.
indinavir	↑atazanavir ↑indinavir	Both EVOTAZ and indinavir are associated with hyperbilirubinemia. Co-administration of EVOTAZ and indinavir is not recommended (see 4.3 Contraindications and/or 4.4 Special warnings and precautions for use)
other HIV protease inhibitors	effects unknown	HIV Protease inhibitors other than those listed above have not been studied. Do not use EVOTAZ in combination with other HIV protease inhibitors because co-administration may not provide adequate protease inhibitor exposure.
HCV Antiviral Agents: *Protease Inhibitors*		
telaprevir	↑atazanavir ↓telaprevir	Concomitant administration of telaprevir with atazanavir/ritonavir resulted in reduced telaprevir exposure, while steady state atazanavir exposure was increased. Co-administration with telaprevir is not recommended.
boceprevir	↑atazanavir ↔boceprevir	Concomitant administration of boceprevir with atazanavir/ritonavir resulted in reduced exposures to atazanavir and ritonavir. The effects of EVOTAZ on boceprevir exposures are unknown. Co-administration with boceprevir is not recommended.
elbasvir/grazoprevir	↑grazoprevir	Concomitant administration of grazoprevir with atazanavir is contraindicated because of the potential increase in the risk of ALT elevations due to a significant increase in grazoprevir plasma

Table 1: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
		concentrations caused by OATP1B1/3 inhibition (see 4.3 Contraindications)
sofosbuvir/ velpatasvir/ voxilaprevir	↑voxilaprevir	Coadministration with EVOTAZ is not recommended.
HIV Antiviral Agents: *Nucleoside Reverse Transcriptase Inhibitors (NRTIs)*		
didanosine buffered formulations	↓ atazanavir ↓didanosine	Co-administration with atazanavir did not alter exposure to didanosine; however, exposure to atazanavir was markedly decreased by co-administration of atazanavir with didanosine buffered tablets (presumably due to the increase in gastric pH caused by buffers in the didanosine tablets). In addition, it is recommended that didanosine be administered on an empty stomach; therefore EVOTAZ should be given (with food) 2 h before or 1 h after didanosine buffered formulations. Thus, EVOTAZ and didanosine EC should be administered at different times. Buffered medications are not expected to have an impact on cobicistat exposures.
tenofovir disoproxil fumarate	↓atazanavir ↑ tenofovir	Tenofovir disoproxil fumarate (DF) may decrease the AUC and C_{min} of atazanavir. When coadministered with tenofovir DF, it is recommended that EVOTAZ and tenofovir DF 300 mg be given together with food. Atazanavir increases tenofovir DF concentrations. The mechanism of the interaction is unknown. Higher tenofovir DF concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving EVOTAZ and tenofovir DF should be monitored for tenofovir-associated adverse events.
HIV Antiviral Agents: *Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)*		
efavirenz	↓atazanavir ↓cobicistat ↔ efavirenz	Do not co-administer EVOTAZ with efavirenz. Efavirenz decreases atazanavir plasma concentration and is expected to decrease cobicistat plasma concentration. This may result in a loss of therapeutic effect of EVOTAZ and development of resistance to atazanavir.
nevirapine	↓atazanavir ↓cobicistat ↑nevirapine	Do not co-administer EVOTAZ with nevirapine. Nevirapine is expected to decrease cobicistat and substantially decrease atazanavir plasma concentrations, which may result in a loss of therapeutic effect of EVOTAZ and development of resistance to atazanavir. Co-administration of nevirapine and EVOTAZ is expected to increase nevirapine plasma concentration, which may increase the risk of nevirapine associated toxicity.
etravirine	↓atazanavir ↓cobicistat	Do not co-administer EVOTAZ with etravirine because it is expected to decrease cobicistat plasma concentration and consequently atazanavir which may result in the loss of therapeutic effect and development of resistance to atazanavir.
rilpivirine	↑ rilpivirine ↔ cobicistat	Co-administration of rilpivirine and cobicistat is expected to increase the plasma concentration of rilpivirine. Rilpivirine is not expected to affect the plasma concentration of cobicistat.

Table 1: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
		Concomitant use of rilpivirine with boosted PIs may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.
OTHER AGENTS		
antacids and buffered medications	↓ atazanavir	Reduced plasma concentrations of atazanavir are expected if antacides, including buffered medications, are administered with EVOTAZ. EVOTAZ should be administered 2 h before or 1 h after these medications. Antacids and buffered medications are not expected to have an impact on cobicistat exposures.
Analeptics		
modafinil	↓ cobicistat	Co-administration of modafinil, a CYP3A inducer, may decrease cobicistat plasma concentrations and consequently that of atazanavir, which may result in loss of therapeutic effect and development of resistance. Alternative analeptics should be considered.
Antiarrhythmics		
amiodarone, mexiletine, disopyramide, flecainide, propafenone, lidocaine (systemic)	↑atazanavir ↑antiarrhythmics	Co-administration with EVOTAZ has the potential to produce serious and/or life-threatening adverse events. Concentration monitoring of these drugs is recommended if they are used concomitantly with EVOTAZ. Caution is warranted if they are used concomitantly with EVOTAZ.
digoxin	↑digoxin	The peak concentration of digoxin is increased when co-administered with cobicistat. The lowest dose of digoxin should initially be prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effects.
Antibacterials (macrolide or ketolide antibiotics)		
macrolide antibiotics: clarithromycin, erythromycin	↑atazanavir ↑cobicistat ↑clarithromycin ↑erythromycin ↓14-OH clarithromycin	Clarithromycin and erythromycin may increase concentrations of atazanavir and cobicistat. Exposure to these antibiotics is expected to increase. Alternative antibiotics should be considered.
Anticancer Agents		
dasatinib nilotinib vinblastine vincristine	↑anticancer agents	Concentrations of these drugs may be increased with co-administered with EVOTAZ resulting in the potential for increased adverse events usually associated with these anticancer agents. A decrease in the dosage or an adjustment of the dosing interval of dasatinib or nilotinib may be necessary upon co-administration with EVOTAZ. Consult the local prescribing information for dosing

Table 1: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
		instructions for these anticancer agents. For vincristine and vinblastine, monitor for hematologic or gastrointestinal side effects.
Anticoagulants		
Direct-acting oral anticoagulants (DOACs)		
apixaban	↑apixaban	When apixaban is co-administered with EVOTAZ, a strong CYP3A4/P-gp inhibitor, apixaban plasma concentrations may increase, resulting in an increased risk of bleeding. Refer to apixaban prescribing information for dosing instructions for co-administration with strong CYP3A4 and P-gp inhibitors.
rivaroxaban	↑rivaroxaban	Co-administration of EVOTAZ and rivaroxaban may result in increased exposure of rivaroxaban and may lead to risk of increased bleeding. Avoid concomitant use of EVOTAZ and rivaroxaban.
dabigatran betrixaban edoxaban	↑dabigatran ↑betrixaban ↑edoxaban	When betrixaban, dabigatran or edoxaban is co-administered with EVOTAZ, a P-gp inhibitor, plasma concentrations of betrixaban, dabigatran or edoxaban may increase, resulting in an increased risk of bleeding. Refer to DOAC prescribing information for DOAC dosing instructions for co-administration with P-gp inhibitors.
Vitamin K antagonists		
warfarin	↑warfarin	Co-administration with EVOTAZ has the potential to produce serious and/or life-threatening bleeding due to increased exposure to warfarin and has not been studied. It is recommended that the INR (International Normalized Ratio) be monitored.
Anticonvulsants		
clonazepam ethosuximide	↓atazanavir ↓cobicistat ↑ clonazepam ↑ ethosuximide	Concentrations of clonazepam and ethosuximude may be increased when coadministered with cobicistat, a component of EVOTAZ. Clinical monitoring is recommended upon co-administration with EVOTAZ.
Antidepressants		
Selective Serotonin Reuptake Inhibitors SSRIs (eg, paroxetine)	↑ SSRIs	Concentrations of these antidepressant agents may be increased when co-administered with cobicistat, a component of EVOTAZ. Dose titration of the SSRI may be required when co-administered with EVOTAZ.
Tricyclic antidepressants: (eg, amitriptyline, desipramine, imipramine, nortriptyline)	↑Tricyclic antidepressants	Co-administration of tricyclic antidepressants with EVOTAZ has the potential to produce serious and/or life-threatening adverse events due to increased exposure to these agents and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with EVOTAZ.

Table 1: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
Other antidepressants: trazodone	↑trazodone	Concentrations of trazodone may increase upon co-administration with EVOTAZ. If trazodone is used with EVOTAZ, the combination should be used with caution, and a lower dose of trazodone should be considered.
Antiepileptics		
carbamazepine, oxycarbazepine	↓atazanavir ↓cobicistat ↑carbamazepine	Co-administration of carbamazepine or oxycarbazepine with EVOTAZ may significantly decrease concentrations of cobicistat and atazanavir, resulting in loss of therapeutic effect of EVOTAZ and development of resistance to atazanavir. Co-administration with EVOTAZ has the potential to produce serious and/or life threatening adverse events and has not been studied. Co-administration of carbamazepine and EVOTAZ is not recommended.
phenytoin, phenobarbital	↓atazanavir ↓cobicistat phenytoin and phenobarbital: effects unknown	Plasma concentrations of atazanavir and cobicistat may be decreased when phenytoin or phenobarbital is administered with EVOTAZ. The effect of EVOTAZ on plasma concentrations of phenytoin and phenobarbital is unknown. Monitoring of phenobarbital or phenytoin concentrations is recommended when co-administered with EVOTAZ.
Antifungals		
ketoconazole, itraconazole	↑cobicistat ↑ketoconazole ↑itraconazole	Concentrations of ketoconazole, itraconazole, and/or cobicistat may be increased with co-administration of ketoconazole or itraconazole and EVOTAZ. Caution is warranted. Specific dosing recommendations are not available for co-administration of EVOTAZ with either itraconazole or ketoconazole.
voriconazole	Effects unknown	Voriconazole should not be co-administered with EVOTAZ unless the benefit/risk assessment justifies the use of voriconazole. Clinical monitoring may be needed upon co-administration with EVOTAZ. Patients should be carefully monitored for voriconazole-associated adverse events (e.g. liver toxicity, eye disorders) and loss of either voriconazole or atazanavir efficacy during the co-administration of voriconazole and EVOTAZ.
Antigout		
colchicine	↑colchicine	EVOTAZ should not be co-administered with colchicine to patients with renal or hepatic impairment. Recommended dosage of colchicine when administered with EVOTAZ: ***Treatment of gout flares:*** 0.6 mg (1 tablet) for 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Not to be repeated before 3 days. ***Prophylaxis of gout flares:*** If the original regimen was 0.6 mg *twice* a day, the regimen should be adjusted to 0.3 mg *once a day*.

Table 1: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
		If the original regimen was 0.6 mg *once* a day, the regimen should be adjusted to 0.3 mg *once every other day*. ***Treatment of familial Mediterranean fever (FMF):*** Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimycobacterials		
rifabutin	Cobicistat: effect unknown ↑ rifabutin	EVOTAZ is contraindicated with rifabutin (see 4.3 Contraindications).
Antineoplastics		
irinotecan	↔ atazanavir	Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities. EVOTAZ is contraindicated with irinotecan (see 4.3 Contraindications).
Beta-agonist (inhaled)		
Corticosteroids (systemic): dexamethasone and other corticosteroids	↓ atazanavir ↓ cobicistat ↑ corticosteroids	Co-administration 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. Co-administration 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.
salmeterol	↑ salmeterol	Concomitant use of salmeterol and EVOTAZ may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia. EVOTAZ is contraindicated with salmeterol (see 4.3 Contraindications).
Beta-Blockers		
metoprolol carvedilol timolol	↔atazanavir ↑beta-blockers	Concentrations of beta-blockers may be increased when co-administered with cobicistat. Clinical monitoring is recommended when co-administered with EVOTAZ and a dose reduction of the beta-blocker may be necessary.
Calcium Channel Blockers		
diltiazem	↑diltiazem and desacetyldiltiazem	Exposure to diltiazem and a metabolite, desacetyl-diltiazem, is increased when diltiazem is co-administered with atazanavir. Caution is warranted. A dose reduction of diltiazem by 50% should be considered, and electrocardiogram monitoring is recommended.
amlodipine, felodipine, nifedipine,	↑calcium channel blocker	Caution is warranted. Dose titration of the calcium channel blockers should be considered. Electrocardiogram monitoring is recommended.

Table 1: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
nicardipine, verapamil		
Corticosteroids (inhaled/nasal)		
Fluticasone and other inhaled or nasal steroids	↑fluticasone ↑ other inhaled/nasal steroids	Concomitant use of fluticasone propionate or other inhaled or nasal corticosteroids and EVOTAZ are not recommended unless the potential benefit to the patient outweighs the risks. Consider alternatives particularly for long-term use.
Endothelin Receptor Antagonists		
bosentan	↓ atazanavir ↓ cobicistat ↑ bosentan	Bosentan is metabolized by CYP3A4 and is an inducer of CYP3A4. Plasma concentrations of atazanavir may be decreased when bosentan is administered with EVOTAZ. Prescribers should consult the complete prescribing information for bosentan when considering using this medicine in combination with EVOTAZ. ***Co-administration of bosentan in patients on EVOTAZ:*** For patients who have been receiving EVOTAZ for at least 10 days, start bosentan at 62.5 mg once daily or every other day based on individual tolerability. ***Co-administration of EVOTAZ in patients on bosentan:*** Discontinue bosentan at least 36 hours before starting EVOTAZ. At least 10 days after starting EVOTAZ, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.
Lipid-Modifying Agents		
HMG-CoA Reductase Inhibitors		
atorvastatin	↑ atorvastatin	Coadministration of EVOTAZ with atorvastatin is not recommended.
rosuvastatin	↑ rosuvastatin	Plasma concentrations of rosuvastatin is expected to increase when coadministered with EVOTAZ. Rosuvastatin dose should not exceed 10 mg/day. The risk of myopathy, including rhabdomyolysis, may be increased.
pravastatin, fluvastatin	unknown	The potential for an interaction when pravastatin or fluvastatin is co-administered with EVOTAZ is unknown. For HMG-CoA reductase inhibitors that are not contraindicated with EVOTAZ, start with the lowest recommended dose and titrate while monitoring for safety (e.g. myopathy).
H_2-Receptor Antagonists		

Table 1: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
famotidine	↓ atazanavir	Reduced plasma concentrations of atazanavir are expected if H_2-receptor antagonists are administered with atazanavir. This may result in loss of therapeutic effect and development of resistance ***Treatment-naive patients:*** EVOTAZ once daily with food should be administered simultaneously with, and/or at least 10 hours after, a dose of the H2-receptor antagonist. The dose of the H2-receptor antagonist should not exceed a dose equivalent to famotidine 40 mg twice daily. ***Treatment-experienced patients:*** - For treatment-experienced patients *who are also receiving concomitant tenofovir DF*: Do not co-administer EVOTAZ with an H2-receptor antagonist in these patients. - For treatment-experienced patients *who are* ***not*** *receiving concomitant tenofovir DF*: EVOTAZ once daily with food should be administered simultaneously with, and/or at least 10 hours after, a dose of the H2-receptor antagonist. The dose of the H2-receptor antagonist should not exceed a dose comparable to famotidine 20 mg twice daily.
Hormonal Contraceptives		
drospirenone/ethinyl estradiol	↑ drospirenone ↔ ethinyl estradiol	Plasma concentrations of drospirenone are increased when coadministered with EVOTAZ. Clinical monitoring is recommended due to the potential for hyperkalemia.
eg, progestin/estrogen, norgestimate, ethinyl estradiol, norethindrone	progestin and estrogen: effects unknown	Concentrations of ethinyl estradiol and norethindrone are increased when a combined oral contraceptive containing those agents is co-administered with atazanavir. Alternative (nonhormonal) forms of contraception should be considered. *Mechanism:* The mechanism of interaction is inhibition of metabolism by atazanavir and/or cobicistat.
Immunosuppressants		
eg, cyclosporin, sirolimus, tacrolimus, rapamycin	↑ immuno-suppressants	Exposure to these immunosuppressant agents may be increased when they are co-administered with EVOTAZ. Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with EVOTAZ. *Mechanism:* The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or cobicistat.
Neuroleptics		
perphenazine, risperidone, thioridazine	↑ neuroleptics	A decrease in the dose of neuroleptics metabolized by CYP3A or CYP2D6 may be required when co-administered with EVOTAZ.

Table 1: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
Opioids		
eg, buprenorphine, naloxone, methadone, fentanyl, tramadol	↑ buprenorphine ↑ norbuprenorphine naloxone and methadone: effects unknown	***Buprenorphine/naloxone/methadone:*** Co-administration of buprenorphine and atazanavir increases the plasma concentration of buprenorphine and norbuprenorphine, due to CYP3A4 and UGT1A1 inhibition. Co-administration of EVOTAZ with buprenorphine warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered.
	↑ fentanyl	***Fentanyl:*** When EVOTAZ is co-administered with fentanyl, careful monitoring of therapeutic and adverse effects of fentanyl (including potentially fatal respiratory depression) is recommended.
	↑ tramadol	***Tramadol:*** When EVOTAZ is co-administered with tramadol, a decreased dose of tramadol may be needed.
PDE5 Inhibitors used for the treatment of pulmonary arterial hypertension Concomitant use of EVOTAZ and PDE-5 inhibitors may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances, and priapism.		
sildenafil	↑sildenafil	Sildenafil: when used for the treatment of pulmonary hypertension (PAH) is contraindicated with EVOTAZ (see 4.3 Contraindications).
tadalafil	↑tadalafil	The following guidelines are recommended when tadalafil (used for the treatment of pulmonary arterial hypertension) is co-administered with EVOTAZ: *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. *For patients receiving tadalafil:* Avoid the use of tadalafil when starting EVOTAZ and 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.
PDE5 inhibitors used for the treatment of erectile dysfunction		
sildenafil tadalafil vardenafil	↑sildenafil ↑tadalafil ↑vardenafil	The following guidelines are recommended when these PDE5 inhibitors (used for the treatment of erectile dysfunction) are co-administered with EVOTAZ: *Increase monitoring for PDE5 inhibitor-associated adverse events:* - sildenafil at a single dose not exceeding 25 mg in 48 hours. - vardenafil at a single dose not exceeding 2.5 mg in 72 hours. - tadalafil at a single dose not exceeding 10 mg in 72 hours.
Proton-Pump Inhibitors		

Table 1: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Specific Drugs	Effect on Concentration	Clinical Comment
omeprazole	↓ atazanavir	Proton-pump inhibitors are expected to decrease atazanavir plasma concentration In treatment-naive patients, administer EVOTAZ a minimum of 12 hours after administration of the proton pump inhibitor. The dose of the proton pump inhibitor should not exceed a dose comparable to omeprazole 20 mg daily. In treatment-experienced patients, co-administration of EVOTAZ with proton pump inhibitors is not recommended.
Sedatives/hypnotics		
midazolam triazolam	↑midazolam ↑triazolam	*Parenteral midazolam:* Caution should be used with co-administration of EVOTAZ and parenteral midazolam. No data are available on concomitant use of EVOTAZ with intravenous midazolam; data from concomitant use of other protease inhibitors suggest a possible 3–4 fold increase in midazolam plasma levels. If EVOTAZ is co-administered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered. *Oral midazolam:* Midazolam is extensively metabolised by CYP3A4. Although not studied, co-administration of midazolam with EVOTAZ may cause a large increase in the concentration of midazolam. By extrapolation of data observed with other CYP3A4 inhibitors, increases in benzodiazepine concentration are expected to be significantly higher with oral administration of the benzodiazepine, relative to parenteral administration. EVOTAZ is contraindicated with orally administered midazolam (see 4.3 Contraindications). *Triazolam:* EVOTAZ is contraindicated with triazolam (see 4.3 Contraindications).
buspirone diazepam zolpidem (oral)	↑sedative /hypnotics	For sedatives other than those listed as contraindicated (triazolam, oral midazolam), a dose reduction of the sedative may be necessary and concentration monitoring is recommended.

Based on known metabolic profiles, clinically significant drug interactions are not expected between atazanavir and fluvastatin, dapsone, trimethoprim/sulfamethoxazole and azithromycin. There were no clinically significant drug interactions observed when atazanavir, a component of EVOTAZ, was coadministered with fluconazole paracetamol or atenolol. Atazanavir does not interact with substrates of CYP2D6 (eg, nortriptyline, desipramine, metoprolol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Atazanavir: Atazanavir produced no effects on mating, fertility, or early embryonic development in rats at doses that provided exposures up to two times the exposure in humans given atazanavir at 400 mg once daily. Altered oestrus cycles were observed in female rats treated with oral doses resulting in similar estimated systemic drug exposures (AUC).

Cobicistat: Cobicistat did not affect mating, fertility, or early embryonic development in rats at exposures approximately three times the exposure in humans given 150 mg once daily. Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) approximately similar to human exposures at the recommended 150 mg daily dose.

Use in pregnancy

Pregnancy Category B2.

***Antiretroviral Pregnancy Registry*:** To monitor maternal-fetal outcomes of pregnant women exposed to atazanavir, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1800 067 567.

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

EVOTAZ is not recommended during pregnancy nor should it be initiated in pregnant patients (see 4.2 Dose and method of administration - Pregnancy); an alternative regimen is recommended. Pharmacokinetic data from studies conducted in pregnant women receiving cobicistat showed substantially lower exposures during the second and third trimesters, compared to postpartum, and consequently of the co-administered antiretroviral agent, including atazanavir. Consult the full prescribing information for cobicistat. Pharmacokinetic data from the evaluation of EVOTAZ in a limited number of pregnant women showed a similar trend in lower exposures of the antiretroviral component, atazanavir.

Hyperbilirubinemia occurred frequently during treatment with atazanavir. It is not known whether EVOTAZ administered to the mother during pregnancy will exacerbate physiological hyperbilirubinemia and lead to kernicterus in neonates and young infants. If EVOTAZ is used during pregnancy additional monitoring should be considered during the prepartum period.

Use in lactation.

Atazanavir has been detected in human milk. It is not known whether cobicistat is secreted in human milk. No data are available regarding atazanavir or cobicistat effects on milk production. Studies in rats have demonstrated that atazanavir and/or its metabolites and cobicistat are excreted in milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving EVOTAZ.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Experience from Clinical Trials

The safety of EVOTAZ has been established in a Phase III randomized, active-controlled clinical trial (GS-US-216-0114), in which 692 treatment-naïve patients received atazanavir boosted with cobicistat (n=344) or atazanavir boosted with ritonavir (n=348) administered with tenofovir DF/emtricitabine for at least 48 weeks. Adverse reactions for atazanavir boosted with cobicistat were consistent with the safety profile of atazanavir boosted with ritonavir. The most frequently reported adverse reactions were associated with elevated bilirubin levels. Table 2 below lists the frequency of adverse reactions

(Grade 2-4) occurring in at least 3% of patients receiving atazanavir boosted with cobicistat + tenofovir DF/emtricitabine in Study GS-US-216-0114.

Table 2: Selected Treatment-Emergent Adverse Drug Reactions[a] (Grades 2-4) Reported in ≥ 3% of Subjects Receiving Atazanavir boosted with Cobicistat + tenofovir DF/emtricitabine in Study GS-US-216-0114. (Week 48 analysis)

	Atazanavir boosted with cobicistat+ tenofovir DF/emtricitabine (n=344)	Atazanavir boosted with ritonavir + tenofovir DF/emtricitabine (n=348)
EYE DISORDERS		
Ocular icterus	3%	1%
GASTROINTESTINAL DISORDERS		
Diarrhoea	3%	5%
Nausea	4%	3%
HEPATOBILLIARY DISORDERS		
Jaundice	7%	3%
Hyperbilirubinaemia	10%	8%

NERVOUS SYSTEM DISORDERS		
Headache	4%	3%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drugs

Laboratory Abnormalities:

The frequency of treatment-emergent laboratory abnormalities (Grade 3-4) occurring in at least 3% of patients receiving atazanavir boosted with cobicistat + tenofovir DF/emtricitabine in Study GS-US-216-0114 are presented in Table 3.

Table 3: Laboratory Abnormalities (Grades 3-4) Reported in ≥ 3% of Patients Receiving Atazanavir boosted with Cobicistat + tenofovir DF/emtricitabine in Study GS-US-216-0114 (Week 48 analysis)

Laboratory Parameter Abnormality:	**Atazanavir boosted with cobicistat + tenofovir DF/emtricitabine (n=344)**	**Atazanavir boosted with ritonavir + tenofovir DF/emtricitabine (n=348)**
Total Bilirubin (> 2.5 × ULN)	65%	57%
Creatine Kinase (≥ 10.0 x ULN)	6%	6%
Serum Amylase[a] (> 2.0 × ULN)	3%	2%
ALT (> 5.0 x ULN)	3%	2%
Urine RBC (Haematuria) (> 75 RBC/HPF)	4%	2%

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

Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. An increase in serum creatinine due to cobicistat's inhibitory effect generally does not exceed 35 µmol/L from baseline. In Study GS-US-216-114, decreases in estimated creatinine clearance occurred early in treatment with cobicistat, after which they stabilized. The mean (± SD) change in estimated glomerular filtration rate (eGFR) by Cockcroft-Gault method after 48 weeks of treatment was -13.4 ± 15.2 mL/min in the atazanavir boosted with cobicistat + tenofovir DF/emtricitabine group and -8.7 ± 14.5 mL/min in the atazanavir boosted with ritonavir + tenofovir DF/emtricitabine group.

Serum Lipids:

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

Table 4: Lipid Values, Mean Change from Baseline, Reported in Patients Receiving Atazanavir boosted with Cobicistat + tenofovir DF/emtricitabine or Atazanavir boosted with Ritonavir + tenofovir DF/emtricitabine in Study GS-US-216-0114 (Week 48 analysis)

	Cobicistat-boosted atazanavir + tenofovir DF/emtricitabine		**Ritonavir-boosted atazanavir + tenofovir DF/emtricitabine**	
	Baseline	Week 48	Baseline	Week 48
	Mean (mg/nmol/L)	Mean (Change from baseline mg/nmol/L[a])	Mean (mg/nmol/L)	Mean (Change from baseline mg/nmol/L[a])
Total Cholesterol (fasted)	4 [N=323]	0.1 [N=278]	4 [N=328]	0.2 [N=287]
HDL-cholesterol (fasted)	1 [N=322]	0. 1 [N=277]	1 [N=328]	0.1 [N=287]
LDL-cholesterol (fasted)	3 [N=322]	0.2 [N=278]	3 [N=328]	0.2 [N=288]
Triglycerides (fasted)	1.4 [N=323]	0.2 [N=278]	1.5 [N=328]	0.4 [N=287]

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

Postmarketing experience

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

Cardiac disorders and vascular disorders:	second degree AV block, third-degree AV block, QTc prolongation, Torsades de pointes
Metabolism and nutrition disorders:	hyperglycemia, diabetes mellitus
Renal and urinary disorders:	nephrolithiasis, interstitial nephritis, chronic kidney disease
Hepatobiliary disorders:	cholelithiasis, cholecystitis, cholestasis
Skin and subcutaneous tissue disorders:	angioedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

Atazanavir: Human experience of acute overdose with atazanavir is limited. Single doses up to 1200 mg have been taken by healthy volunteers without symptomatic untoward effects. A single self-administered overdose of 29.2 g of atazanavir in a HIV-infected patient (73 times the 400 mg recommended dose) was associated with asymptomatic bifascicular block and PR interval prolongation. These events resolved spontaneously. At high doses that lead to high drug exposures, jaundice, predominantly due to indirect (unconjugated) hyperbilirubinemia (without associated liver function test changes) or cardiac conduction abnormalities, including PR and/or QT interval prolongations, may be observed (see 4.4 Special warnings and precautions for use and 4.8 Adverse effects (Undesirable effects)).

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

For information on the management of overdose, contact the Poison Information Centre on 131 126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

EVOTAZ is a fixed dose combination of the HIV-1 antiviral drug atazanavir sulfate boosted by the pharmacokinetic enhancer cobicistat. Atazanavir is an azapeptide HIV-1 protease inhibitor. The compound selectively inhibits the virus-specific processing of viral gag-pol proteins in HIV-1 infected cells, thus preventing formation of mature virions and infection of other cells. Cobicistat is a selective, mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates, such as atazanavir or darunavir, where bioavailability is limited and half-life is shortened due to CYP3A-dependent metabolism.

Clinical trials

There have been no clinical efficacy studies conducted with EVOTAZ, however the bioequivalence of EVOTAZ with co-administered atazanavir and cobicistat was demonstrated.

The safety and efficacy of atazanavir with cobicistat in HIV-1 infected patients were evaluated in a randomized, double-blind, active-controlled Phase III trial (Study GS-US-216-0114) in HIV-1 infected patients with baseline estimated creatinine clearance above 70 mL/min who were treatment-naïve (n=692). In Study GS-US-216-0114, patients were randomized in a 1:1 ratio to receive either atazanavir 300 mg + cobicistat 150 mg once daily or atazanavir 300 mg + ritonavir 100 mg once daily, each administered with a fixed background regimen (BR) containing tenofovir DF 300 mg and emtricitabine 200 mg administered as single tablet. Randomization was stratified by screening HIV-1 RNA level (≤ 100,000 copies/mL or >100,000 copies/mL). The mean age of patients 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 of patients had baseline viral loads > 100,000 copies/mL. Treatment outcomes at 48 weeks are presented in Table 5.

Table 5: Virologic Outcomes of Randomized Treatment of Study 114 at Week 48[a]

	Atazanavir + cobicistat + tenofovir DF/emtricitabine (n=344)	Atazanavir + ritonavir + tenofovir DF/emtricitabine (n=348)
Virologic Success		
HIV-1 RNA <50 copies/mL	85%	87%
Treatment Difference[b]	−2.2% (95% Cl = −7.4%, 3.0%)	
Virologic Failure[c]	6%	4%
No Virologic Data at Week 48 Window	17%	19%
Discontinued Study Drug Due to AE or Death[d]	6%	7%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL[e]	3%	2%
Missing Data During Window but on Study Drug	0%	0%

a. Week 48 window is between Day 309 and 378 (inclusive)

b The treatment difference was stratified by baseline HIV-1 RNA (HIV-1 RNA ≤ 100,000 copies/mL or > 100,000 copies/mL)

c. Includes patients who had ≥50 copies/mL in the Week 48 window, patients who discontinued early due to lack or loss of efficacy, patients 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.

d. Includes patients 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.

e. Includes patients who discontinued for reasons other than an adverse event, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Atazanavir + cobicistat + tenofovir DF/emtricitabine was non-inferior in achieving HIV-1 RNA <50 copies/mL when compared to atazanavir + ritonavir + tenofovir DF/emtricitabine. In Study GS-US-216-0114, the mean increase from baseline in CD4+ cell count at Week 48 was 213 cells/mm^3 in patients receiving atazanavir + cobicistat + tenofovir DF/emtricitabine and 219 cells/mm^3 in patients receiving atazanavir + ritonavir + tenofovir DF/emtricitabine.

5.2 PHARMACOKINETIC PROPERTIES

One EVOTAZ tablet is bioequivalent to one atazanavir capsule (300 mg) plus one cobicistat tablet (150 mg) following single, oral dose administration with a light meal in healthy subjects (n=62).

The effect of cobicistat on atazanavir pharmacokinetics was demonstrated in the pharmacokinetic substudy (n=48) of the Phase III Study GS-US-216-0114 in which HIV-1 infected patients received atazanavir + cobicistat or atazanavir + ritonavir, both in combination with tenofovir disoproxil fumarate (DF) 300 mg/emtricitabine 200 mg. The steady-state pharmacokinetic parameters of atazanavir were comparable when boosted with cobicistat versus ritonavir as shown in Table 6 (see 5.1 Pharmacodynamic properties: Clinical trials).

Table 6: Pharmacokinetic Parameters (mean ± SD) of Atazanavir in the Pharmacokinetic Substudy of Study 114.

Parameter	Atazanavir and cobicistat with tenofovir DF/emtricitabine (n=22)	Atazanavir and ritonavir with tenofovir DF/emtricitabine (n=26)
AUC (µg.h/mL)	46.13 ± 26.18	47.59 ± 24.39
Cmax (µg/mL)	3.91 ± 1.94	4.76 ± 1.94
Ctau (µg/mL)	0.80 ± 0.72	0.85 ± 0.72

Absorption

Atazanavir: The steady-state atazanavir C_{max}, AUC_{tau}, and C_{tau} (mean ± SD) following multiple doses of atazanavir 300 mg with cobicistat 150 mg once daily in HIV-infected subjects (n = 22) with a light meal were 3.9 ± 1.9 µg/mL, 46.1 ± 26.2 µg·hr/mL, and 0.80 ± 0.72 µg/mL, respectively, and median T_{max} was approximately 3.5 hours post-dose.

Cobicistat: In a trial where subjects were instructed to take co-administered 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 (1038 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. Atazanavir C_{max} and AUCs after a high fat meal decreased 36% and 25%, respectively, in comparison to a light meal; however the 24-hour atazanavir concentration was similar when EVOTAZ was given with a light meal or a high fat meal.

Distribution

Atazanavir: Atazanavir was approximately 86% bound to human serum proteins over a concentration range of 100 to 10,000 ng/ml. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively, at 1,000 ng/ml).

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

Metabolism

Atazanavir: studies in humans and *in vitro* studies using human liver microsomes have demonstrated that atazanavir is principally metabolised by CYP3A4 isozyme to oxygenated metabolites which are then excreted in the bile as either free or glucuronidated metabolites. Additional minor metabolic pathways consist of N-dealkylation and hydrolysis. Two metabolites of atazanavir, possessing no anti-HIV activity, have been detected in the systemic circulation.

Cobicistat: Cobicistat is metabolized via CYP3A (major)- and CYP2D6 (minor)-mediated oxidation and does not undergo glucuronidation.

Excretion

Atazanavir: Following a single 400 mg dose of ^{14}C-atazanavir, 79% and 13% of the total radioactivity was recovered in the faeces and urine, respectively. Approximately 26% of the radioactivity in the faeces was due to parent drug, corresponding to 20% of the dose, and 44% of the radioactivity in the urine was due to parent drug, corresponding to 7% of the dose. The mean elimination half-life of atazanavir in healthy volunteers and HIV-infected patients adult patients was approximately 7 hours at steady state following a dose of 400mg daily with a light meal.

Cobicistat: Following oral administration of ^{14}C cobicistat, 99% of circulating radioactivity in plasma was unchanged cobicistat. Low levels of metabolites are observed in urine and faeces and do not contribute to the CYP3A inhibitory activity of cobicistat. Eighty-six percent and 8.2% of the dose were recovered in faeces and urine, respectively. The median terminal plasma half-life of cobicistat following administration of cobicistat is approximately 3.5 hours.

Pharmacokinetics in Special Populations

Hepatic Impairment

EVOTAZ is not recommended in patients with hepatic impairment. The impact of hepatic impairment on the pharmacokinetics of the combination of atazanavir and cobicistat has not been assessed.

Atazanavir: Atazanavir is metabolised and eliminated primarily by the liver. Atazanavir has been studied in adult patients with moderate to severe hepatic impairment after a single 400 mg dose. The mean AUC (0-∞) was 42% greater in patients with impaired hepatic function than in healthy volunteers. The mean half-life of atazanavir in hepatically impaired patients was 12.1 hours compared to 6.4 hours in healthy volunteers (see 4.3 Contraindications, 4.4 Special warnings and precautions for use, and 4.2 Dose and method of administration).

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

Renal Impairment

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; estimated creatinine clearance <30 mL/min using 24 hour urinary creatinine and serum creatinine levels), including those on haemodialysis, at multiple doses of 400mg 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 haemodialysis (n=10), than in age, weight, and gender matched subjects with normal renal function. Atazanavir was not appreciably cleared during haemodialysis. In a 4-hour dialysis session, 2.1% of the administered dose was removed. When atazanavir was administered either prior to, or following haemodialysis (n=10), the geometric means for C_{max} were 25% and 37% lower, AUC were 28% and 42% lower, and C_{min} were 43% and 54% lower, respectively, compared to subjects with normal renal function. The mechanism of this decrease is unknown (see 4.2 Dose and method of administration).

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 meaningful differences in cobicistat pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects, consistent with low renal clearance of cobicistat.

Age, Gender, and Race

The pharmacokinetics of atazanavir or cobicistat in elderly (65 years of age and older) have not been fully evaluated. No clinically important differences in atazanavir pharmacokinetics were observed based on age or gender. No clinically relevant differences in cobicistat pharmacokinetics were observed based on race or gender.

Hepatitis B and/or hepatitis C virus co-infection:

Pharmacokinetics of cobicistat have not been fully evaluated in the hepatitis B and/or C co-infection patients.

Antiviral activity in vitro:

Atazanavir exhibits anti-HIV-1 activity (EC_{50} of 2.6 to 5.3 nM) against a variety of HIV isolates in the absence of human serum. Atazanvir administered 400 mg once daily results in a mean (SD) C_{min} of 250 (175) ng/ml. The estimated protein-adjusted (in 40% human serum) C_{min} is approximately 17 to 98 fold higher than a representative EC_{50}. Combinations of atazanavir with stavudine, didanosine, lamivudine, zidovudine, nelfinavir, indinavir, ritonavir, saquinavir, or amprenavir in HIV-infected peripheral blood mononuclear cells yielded additive antiviral effects. Combinations of drug pairs did not result in antagonistic anti-HIV activity or enhanced cytotoxic effects at the highest concentrations used for antiviral evaluation.

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

Resistance in vitro:

HIV–1 isolates with reduced susceptibility to atazanavir (93- to 183-fold resistant) from three different viral strains were selected *in vitro*. The mutations in these HIV–1 viruses that appeared to contribute to atazanavir resistance included N88S, I50L, I84V, A71V, and M46I. Changes were also observed at the protease cleavage sites following drug selection. The I50L substitution, with or without an A71V substitution, conferred atazanavir resistance in recombinant viral clones in a variety of genetic backgrounds. Recombinant viruses containing the I50L mutation were growth impaired and showed increased susceptibility to other protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir).

Resistance in vivo:

Clinical Studies of Treatment-Naive Patients Receiving Atazanavir 300 mg With Cobicistat 150 mg: In an analysis of treatment-failure subjects who received atazanavir co-administered 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:

Atazanavir susceptibility was evaluated *in vitro* using a diverse panel of 551 clinical isolates from patients without prior atazanavir exposure. The isolates exhibited resistance to at least one approved protease inhibitor, with resistance defined as ≥2.5-fold change in EC_{50} relative to a reference strain. Greater than 80% of the isolates resistant to 1 or 2 protease inhibitors (with the majority resistant to nelfinavir) retained susceptibility to atazanavir despite the presence of key mutations (eg, D30N) associated with protease inhibitor resistance. Of 104 isolates displaying nelfinavir-specific resistance, 84 retained susceptibility to atazanavir. There was a clear trend toward decreased atazanavir susceptibility as isolates exhibited resistance to multiple protease inhibitors. Baseline phenotypic and

genotypic analyses of clinical isolates from atazanavir clinical trials of protease inhibitor-experienced subjects showed that isolates cross-resistant to multiple protease inhibitors were also highly cross-resistant (61%-95%) to atazanavir. Greater than 90% of the isolates containing mutations I84V or G48V were resistant to atazanavir. Greater than 60% of isolates containing L90M, A71V/T, M46I, or a change at V82 were resistant to atazanavir, and 38% of isolates containing a D30N mutation in addition to other changes were resistant to atazanavir. Atazanavir-resistant isolates were highly cross-resistant (51%-100%) to other protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). The I50L and I50V substitutions yielded selective resistance to atazanavir and amprenavir, respectively, and did not appear to confer cross-resistance.

Electrocardiogram

Atazanavir: Concentration- and dose-dependent prolongation of the PR interval in the electrocardiogram has been observed in healthy volunteers receiving atazanavir in a clinical pharmacology study (study 076), in which oral doses of 400mg and 800mg were compared with placebo in 72 healthy subjects. The mean (±SD) maximum change in PR interval from the predose value was 24 (±15) msec following oral dosing with 400mg of atazanavir (n=65) and 60 (±25) msec following oral dosing with 800mg of atazanavir (n=65) compared to 13 (±11) msec following dosing with placebo (n=67). The PR interval prolongations in this study were asymptomatic. There is limited information on the potential for a pharmacodynamic interaction in humans between atazanavir and other drugs that prolong the PR interval of the electrocardiogram. (see 4.4 Special warnings and precautions for use). In the placebo-controlled study 076, there was no concentration-dependent effect of atazanavir on the QTc interval (using Fridericia's correction). For HIV-infected patients in study 045 treated with atazanavir + ritonavir, atazanavir + saquinavir, or lopinavir + ritonavir, each with tenofovir and an NRTI (see 5.1 Pharmacodynamic properties – Clinical Trials), no female patients had a QTc interval >470 msec and two male patients has a QTc interval of 450-500 msec. No patients receiving atazanavir + ritonavir, 2 (2%) patients receiving atazanavir + saquinavir, and 1 (<1%) patient receiving lopinavir + ritonavir had an on-study change in QTc > 60 msec. No atazanavir-treated healthy subject or HIV-infected patient had a QTc interval > 500 msec.

Cobicistat: The electrocardiographic effects of cobicistat were determined in a study of 48 healthy adult patients. Cobicistat did not prolong QTcF interval at doses of 250 mg and 400 mg, providing exposures 2- and 4-fold above the recommended therapeutic dose. A modest increase in PR interval (+9.6 msec) occurred around C_{max}, 3 to 5 hours after dosing. This finding was not considered to be clinically significant.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Atazanavir: Atazanavir was negative in reverse-mutation assays in bacteria and in *in vivo* micronucleus and *ex vivo* DNA repair tests in rats. In an *in vitro* primary human lymphocyte cytogenetic assay, atazanavir increased the frequency of chromosome aberrations at cytotoxic concentrations in the absence and presence of metabolic activation. However, atazanavir did not induce chromosome aberrations in the absence and presence of metabolic activation at concentrations that were approximately 3 and 22 times the C_{max}, respectively, and 12 and 98 times the average steady-state concentration, respectively, in humans given the recommended dose. In *in vivo* studies in rats, atazanavir did not induce micronuclei in bone marrow, DNA damage in duodenum (comet assay), or unscheduled DNA repair in liver at plasma and tissue concentrations exceeding those that were clastogenic *in vitro.*

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

Carcinogenicity

Atazanavir: Carcinogenicity studies with atazanavir were conducted in mice and rats. Mice were administered doses of 20, 40, and 80 mg/kg/day in males and 40, 120, and 360 mg/kg/day in females. In female mice, there was an increase in the incidences of benign hepatocellular adenomas at the highest dose. The exposure in female mice at the high dose is approximately seven times exposure in humans given atazanavir 400 mg once daily. No increase in the incidence of tumors was observed in female mice at nontumorigenic doses or male mice at any dose. Exposures in male and female mice at nontumorigenic doses are approximately four times human exposure at 400 mg/day. In rats administered doses of 100, 350, and 1200 mg/kg/day, there was no increased incidence of any tumor type. Exposures in rats at the highest dose are approximately two (males) and six (females) times the exposure in humans given atazanavir 400 mg daily. The increased incidence of benign hepatic adenomas in high-dose female mice was likely the result of increased hepatocellular proliferation secondary to cytotoxic liver changes (single-cell necrosis) and is considered unlikely to have clinical relevance at human therapeutic exposures.

Cobicistat: In a long-term carcinogenicity study in mice, no drug-related increases in tumour 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.

Fetal-Risk Summary

Atazanavir: No teratogenic effects were observed in rabbits exposed to a comparable human dose of 400mg daily. No teratogenic effects were observed in rats exposed to the human equivalent of 800mg daily. In the pre- and postnatal development assessment of rats, transient weight loss or suppression of weight gain occurred in the offspring at maternally toxic doses. Offspring were unaffected at a lower dose which produced maternal exposure equivalent to that observed in humans given 400mg twice daily. Transient reductions in offspring body weights were observed in a pre- and post-natal development study in rats, at a dose that resulted in a systemic drug exposure (AUC) that was approximately 2-fold higher than that expected in humans given the recommended dose.

Cobicistat: In a rat study, foetal development was unaffected by an oral dose of cobicstat resulting in a drug exposure (AUC) that was 1.9-fold higher than in humans receiving the 150 mg daily dose. There was a tendency for reduced foetal weight and increases in skeletal variations with a higher dose that was associated with reduced maternal food consumption and bodyweight gain. Treatment of rabbits with a dose resulting in a drug exposure approximately 3 times that in humans receiving the 150 mg daily dose did not affect foetal development.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core: microcrystalline cellulose, croscarmellose sodium, sodium starch glycollate, crospovidone, stearic acid, magnesium stearate, hydroxypropylcellulose, and silicon dioxide.

Film-coating: hypromellose, titanium dioxide, purified talc, glycerol triacetate, and iron oxide red.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging

6.4 SPECIAL PRECAUTIONS FOR STORAGE

EVOTAZ should be stored below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

EVOTAZ is supplied in a high density polyethylene (HDPE) bottle.

Each bottle contains 30 tablets, a silica gel desiccant and is closed with a child-resistant closure.

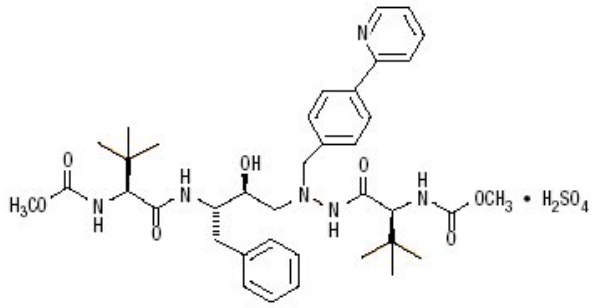
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Atazanavir: 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). Atazanavir sulfate has the following structural formula:

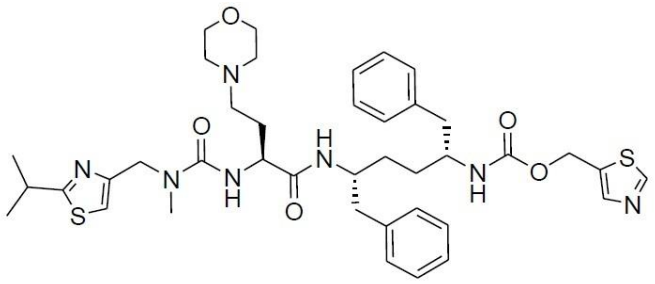


Molecular formula: $C_{38}H_{52}N_6O_7.H_2SO_4$

Molecular mass: 802.9 (sulfate): 704.9 (free base).

Atazanavir sulfate is a white to pale yellow crystalline powder with a solubility of 4 to 5 mg/mL free base equivalents in water at 24°C. The partition coefficient (log $P_{o/b}$) for atazanavir sulfate is 3.8 (pH of aqueous medium: 7.0 (sodium phosphate buffer)) and the pKa is 4.7.

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 the following structural formula:



Molecular formula: $C_{40}H_{53}N_7O_5S_2$.

Molecular mass: 776.0.

Cobicistat is a white to pale yellow solid with a solubility of 0.1 mg/mL in water at 20°C. The partition coefficient of cobicistat is 4.3 (*n*-octanol/phosphate buffer pH 8.5) and the pKa are 1.8, 2.5 and 6.4.

CAS number

Atazanavir: CAS Registry No: 229975-97-7

Cobicistat: CAS Registry No: 1004316-88-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

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Victoria 3170, Australia.
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9 DATE OF FIRST APPROVAL (ARTG ENTRY)

23 September 2015

10 DATE OF REVISION OF THE TEXT

11 October 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	New warning – EVOTAZ is not recommended for use during pregnancy, and should not be initiated in pregnant patients.
4.3	New contraindicated medication: *Other lipid-modifying agents: lomitapide.* Minor editorial change: *Lipid-modifying agents:* HMG-CoA reductase inhibitors: lovastatin, simvastatin.
4.5, Table 1	Minor editorial change – new subheading "*Direct-acting oral anticoagulants (DOACS)"*.

	Minor editorial change – new subheading "*Vitamin K antagonists"*. Minor editorial change – warfarin narrative relocated to end of "*Direct-acting oral anticoagulants (DOACS)"* subheading narrative. Addition of potentially significant drug interactions for EVOTAZ under "*Direct-acting oral anticoagulants (DOACS)"* subheading: - Apixaban - Dabigatran - Betrixaban - Edoxaban New heading preceding "HMG-CoA Reductase Inhibitors: *"Lipid-Modifying Agents"*.
4.6	Revised narrative – EVOTAZ is not recommended during pregnancy nor should it be initiated in pregnant patients.

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