ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EVOTAZ 300 mg/150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains atazanavir sulphate corresponding to 300 mg atazanavir and 150 mg of cobicistat.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Pink, oval, biconvex, film-coated tablet of approximate dimensions of 19 mm x 10.4 mm, 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 medicinal products for the treatment of HIV-1 infected adults and adolescents (aged 12 years and older weighing at least 35 kg) without known mutations associated with resistance to atazanavir (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

The recommended dose of EVOTAZ for adults and adolescents (aged 12 years and older weighing at least 35 kg) is one tablet once daily taken orally with food (see section 5.2).

Advice on missed doses
If EVOTAZ is missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of EVOTAZ with food as soon as possible. If this is noticed later than 12 hours of the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

Special populations

Renal impairment
Based on the very limited renal elimination of cobicistat and atazanavir, no special precautions or dose adjustments of EVOTAZ are required for patients with renal impairment.

EVOTAZ is not recommended for patients undergoing haemodialysis (see sections 4.4 and 5.2).

Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. EVOTAZ should not be

initiated in patients with creatinine clearance less than 70 ml/min if any co-administered medicinal product (e.g. emtricitabine, lamivudine, tenofovir disoproxil or adefovir) requires dose adjustment based on creatinine clearance (see sections 4.4, 4.8 and 5.2).

Hepatic impairment
There are no pharmacokinetic data regarding the use of EVOTAZ in patients with hepatic impairment.

Atazanavir and cobicistat are metabolised by the hepatic system. Atazanavir should be used with caution in patients with mild (Child-Pugh Class A) hepatic impairment. However, atazanavir must not be used in patients with moderate (Child-Pugh Class B) to severe (Child-Pugh Class C) hepatic impairment. No dose adjustment of cobicistat is required in patients with mild or moderate hepatic impairment. Cobicistat has not been studied in patients with severe hepatic impairment and is not recommended in these patients.

EVOTAZ should be used with caution in patients with mild hepatic impairment. EVOTAZ must not be used in patients with moderate to severe hepatic impairment (see section 4.3).

Paediatric population

Children from birth to 3 months of age
EVOTAZ should not be used in children less than 3 months of age because of safety concerns especially taking into account the potential risk of kernicterus associated with the atazanavir component.

Children from 3 months to <12 years of age or weighing < 35 kg
The safety and efficacy of EVOTAZ in children less than 12 years of age or weighing less than 35 kg have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

Pregnancy and postpartum
Treatment with EVOTAZ during pregnancy results in low atazanavir exposure. Therefore, therapy with EVOTAZ should not be initiated during pregnancy, and women who become pregnant during therapy with EVOTAZ should be switched to an alternative regimen (see sections 4.4 and 4.6).

Method of administration

EVOTAZ is to be taken orally with food (see section 5.2). The film-coated tablet should be swallowed whole and must not be chewed, broken, cut or crushed.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Co-administration with the following medicinal products that are strong inducers of the CYP3A4 isoform of cytochrome P450 due to the potential for loss of therapeutic effect (see section 4.5):
- carbamazepine, phenobarbital, phenytoin (antiepileptics)
- St John's wort (*Hypericum perforatum*) (herbal product)
- rifampicin (antimycobacterial)

Co-administration with the following medicinal products due to the potential for serious and/or life-threatening adverse reactions (see section 4.5):
- colchicine, when used in patients with renal and/or hepatic impairment (antigout) (see section 4.5)

- sildenafil - when used for the treatment of pulmonary arterial hypertension (see sections 4.4 and 4.5 for co-administration for the treatment of erectile dysfunction), avanafil (PDE5 inhibitors)
- dabigatran (anticoagulant)
- simvastatin and lovastatin (HMG-CoA reductase inhibitors) (see section 4.5)
- lomitapide (lipid-modifying agent)
- grazoprevir-containing products, including elbasvir/grazoprevir fixed dose combination (used to treat chronic hepatitis C infection) (see section 4.5)
- glecaprevir/pibrentasvir fixed dose combination (see section 4.5)
- substrates of CYP3A4 or the UGT1A1 isoform of UDP-glucuronyltransferase and have narrow therapeutic windows:
  - alfuzosin (alpha-1-adrenoreceptor antagonist)
  - amiodarone, bepridil, dronedarone, quinidine, systemic lidocaine (antiarrhythmics/antianginals)
  - astemizole, terfenadine (antihistamines)
  - cisapride (gastrointestinal motility agent)
  - ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
  - pimozide, quetiapine, lurasidone (antipsychotics/neuroleptics) (see section 4.5)
  - ticagrelor (platelet aggregation inhibitor)
  - triazolam, midazolam administered orally (sedatives/hypnotics) (for caution on parenterally administered midazolam, see section 4.5).

Moderate to severe hepatic impairment.

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

The choice of EVOTAZ in patients should be based on individual viral resistance testing and the patient's treatment history (see section 5.1).

Pregnancy
Treatment with atazanavir/cobicistat 300/150 mg during the second and third trimester has been shown to result in low atazanavir exposure. Cobicistat levels decrease and may not provide sufficient boosting. The substantial reduction in atazanavir exposure may result in virological failure and an increased risk of mother to child transmission of HIV infection. Therefore, therapy with EVOTAZ should not be initiated during pregnancy, and women who become pregnant during therapy with EVOTAZ should be switched to an alternative regimen (see sections 4.2 and 4.6).

Patients with co-existing conditions

Hepatic impairment
The use of EVOTAZ is contraindicated in patients with moderate to severe hepatic impairment. EVOTAZ should be used with caution in patients with mild hepatic impairment (see sections 4.2, 4.3 and 5.2).

Atazanavir
Atazanavir is primarily hepatically metabolised and increased plasma concentrations were observed in patients with hepatic impairment (see sections 4.2 and 5.2). The safety and efficacy of atazanavir have not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions (see section 4.8). In case of concomitant antiviral

therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products.

Patients with previous liver dysfunction or patients with chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Cobicistat
Cobicistat has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Renal impairment
EVOTAZ is not recommended in patients undergoing haemodialysis (see sections 4.2 and 5.2).

Effects on estimated creatinine clearance
Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine. This effect on serum creatinine, leading to a decrease in the estimated creatine clearance, should be taken into consideration when EVOTAZ is administered to patients in whom the estimated creatinine clearance is used to guide aspects of their clinical management, including adjusting doses of co-administered medicinal products. For more information consult the cobicistat Summary of Product Characteristics.

EVOTAZ should not be initiated in patients with creatinine clearance less than 70 ml/min if one or more co-administered medicinal product requires dose adjustment based on creatinine clearance (e.g. emtricitabine, lamivudine, tenofovir disoproxil or adefovir; see sections 4.2, 4.8 and 5.2).

As atazanavir and cobicistat are highly bound to plasma proteins, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis (see sections 4.2 and 5.2).

There are currently inadequate data to determine whether co-administration of tenofovir disoproxil and cobicistat is associated with a greater risk of renal adverse reactions compared with regimens that include tenofovir disoproxil without cobicistat.

QT prolongation
Dose related asymptomatic prolongations in PR interval with atazanavir, a component of EVOTAZ have been observed in clinical studies. Caution should be used with medicinal products known to induce PR prolongations. In patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), EVOTAZ should be used with caution and only if the benefits exceed the risk (see section 5.1). Particular caution should be used when prescribing EVOTAZ in association with medicinal products which have the potential to increase the QT interval and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances (see sections 4.8 and 5.3).

Haemophiliac patients
There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in type A and B haemophiliac patients 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 if treatment had been discontinued. A causal relationship has been suggested, although the mechanism of action has not been elucidated. Haemophiliac patients should, therefore, be made aware of the possibility of increased bleeding.

<u>Weight and metabolic parameters</u>

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to the disease control and life style. For lipids, there is in

some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose, reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

In clinical studies, atazanavir has been shown to induce dyslipidaemia to a lesser extent than comparators.

Hyperbilirubinaemia

Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving atazanavir (see section 4.8). Hepatic transaminase elevations that occur with elevated bilirubin in patients receiving EVOTAZ should be evaluated for alternative aetiologies. Alternative antiretroviral therapy to EVOTAZ may be considered if jaundice or scleral icterus is unacceptable to a patient.

Indinavir is also associated with indirect (unconjugated) hyperbilirubinaemia due to inhibition of UGT. Combinations of EVOTAZ and indinavir have not been studied and co-administration of these medicinal products is not recommended (see section 4.5).

Cholelithiasis

Cholelithiasis has been reported in patients receiving atazanavir (see section 4.8). Some patients required hospitalisation for additional management and some had complications. If signs or symptoms of cholelithiasis occurs, temporary interruption or discontinuation of treatment may be considered.

Chronic kidney disease

Chronic kidney disease in HIV-infected patients treated with atazanavir, with or without ritonavir, has been reported during post-marketing surveillance. A large prospective observational study has shown an association between an increased incidence of chronic kidney disease and cumulative exposure to atazanavir/ritonavir-containing regimen in HIV-infected patients with an initially normal eGFR. This association was observed independently of exposure to tenofovir disoproxil. Regular monitoring of the renal function of patients should be maintained throughout the treatment duration (see section 4.8).

Nephrolithiasis

Nephrolithiasis has been reported in patients receiving atazanavir (see section 4.8). Some patients required hospitalisation for additional management and some had complications. In some cases, nephrolithiasis has been associated with acute renal failure or renal insufficiency. If signs or symptoms of nephrolithiasis occurs, temporary interruption or discontinuation of treatment may be considered.

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) 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.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Rash and associated syndromes

Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 3 weeks of starting therapy with atazanavir, a component of EVOTAZ.

Stevens-Johnson syndrome (SJS), erythema multiforme, toxic skin eruptions and drug rash with 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. EVOTAZ or any other medicinal product containing atazanavir should be discontinued if severe rash develops.

The best results in managing these events come from early diagnosis and immediate interruption of any suspect medicines. If the patient has developed SJS or DRESS associated with the use of EVOTAZ, EVOTAZ may not be restarted.

Co-administration with antiretroviral medicinal products

EVOTAZ is indicated for use with other antiretrovirals for the treatment of HIV-1 infection. EVOTAZ should not be used in combination with products containing the same active components including atazanavir, cobicistat or with fixed-dose products that contain cobicistat. EVOTAZ should not be used in combination with another antiretroviral that requires pharmacokinetic enhancement (i.e., another protease inhibitor or elvitegravir) since dosing recommendations for such combinations have not been established and may result in decreased plasma concentrations of atazanavir and/or the other antiretroviral leading to loss of therapeutic effect and development of resistance. Co-administration of EVOTAZ with other protease inhibitors is not recommended. Because atazanavir is a component of EVOTAZ, co-administration of EVOTAZ with nevirapine or efavirenz is not recommended (see section 4.5).

EVOTAZ should not be used in combination with ritonavir or medicinal products containing ritonavir due to similar pharmacological effects of cobicistat and ritonavir on CYP3A (see section 4.5).

Interactions with other medicinal products

Atazanavir is metabolised principally by CYP3A4. Cobicistat is a strong mechanism-based CYP3A inhibitor and is a CYP3A substrate. Co-administration of EVOTAZ and medicinal products that induce CYP3A4 is contraindicated or not recommended (see sections 4.3 and 4.5) because, in addition to decreased plasma concentrations of atazanavir due to induction of CYP3A4, decreased plasma concentrations of cobicistat could result in cobicistat plasma levels that are insufficient to achieve adequate pharmacoenhancement of atazanavir.

Increased plasma concentrations of medicinal products that are metabolised by CYP3A (including atazanavir) are observed on co-administration with cobicistat. Higher plasma concentrations of co-administered medicinal products can result in increased or prolonged therapeutic effects or adverse reactions. For medicinal products metabolised by CYP3A these higher plasma concentrations may potentially lead to severe, life-threatening or fatal events (see sections 4.3 and 4.5).

Co-administration of EVOTAZ with medicinal products that inhibit CYP3A may decrease the clearance of atazanavir and cobicistat, resulting in increased atazanavir and cobicistat plasma concentrations (see section 4.5).

Unlike ritonavir, cobicistat is not an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or UGT1A1. If switching from atazanavir boosted with ritonavir to EVOTAZ, caution is required during the first two weeks of treatment with EVOTAZ, particularly if doses of any concomitantly administered medicinal products have been titrated or adjusted during use of ritonavir as a pharmacoenhancer (see section 4.5).

Cobicistat is a weak CYP2D6 inhibitor and is metabolised to a minor extent by CYP2D6. Co-administration with EVOTAZ can increase plasma concentrations of medicinal products that are metabolised by CYP2D6 (see sections 4.3 and 4.5).

Because atazanavir is a component of EVOTAZ, the combination of EVOTAZ with atorvastatin is not recommended (see section 4.5).

PDE5 inhibitors used for the treatment of erectile dysfunction
Particular caution should be used when prescribing PDE5-inhibitors (sildenafil, tadalafil, vardenafil, or avanafil) for the treatment of erectile dysfunction in patients receiving EVOTAZ. Co-administration of EVOTAZ with these medicinal products is expected to substantially increase their concentrations and may result in PDE5-associated adverse reactions such as hypotension, visual changes and priapism (see section 4.5).

Co-administration of voriconazole and EVOTAZ is not recommended unless an assessment of the benefit/risk justifies the use of voriconazole (see section 4.5).

Concomitant use of EVOTAZ and fluticasone or other glucocorticoids that are metabolized by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

Co-administration of EVOTAZ with warfarin has the potential to produce serious and/or life-threatening bleeding due to increased warfarin plasma concentrations, and it is recommended that the INR (International Normalized Ratio) be monitored (see section 4.5).

Co-administration of EVOTAZ with proton pump inhibitors (PPIs) is not recommended due to the decreased solubility of atazanavir as intra-gastric pH increase with PPIs (see section 4.5).

Contraception requirements
Plasma concentrations of drospirenone are increased following administration of drospirenone/ethinyloestradiol with atazanavir/cobicistat. If drospirenone/ethinyloestradiol is co-administered with atazanavir/cobicistat, clinical monitoring is recommended due to the potential for hyperkalemia.

Data are not available to make recommendations regarding the use of EVOTAZ with other oral contraceptives. Alternative forms of contraception (non-hormonal) should be considered (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Drug interaction trials were not conducted for EVOTAZ. As EVOTAZ contains atazanavir and cobicistat, any interactions that have been identified with these active substances individually may occur with EVOTAZ.

Complex or unknown mechanisms of drug interaction preclude extrapolation of ritonavir drug interactions to certain cobicistat drug interactions. The recommendations given for concomitant use of atazanavir and other medicinal products may, therefore, differ depending on whether atazanavir is boosted with ritonavir or cobicistat. In particular, atazanavir boosted with cobicistat is more sensitive

for CYP3A induction (see section 4.3 and the interaction table). Caution is also required during the first time of treatment if switching the pharmacoenhancer from ritonavir to cobicistat (see section 4.4).

Medicinal products that affect atazanavir/cobicistat exposure

Atazanavir is metabolised in the liver through CYP3A4.
Cobicistat is a CYP3A substrate and is metabolised to a minor extent by CYP2D6.

Concomitant use contraindicated
Co-administration of EVOTAZ with medicinal products that are strong inducers of CYP3A (such as carbamazepine, phenobarbital, phenytoin, rifampicin, and St. John's wort [*Hypericum perforatum*]) may result in decreased plasma concentrations of atazanavir and/or cobicistat, leading to loss of therapeutic effect and possible development of resistance to atazanavir (see section 4.3 and Table 1).

Concomitant use not recommended
Co-administration of EVOTAZ with medicinal products containing ritonavir or cobicistat, which are strong inhibitors of CYP3A, may result in additional boosting and increased plasma concentration of atazanavir.

Co-administration of EVOTAZ with medicinal products that inhibit CYP3A may result in increased plasma concentration of atazanavir and/or cobicistat. Some examples include, but are not limited to, itraconazole, ketoconazole and voriconazole (see Table 1).

Co-administration of EVOTAZ with medicinal products that are moderate to weak inducers of CYP3A may result in decreased plasma concentration of atazanavir and/or cobicistat, leading to loss of therapeutic effect and possible development of resistance to atazanavir. Some examples include, but are not limited to etravirine, nevirapine, efavirenz, fluticasone and bosentan (see Table 1).

Medicinal products that may be affected by atazanavir/cobicistat

Atazanavir is an inhibitor of CYP3A4 and UGT1A1. Atazanavir is a weak to moderate inhibitor of CYP2C8. Atazanavir has been shown *in vivo* not to induce its own metabolism, nor to increase the biotransformation of some medicinal products metabolised by CYP3A4.

Cobicistat is a strong mechanism-based CYP3A inhibitor and a weak CYP2D6 inhibitor. Cobicistat inhibits the transporters p-glycoprotein (P-gp), BCRP, MATE1, OATP1B1 and OATP1B3. Cobicistat is not expected to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9 or CYP2C19. Cobicistat is not expected to induce CYP3A4 or P-gp. Unlike ritonavir, cobicistat is not an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or UGT1A1.

Concomitant use contraindicated
Co-administration of medicinal products that are substrates of CYP3A and have narrow therapeutic indeces and for which elevated plasma concentrations are associated with serious and/or life-threatening events are contraindicated with EVOTAZ. These medicinal products include alfuzosin, amiodarone, astemizole, bepridil, cisapride, colchicine, dronedarone, ergot deriviatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine), lomitapide, lovastatin, orally administered midazolam, pimozide, quetiapine, quinidine, lurasidone, simvastatin, sildenafil (when used to treat pulmonary arterial hypertension), avanafil, systemic lidocaine, ticagrelor, terfenadine and triazolam.

Co-administration of EVOTAZ with grazoprevir-containing products, including elbasvir/grazoprevir fixed dose combination (used to treat chronic hepatitis C infection) is contraindicated because of the increase in grazoprevir and elbasvir plasma concentrations and potential for the increase in risk of ALT elevations associated with the increase in grazoprevir concentrations (see section 4.3 and Table 1). Co-administration of EVOTAZ with glecaprevir/pibrentasvir fixed dose combination is

contraindicated because of the potential increase in the risk of ALT elevations due to a significant increase in glecaprevir and pibrentasvir plasma concentrations (see section 4.3).

Increased plasma concentrations of medicinal products that are metabolised by CYP3A, CYP2C8, CYP2D6 and/or UGT1A1 are expected when co-administered with EVOTAZ. Co-administration of EVOTAZ in patients receiving medicinal products that are substrates of the transporters P-gp, BCRP, MATE1, OATP1B1 and OATP1B3 may result in increased plasma concentrations of the co-administered medicinal products (see section 4.4). Co-administration with dabigatran, a substrate of P-gp, is contraindicated. Clinically significant interactions between EVOTAZ and substrates of CYP1A2, CYP2B6, CYP2C9 or CYP2C19 are not expected.

Interaction table

Interactions between EVOTAZ and other medicinal products are listed in Table 1 below (increase is indicated as "↑", decrease as "↓", no change as "↔"). The recommendations shown in Table 1 are based on either drug interaction trials of unboosted atazanavir, atazanavir boosted with ritonavir, cobicistat or predicted interactions due to the expected magnitude of the interaction and potential for serious adverse reactions or loss of therapeutic effect of EVOTAZ. If available, 90% confidence intervals (CI) are shown in parentheses. The studies presented in Table 1 were conducted in healthy subjects unless otherwise noted.

Table 1: Interactions between EVOTAZ and other medicinal products

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
ANTI-HCV AGENTS		
Grazoprevir 200 mg once daily (atazanavir 300 mg / ritonavir 100 mg once daily)	Atazanavir AUC ↑43% (↑30% ↑57%) Atazanavir C_{max} ↑12% (↑1% ↑24%) Atazanavir C_{min} ↑23% (↑13% ↑134%) Grazoprevir AUC: ↑958% (↑678% ↑1339%) Grazoprevir C_{max}: ↑524% (↑342% ↑781%) Grazoprevir C_{min}: ↑1064% (↑696% ↑1602%) Grazoprevir concentrations were greatly increased when co-administered with atazanavir/ritonavir.	Co-administration of EVOTAZ and elbasvir/grazoprevir is contraindicated because of the expected increase in grazoprevir plasma concentrations and the associated potential increase in the risk of ALT elevations (see section 4.3).

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
Elbasvir 50 mg once daily **(**atazanavir 300 mg / ritonavir 100 mg once daily	Atazanavir AUC ↑7% (↓2% ↑17%) Atazanavir C_{max} ↑2% (↓4% ↑8%) Atazanavir C_{min} ↑15% (↑2% ↑29%) Elbasvir AUC: ↑376% (↑307% ↑456%) Elbasvir C_{max}: ↑315% (↑246% ↑397%) Elbasvir C_{min}: ↑545% (↑451% ↑654%) Elbasvir concentrations were increased when co-administered with atazanavir/ritonavir	
Sofosbuvir 400 mg/velpatasvir, 100 mg/voxilaprevir 100 mg single dose* **(**atazanavir 300 mg with ritonavir 100 mg once daily)	Sofosbuvir AUC : ↑40% (↑25% ↑57%) Sofosbuvir C_{max} :↑29% (↑9% ↑52%) Velpatasvir AUC: ↑93% (↑58% ↑136%) Velpatasvir C_{max} : ↑29% (↑7% ↑56%) Voxilaprevir AUC : ↑331% (↑276% ↑393%) Voxilaprevir C_{max} : ↑342% (↑265% ↑435%) *Lack of pharmacokinetics interaction bounds 70-143% Effect on atazanavir and ritonavir exposure has not been studied. Expected: ↔ Atazanavir ↔ Ritonavir The mechanism of interaction between atazanavir/ritonavir and sofosbuvir/velpatasvir/voxilaprevir is inhibition of OATP1B, Pgp, and CYP3A.	Co-administration of EVOTAZ with voxilaprevir-containing products is expected to increase the concentration of voxilaprevir. Co-administration of EVOTAZ with voxilaprevir-containing regimens is not recommended.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily (atazanavir 300 mg with ritonavir 100 mg once daily*)	Glecaprevir AUC : ↑553% (↑424% ↑714%) Glecaprevir C_{max} : ↑306% (↑215% ↑423%) Glecaprevir C_{min} : ↑1330% (↑885% ↑1970%) Pibrentasvir AUC : ↑64% (↑48% ↑82%) Pibrentasvir C_{max} : ↑29% (↑15% ↑45%) Pibrentasvir C_{min}: ↑129% (↑95% ↑168%) Atazanavir AUC : ↑11% (↑3% ↑19%) Atazanavir C_{max} : ↔ 0% (↓ 10% ↑10%) Atazanavir C_{min}: ↑16% (↑7% ↑25%) * Effect of atazanavir and ritonavir on the first dose of glecaprevir and pibrentasvir is reported.	Contraindicated because of the potential increase in the risk of ALT elevations due to a significant increase in glecaprevir and pibrentasvir plasma concentrations (see section 4.3)
ANTI-RETROVIRALS		
Protease inhibitors: EVOTAZ in combination with other protease inhibitors is not recommended because co-administration may not provide adequate protease inhibitor exposure.		
Indinavir	Indinavir is associated with indirect unconjugated hyperbilirubinaemia due to inhibition of UGT.	Co-administration of EVOTAZ and indinavir is not recommended (see section 4.4).
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)		
Lamivudine 150 mg twice daily + zidovudine 300 mg twice daily (atazanavir 400 mg once daily)	No significant effect on lamivudine and zidovudine concentrations was observed when co-administered with atazanavir.	Based on these data and because cobicistat is not expected to have a significant impact on the pharmacokinetics of NRTIs, the co-administration of EVOTAZ with these medicinal products is not expected to significantly alter the exposure of the co-administered medicinal products.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Didanosine (buffered tablets) 200 mg/stavudine 40 mg, both single dose (atazanavir 400 mg single dose)	Atazanavir, simultaneous administration with ddI+d4T (fasted) Atazanavir AUC ↓87% (↓92% ↓79%) Atazanavir C_{max} ↓89% (↓94% ↓82%) Atazanavir C_{min} ↓84% (↓90% ↓73%) Atazanavir, dosed 1 hr after ddI+d4T (fasted) Atazanavir AUC ↔3% (↓36% ↑67%) Atazanavir C_{max} ↑12% (↓33% ↑18%) Atazanavir C_{min} ↔3% (↓39% ↑73%) Atazanavir concentrations were greatly decreased when co-administered with didanosine (buffered tablets) and stavudine. The mechanism of interaction is a reduced solubility of atazanavir with increasing pH related to the presence of anti-acid agent in didanosine buffered tablets. No significant effect on didanosine and stavudine concentrations was observed.	Didanosine should be taken in the fasted state 2 hours after EVOTAZ taken with food. The co-administration of EVOTAZ with stavudine is not expected to significantly alter the exposure of stavudine.
Didanosine (enteric coated capsules) 400 mg single dose (atazanavir 400 mg once daily)	Didanosine (with food) Didanosine AUC ↓34% (↓40% ↓26%) Didanosine C_{max} ↓36% (↓45% ↓26%) Didanosine C_{min} ↑13% (↓9% ↑41%) No significant effect on atazanavir concentrations was observed when administered with enteric-coated didanosine, but administration with food decreased didanosine concentrations.	

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Tenofovir disoproxil fumarate (tenofovir DF) 300 mg once daily (atazanavir 400 mg once daily) 300 mg tenofovir disoproxil fumarate is equivalent to 245 mg tenofovir disoproxil.	Atazanavir AUC ↓25% (↓30% ↓19%) Atazanavir C_{max} ↓21% (↓27% ↓14%) Atazanavir C_{min} ↓40% (↓48% ↓32%) Tenofovir: AUC: ↑24% (↑21% ↑28%) C_{max}: ↑14% (↑8% ↑20%) C_{min}: ↑22% (↑15% ↑30%) Co-administration of tenofovir DF with cobicistat is expected to increase tenofovir plasma concentrations. Tenofovir: AUC: ↑23% C_{min}: ↑55% The mechanism of interaction between atazanavir and tenofovir DF is unknown.	Tenofovir DF may decrease the AUC and C_{min} of atazanavir. When co-administered with tenofovir DF, it is recommended that EVOTAZ and tenofovir DF 300 mg be given together with food. Atazanavir increases tenofovir concentrations. Higher concentrations could potentiate tenofovir-associated adverse reactions, including renal disorders. Patients receiving tenofovir disoproxil should be monitored for tenofovir-associated adverse reactions.
Tenofovir alafenamide 10 mg once daily/emtricitabine 200 mg once daily (atazanavir 300 mg once daily with cobicistat 150 mg once daily)	Tenofovir alafenamide AUC ↑75% (↑55% ↑98%) C_{max} ↑80% (↑48% ↑118%) Tenofovir: AUC ↑247% (↑229% ↑267%) C_{max} ↑216% (↑200% ↑233%) C_{min} ↑273% (↑254% ↑293%) Cobicistat: AUC ↑5% (↔0% ↑9%) C_{max} ↓4% (↓8% ↔0%) C_{min} ↑35% (↑21% ↑51%) Co-administration of tenofovir alafenamide with cobicistat is expected to increase tenofovir alafenamide and tenofovir plasma concentrations. Atazanavir: AUC ↑6% (↑1% ↑11%) C_{max} ↓2% (↓4% ↑2%) C_{min} ↑18% (↑6% ↑31%)	When co-administering tenofovir alafenamide/emtricitabine and EVOTAZ, the recommended dose of tenofovir alafenamide/emtricitabine is 10/200 mg once daily.
Tenofovir alafenamide 10 mg once daily (atazanavir 300 mg once daily with cobicistat 150 mg once daily)		Co-administration of EVOTAZ and tenofovir alafenamide 25 mg for treatment of HBV infection is not recommended

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg once daily (atazanavir 400 mg once daily)	Atazanavir Atazanavir AUC ↓74% (↓78% ↓68%) Atazanavir C_{max} ↓59% (↓77% ↓49%) Atazanavir C_{min} ↓93% (↓95% ↓90%)	EVOTAZ is not recommended for co-administration with efavirenz. Efavirenz decreases atazanavir concentrations and is expected to decrease cobicistat plasma concentrations. This may result in loss of therapeutic effect of EVOTAZ and development of resistance to atazanavir (see section 4.4).
Efavirenz 600 mg single dose (cobicistat 150 mg once daily)	Efavirenz: AUC: ↔7% (↓11% ↓3%) C_{max}: ↓13% (↓20% ↓6%) C_{min}: Not determined The mechanism of interaction between efavirenz and atazanavir, or efavirenz and cobicistat is CYP3A4 induction by efavirenz.	
Etravirine	Co-administration of etravirine and EVOTAZ is expected to decrease atazanavir and cobicistat plasma concentrations. The mechanism of interaction is CYP3A4 induction by etravirine.	EVOTAZ is not recommended for co-administration with etravirine because it may result in the loss of therapeutic effect and development of resistance to atazanavir.
Nevirapine 200 mg twice daily (atazanavir 300 mg once daily with ritonavir 100 mg once daily) Study conducted in HIV infected patients	Nevirapine AUC ↑25% (↑17% ↑34%) Nevirapine C_{max} ↑17% (↑9% ↑25%) Nevirapine C_{min} ↑32% (↑22% ↑43%) Atazanavir AUC ↓42% (↓52% ↓29%) Atazanavir C_{max} ↓28% (↓40% ↓14%) Atazanavir C_{min} ↓72% (↓80% ↓60%) Co-administration of nevirapine and cobicistat is expected to decrease cobicistat plasma concentrations while nevirapine plasma concentrations may be increased. The mechanism of interaction is CYP3A4 induction by nevirapine and CYP3A4 inhibition by atazanavir and cobicistat.	Co-administration of EVOTAZ and nevirapine is not recommended and 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 concentrations which may increase the risk of nevirapine-associated toxicity (see section 4.4).

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Rilpivirine	EVOTAZ is expected to increase rilpivirine plasma concentrations. The mechanism of interaction is CYP3A inhibition.	Co-administration of EVOTAZ and rilpivirine can be used without dose adjustments, as the expected increase in rilpivirine concentrations is not considered clinically relevant.
Integrase Inhibitors		
Dolutegravir	Co-administration with EVOTAZ is expected to increase dolutegravir plasma concentrations. Dolutegravir is not expected to affect the pharmacokinetics of EVOTAZ. The mechanism of interaction is inhibition of UGT1A1 by atazanavir.	EVOTAZ and dolutegravir can be used without dose adjustments.
Raltegravir 400 mg twice daily (atazanavir 400 mg)	Raltegravir AUC ↑72% Raltegravir C_{max} ↑53% Raltegravir C_{12hr} ↑95% The mechanism is UGT1A1 inhibition by atazanavir.	No dose adjustment is required for raltegravir if co-administered with EVOTAZ.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
CCR5 Antagonists		
Maraviroc	Maraviroc is a substrate of CYP3A and its plasma concentration increases when co-administered with potent CYP3A inhibitors. Maraviroc is not expected to have an impact on concentrations of atazanavir and cobicistat. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	When co-administering maraviroc and EVOTAZ, patients should receive maraviroc 150 mg twice daily. For further details, consult the Summary of Product Characteristics for maraviroc.
ANTIBIOTICS		
Clarithromycin 500 mg twice daily (atazanavir 400 mg once daily)	Clarithromycin AUC ↑94% (↑75% ↑116%) Clarithromycin C_{max} ↑50% (↑32% ↑71%) Clarithromycin C_{min} ↑160% (↑135% ↑188%) 14-OH clarithromycin 14-OH clarithromycin AUC ↓70% (↓74% ↓66%) 14-OH clarithromycin C_{max} ↓72% (↓76% ↓67%) 14-OH clarithromycin C_{min} ↓62% (↓66% ↓58%) Atazanavir AUC ↑28% (↑16% ↑43%) Atazanavir C_{max} ↔6% (↓7% ↑20%) Atazanavir C_{min} ↑91% (↑66% ↑121%) Clarithromycin may increase concentrations of atazanavir and cobicistat. Exposure to clarithromycin is expected to increase if co-administered with EVOTAZ. The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or cobicistat and clarithromycin.	Alternative antibiotics should be considered.
ANTIDIABETICS		

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Metformin	Cobicistat reversibly inhibits MATE1, and concentrations of metformin may be increased when co-administered with EVOTAZ.	Careful patient monitoring and dose adjustment of metformin is recommended in patients who are taking EVOTAZ.
ANTIFUNGALS		
Ketoconazole 200 mg once daily (atazanavir 400 mg once daily)	No significant effect on atazanavir concentrations was observed.	Caution is warranted. Specific dosing recommendations are not available for co-administration of EVOTAZ with either ketoconazole or itraconazole. If co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg.
Itraconazole	Itraconazole, like ketoconazole, is a potent inhibitor as well as a substrate of CYP3A4. Concentrations of ketoconazole, itraconazole, and/or cobicistat may be increased with co-administration of ketoconazole or itraconazole with EVOTAZ. The mechanism of interaction is CYP3A4 inhibition by atazanavir, cobicistat and ketoconazole or itraconazole.	
Voriconazole	Effects unknown	Voriconazole should not be co-administered with EVOTAZ unless the benefit/risk assessment justifies the use of voriconazole (see section 4.4). Clinical monitoring may be needed upon co-administration with EVOTAZ.
Fluconazole 200 mg once daily (atazanavir 300 mg and ritonavir 100 mg once daily)	Atazanavir and fluconazole concentrations were not significantly modified when atazanavir/ritonavir was co-administered with fluconazole. Concentration of fluconazole may be increased if co-administered with cobicistat.	Clinical monitoring is recommended upon co-administration with EVOTAZ.
ANTIGOUT		

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Colchicine	Colchicine plasma concentrations may be increased when co-administered with EVOTAZ. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	EVOTAZ must not be co-administered with colchicine to patients with renal or hepatic impairment. **Recommended dosage of colchicine when administered with EVOTAZ in patients without renal or hepatic impairment:** a dose reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with EVOTAZ is required.
ANTIMYCOBACTERIALS		

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Rifabutin 150 mg twice weekly (atazanavir 300 mg once daily with ritonavir 100 mg once daily)	Rifabutin AUC ↑48% (↑19% ↑84%)* Rifabutin C_{max} ↑149% (↑103% ↑206%)* Rifabutin C_{min} ↑40% (↑5% ↑87%)* 25-O-desacetyl-rifabutin AUC ↑990% (↑714% ↑1361%)* 25-O-desacetyl-rifabutin C_{max} ↑677% (↑513% ↑883%)* 25-O-desacetyl-rifabutin C_{min} ↑1045% (↑715% ↑1510%)* *When compared to rifabutin 150 mg once daily alone. Total rifabutin and 25-O-desacetyl-rifabutin AUC ↑119% (↑78% ↑169%).	Co-administration of EVOTAZ and rifabutin is not recommended. If the combination is needed, the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to rifabutin. Further dosage reduction of rifabutin to 150 mg twice weekly on set days is recommended for patients in whom the 150 mg dose 3 times per week is not tolerated. It should be kept in mind that the twice weekly dosage of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifamycin resistance and a treatment failure. Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV infected patients.
Rifabutin 150 mg every other day/elvitegravir 150 mg once daily/cobicistat 150 mg once daily	Cobicistat: AUC: ↔ C_{max}: ↔ C_{min}: ↓66% Rifabutin: AUC: ↔8% C_{max}: ↔9% C_{min}: ↔6% 25-O-desacetyl-rifabutin: AUC: ↑525% C_{max}: ↑384% C_{min}: ↑394% The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	
Rifampicin 600 mg once daily (atazanavir 300 mg once daily with ritonavir 100 mg once daily)	Rifampicin is a strong CYP3A4 inducer and has been shown to cause a 72% decrease in atazanavir AUC which can result in virological failure and resistance development. The mechanism of interaction is CYP3A4 induction by rifampicin.	Rifampicin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect of EVOTAZ and development of resistance to atazanavir. The combination of rifampicin and EVOTAZ is contraindicated (see section 4.3).
ACID REDUCING AGENTS		
H_2-Receptor antagonists		
Without Tenofovir		

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Famotidine 20 mg twice daily (atazanavir 300 mg/ritonavir 100 mg once daily) in HIV-infected patients	Atazanavir AUC ↓18% (↓25% ↑1%) Atazanavir C_{max} ↓20% (↓32% ↓7%) Atazanavir C_{min} ↔1% (↓16% ↑18%)	**For patients not taking tenofovir,** EVOTAZ once daily with food should be administered simultaneously with, and/or at least 10 hours after, a dose of the H_2-receptor antagonist. The dose of the H_2-receptor antagonist should not exceed a dose comparable to famotidine 20 mg twice daily.
With Tenofovir DF 300 mg once daily		
Famotidine 20 mg twice daily (atazanavir 300 mg/ritonavir 100 mg/tenofovir DF 300 mg once daily, simultaneous administration)	Atazanavir AUC ↓10% (↓18% ↓2%) Atazanavir C_{max} ↓9% (↓16% ↓1%) Atazanavir C_{min} ↓19% (↓31% ↓6%) The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with H_2 blockers.	**For patients who are taking tenofovir DF,** it is not recommended to co-administer EVOTAZ with an H_2-receptor antagonist.
Proton pump inhibitors		
Omeprazole 40 mg once daily (atazanavir 400 mg once daily, 2 hours after omeprazole)	Atazanavir AUC ↓94% (↓95% ↓93%) Atazanavir C_{max} ↓96% (↓96% ↓95%) Atazanavir C_{min} ↓95% (↓97% ↓93%)	Co-administration of EVOTAZ with proton pump inhibitors is not recommended.
Omeprazole 40 mg once daily (atazanavir 300 mg once daily with ritonavir 100 mg once daily, 2 hours after omeprazole)	Atazanavir AUC ↓76% (↓78% ↓73%) Atazanavir C_{max} ↓72% (↓76% ↓68%) Atazanavir C_{min} ↓78% (↓81% ↓74%)	
Omeprazole 20 mg once daily am (atazanavir 300 mg once daily with ritonavir 100 mg once daily pm, 12 hours after omeprazole)	Atazanavir AUC ↓42% (↓66% ↓25%) Atazanavir C_{max} ↓39% (↓64% ↓19%) Atazanavir C_{min} ↓46% (↓59% ↓29%) The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with proton pump inhibitors.	
Antacids		

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Antacids and medicinal products containing buffers	Reduced plasma concentrations of atazanavir may be the consequence of increased gastric pH if antacids, including buffered medicinal products, are administered with EVOTAZ.	EVOTAZ should be administered 2 hours before or 1 hour after antacids or buffered medicinal products.
ALPHA 1-ADRENORECEPTOR ANTAGONIST		
Alfuzosin	Potential for increased alfuzosin concentrations which can result in hypotension. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	Co-administration of EVOTAZ with alfuzosin is contraindicated (see section 4.3)
ANTICOAGULANTS		
Dabigatran	Co-administration with EVOTAZ may increase dabigatran plasma levels with similar effects as seen with other strong P-gp inhibitors. The mechanism of interaction is P-gp inhibition by cobicistat.	Co-administration of EVOTAZ with dabigatran is contraindicated (see section 4.3).
Ticagrelor	Co-administration of EVOTAZ and ticagrelor may increase concentrations of the anticoagulant. The mechanism of interaction is CYP3A and/or P-glycoprotein inhibition by atazanavir and cobicistat.	Concomitant administration of EVOTAZ with ticagrelor is contraindicated. Use of other antiplatelets not affected by CYP inhibition or induction (e.g. prasugrel) is recommended (see section 4.3).
Warfarin	Co-administration with EVOTAZ has the potential to increase warfarin plasma concentrations. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	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.
Apixaban **Edoxaban** **Rivaroxaban**	Co administration with EVOTAZ may result in increased plasma concentrations of the DOACs, which may lead to an increased risk of bleeding. The mechanism of interaction is CYP3A4 and/or P-gp inhibition by cobicistat.	Co-administration of apixaban, edoxaban or rivaroxaban is not recommended with EVOTAZ.
ANTIEPILEPTICS		

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Carbamazepine **Phenobarbital** **Phenytoin**	These antiepileptics are expected to decrease atazanavir and/or cobicistat plasma concentrations. The mechanism of interaction is CYP3A induction by the antiepileptic.	Co-administration of EVOTAZ and these antiepileptics is contraindicated (see section 4.3).
ANTIHISTAMINE AGENTS		
Astemizole **Terfenadine**	EVOTAZ must not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.	Co-administration of EVOTAZ with astemizole and terfenadine is contraindicated (see section 4.3).
ANTINEOPLASTICS AND IMMUNOSUPRESSANTS		
Antineoplastics		
Irinotecan	Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.	If EVOTAZ is co-administered with irinotecan, patients should be closely monitored for adverse reactions related to irinotecan.
Dasatinib **Nilotinib** **Vinblastine** **Vincristine**	Concentrations of these medicinal products may be increased when co-administered with EVOTAZ. The mechanism of interaction is CYP3A4 inhibition by cobicistat.	Concentrations of these medicinal products may be increased when co-administered with EVOTAZ resulting in the potential for increased adverse events usually associated with these anticancer medicinal products.
Immunosuppressants		
Ciclosporin **Tacrolimus** **Sirolimus**	Concentrations of these immunosuppressants may be increased when co-administered with EVOTAZ. The mechanism of interaction is inhibition of CYP3A4 by atazanavir and cobicistat.	More frequent therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with EVOTAZ.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
ANTIPSYCHOTICS		
Pimozide **Quetiapine** **Lurasidone**	Concentrations of these medicinal products may be increased when co-administered with EVOTAZ. The mechanism of interaction is CYP3A inhibition by atazanavir and cobicistat.	The combination of pimozide, quetiapine or lurasidone and EVOTAZ is contraindicated (see section 4.3).
CARDIOVASCULAR AGENTS		
Antiarrhythmics		
Disopyramide **Flecainide** **Mexiletine** **Propafenone**	Concentrations of these antiarrhythmics may be increased when co-administered with EVOTAZ. The mechanism of interaction is CYP3A inhibition by atazanavir and cobicistat.	Co-administration with EVOTAZ has the potential to produce serious and/or life-threatening adverse reactions. Caution is warranted and therapeutic concentration monitoring of these medicinal products is recommended if they are used concomitantly with EVOTAZ.
Amiodarone **Dronedarone** **Quinidine** **Systemic lidocaine**	Concentrations of these antiarrhythmics may be increased when co-administered with EVOTAZ. The mechanism of interaction is CYP3A inhibition by atazanavir and cobicistat.	Amiodarone, dronedarone, quinidine and systemic lidocaine have a narrow therapeutic window and are contraindicated due to potential inhibition of CYP3A by EVOTAZ (see section 4.3).
Digoxin (0.5 mg single dose)/cobicistat (150 mg multiple doses)	Plasma concentrations of digoxin may be increased when co-administered with EVOTAZ. Digoxin: AUC: ↔ C_{max}: ↑41% C_{min}: not determined The mechanism of interaction is inhibition of P-gp by cobicistat.	The peak concentration of digoxin is increased when co-administered with cobicistat. When co-administering with EVOTAZ, titrate the digoxin dose and monitor digoxin concentrations. The lowest dose of digoxin should initially be prescribed.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Antihypertensives		
Metoprolol **Timolol**	Concentrations of beta-blockers may be increased when co-administered with EVOTAZ. The mechanism of interaction is inhibition of CYP2D6 by cobicistat.	Clinical monitoring is recommended when co-administered with EVOTAZ and a dose reduction of the beta-blocker may be necessary.
Calcium channel blockers		
Bepridil	EVOTAZ must not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.	Co-administration with bepridil is contraindicated (see section 4.3).
Diltiazem 180 mg once daily (atazanavir 400 mg once daily)	Diltiazem AUC ↑125% (↑109% ↑141%) Diltiazem C_{max} ↑98% (↑78% ↑119%) Diltiazem C_{min} ↑142% (↑114% ↑173%) Desacetyl-diltiazem AUC ↑165% (↑145% ↑187%) Desacetyl-diltiazem C_{max} ↑172% (↑144% ↑203%) Desacetyl-diltiazem C_{min} ↑121% (↑102% ↑142%) No significant effect on atazanavir concentrations was observed. There was an increase in the maximum PR interval compared to atazanavir alone. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	Exposure to diltiazem and a metabolite, desacetyl-diltiazem, is increased when diltiazem is co-administered with atazanavir, a component of EVOTAZ. An initial dose reduction of diltiazem by 50% should be considered, and electrocardiogram monitoring is recommended.
Amlodipine **Felodipine** **Nicardipine** **Nifedipine** **Verapamil**	Concentrations of these calcium channel blockers may be increased when co-administered with EVOTAZ. The mechanism of interaction is inhibition of CYP3A4 by atazanavir and cobicistat.	Caution is warranted. Dose titration of the calcium channel blockers should be considered. Electrocardiogram monitoring is recommended. Clinical monitoring of therapeutic effect and adverse events is recommended when these medicinal products are co-administered with EVOTAZ.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Endothelin Receptor Antagonists		
Bosentan	Co-administration of bosentan with cobicistat may lead to decreased cobicistat plasma concentrations. The mechanism of interaction is induction of CYP3A4 by bosentan.	Atazanavir plasma concentrations may decrease as a consequence of a reduction in cobicistat plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Co-administration is not recommended (see section 4.4).
CORTICOSTEROIDS		
Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone).	Interaction not studied with any of the components of EVOTAZ. Plasma concentrations of these medicinal products may be increased when co–administered with EVOTAZ, resulting in reduced serum cortisol concentrations.	Concomitant use of EVOTAZ and corticosteroids that are metabolised by CYP3A (e.g. fluticasone propionate or other inhaled or nasal corticosteroids) may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Co-administration with CYP3A-metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects. Alternative corticosteroids which are less dependent on CYP3A metabolism, e.g. beclomethasone for intranasal or inhalational use, should be considered, particularly for long term use.
ANTIDEPRESSANTS		
Other antidepressants:		
Trazodone	Plasma concentrations of trazodone may be increased when co-administered with EVOTAZ. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	If trazodone is co-administered with EVOTAZ, the combination should be used with caution and a lower dose of trazodone should be considered.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
ERECTILE DYSFUNCTION		
PDE5 Inhibitors		
Sildenafil **Tadalafil** **Vardenafil** **Avanafil**	Sildenafil, tadalafil, and vardenafil are metabolised by CYP3A4. Co-administration with EVOTAZ may result in increased concentrations of the PDE5 inhibitor and an increase in PDE5-associated adverse events, including hypotension, visual changes, and priapism. The mechanism of this interaction is CYP3A4 inhibition by atazanavir and cobicistat.	Patients should be warned about these possible side effects when using PDE5 inhibitors for erectile dysfunction with EVOTAZ (see section 4.4). For the treatment of erectile dysfunction, it is recommended that when co-administered with EVOTAZ, sildenafil should be used with caution at reduced doses of 25 mg every 48 hours; tadalafil should be used with caution at reduced doses of 10 mg every 72 hours; vardenafil should be used with caution at reduced doses of no more than 2.5 mg every 72 hours. Increase monitoring for adverse reactions. The combination of avanafil and EVOTAZ is contraindicated (see section 4.3). Also see PULMONARY ATERIAL HYPERTENSION in this table for further information regarding co-administration of EVOTAZ with sildenafil.
HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum*)	Concomitant use of St. John's wort with EVOTAZ may be expected to result in significant reduction in plasma levels of cobicistat and atazanavir. This effect may be due to an induction of CYP3A4. There is a risk of loss of therapeutic effect and development of resistance to atazanavir (see section 4.3).	Co-administration of EVOTAZ with products containing St. John's wort is contraindicated (see section 4.3).

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
HORMONAL CONTRACEPTIVES		
Progestin/estrogen	Concentrations of ethinyl estradiol and norethindrone are increased when a combined oral contraceptive containing those agents is co-administered with atazanavir. The mechanism of interaction is inhibition of metabolism by atazanavir. Effects of co-administration of EVOTAZ on progestin and estrogen are unknown.	Co-administration of EVOTAZ and hormonal contraceptives should be avoided. An alternate (non-hormonal) reliable method of contraception is recommended.
Drospirenone/ethinyloestradiol 3 mg/0.02 mg single dose (atazanavir 300 mg once daily with cobicistat 150 mg once daily)	Drospirenone AUC: ↑ 130% Drospirenone C_{max}: ↔ Drospirenone C_{min}: Not calculated Ethinyloestradiol AUC: ↔ Ethinyloestradiol C_{max}: ↔ Ethinyloestradiol C_{min}: Not calculated	Plasma concentrations of drospirenone are increased following co-administration of drospirenone/ethinyloestradiol with atazanavir/cobicistat. If drospirenone/ethinyloestradiol is co-administered with atazanavir/cobicistat clinical monitoring is recommended due to the potential for hyperkalemia.
LIPID-MODIFYING AGENTS		
Lomitapide	The co-administration of lomitapide with any of the components of EVOTAZ has not been studied. Lomitapide is highly dependent on CYP3A4 for its metabolism and co-administration with EVOTAZ may result in increased concentrations of lomitapide.	There is a potential for risk of markedly increased transaminase levels and hepatotoxicity associated with increased plasma concentrations of lomitapide. Co-administration of lomitapide with EVOTAZ is contraindicated (see section 4.3).
HMG-CoA reductase inhibitors		
Simvastatin **Lovastatin**	Simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and co-administration with EVOTAZ may result in increased concentrations.	Co-administration of simvastatin or lovastatin with EVOTAZ is contraindicated due to an increased risk of myopathy including rhabdomyolysis (see section 4.3).
Atorvastatin 10 mg single dose (atazanavir 300 mg once daily with cobicistat 150 mg once daily)	Atorvastatin AUC: ↑ 822% Atorvastatin C_{max}: ↑ 1785% Atorvastatin C_{min}: Not calculated *Atazanavir AUC ↓5%* *Atazanavir C_{max} ↓7%* *Atazanavir C_{min} ↓10%*	Plasma concentrations of atorvastatin are increased when co-administered with atazanavir/cobicistat Co-administration of atorvastatin with EVOTAZ is not recommended.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Pravastatin **Fluvastatin** **Pitavastatin**	Although not studied, there is a potential for an increase in pravastatin or fluvastatin exposure when co-administered with protease inhibitors. Pravastatin is not metabolised by CYP3A4. Fluvastatin is partially metabolised by CYP2C9. Plasma concentrations of pitavastatin may be increased if co-administered with EVOTAZ.	Caution should be exercised.
Rosuvastatin (10 mg single dose) (atazanavir 300 mg once daily with cobicistat 150 mg once daily)	Rosuvastatin AUC: ↑ 242% Rosuvastatin C_{max}: ↑ 958% Rosuvastatin C_{min}: Not calculated *Atazanavir AUC:* ↔ *Atazanavir C_{max}:*↔ *Atazanavir C_{min}: ↑ 6%*	Plasma concentrations of rosuvastatin are increased when co-administered with atazanavir/cobicistat. When co-administration is necessary, do not exceed 10 mg rosuvastatin daily, and clinical monitoring for safety (e.g. myopathy) is recommended.
INHALED BETA AGONISTS		
Salmeterol	Co-administration with EVOTAZ may result in increased concentrations of salmeterol and an increase in salmeterol-associated adverse events. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	Co-administration of salmeterol with EVOTAZ is not recommended (see section 4.4).
ERGOT DERIVATES		
Dihydroergotamine **Ergometrine** **Ergotamine** **Methylergonovine**	EVOTAZ must not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.	Co-administration of EVOTAZ and these ergot derivates is contraindicated (see section 4.3).
NEUROLEPTICS		
Perphenazine **Risperidone** **Thioridazine**	Co-administration of neuroleptics with EVOTAZ may result in increased plasma concentrations of neuroleptics. The mechanism of interaction is inhibition of CYP3A4 and/or CYP2D6 by atazanavir and/or cobicistat.	A decrease in the dose of neuroleptics metabolized by CYP3A or CYP2D6 may be required when co-administered with EVOTAZ.
OPIOIDS		

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Buprenorphine, once daily, stable maintenance dose (atazanavir 300 mg once daily with ritonavir 100 mg once daily)	Buprenorphine AUC ↑67% Buprenorphine C_{max} ↑37% Buprenorphine C_{min} ↑69% Norbuprenorphine AUC ↑105% Norbuprenorphine C_{max} ↑61% Norbuprenorphine C_{min} ↑101% The mechanism of interaction is CYP3A4 and UGT1A1 inhibition by atazanavir. Concentrations of atazanavir were not significantly affected.	Co-administration warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered.
Buprenorphine/naloxone in combination with cobicistat	Buprenorphine AUC: ↑35% Buprenorphine C_{max}: ↔ Buprenorphine C_{min}: ↑66% Naloxone AUC: ↓28% Naloxone C_{max}: ↓28% The mechanism of interaction is CYP3A4 inhibition by cobicistat.	
Methadone, stable maintenance dose (atazanavir 400 mg once daily)	No significant effect on methadone concentrations was observed when co-administered with atazanavir. Given that cobicistat has been shown to have no significant effect on methadone concentrations, no interaction is expected if methadone is co-administered with EVOTAZ.	No dosage adjustment is necessary if methadone is co-administered with EVOTAZ.
PULMONARY ARTERIAL HYPERTENSION		
PDE5 Inhibitors		
Sildenafil	Co-administration with EVOTAZ may result in increased concentrations of the PDE5 inhibitor and an increase in PDE5 inhibitor-associated adverse events. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	A safe and effective dose in combination with EVOTAZ has not been established for sildenafil when used to treat pulmonary arterial hypertension. Sildenafil, when used for the treatment of pulmonary arterial hypertension, is contraindicated (see section 4.3).

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
SEDATIVES/HYPNOTICS		
Midazolam **Triazolam**	Midazolam and triazolam are extensively metabolized by CYP3A4. Co-administration with EVOTAZ may cause a large increase in the concentration of these benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels.	EVOTAZ should not be co-administered with triazolam or orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of EVOTAZ and parenteral midazolam. If EVOTAZ is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.
Buspirone **Clorazepate** **Diazepam** **Estazolam** **Flurazepam** **Zolpidem**	Concentrations of these sedatives/hypnotics may be increased when co-administered with EVOTAZ. The mechanism of interaction is inhibition of CYP3A4 by cobicistat.	For these sedatives/hypnotics, dose reduction may be necessary and concentration monitoring is recommended.
GASTROINTESTINAL MOTILITY AGENTS		
Cisapride	EVOTAZ must not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.	Co-administration of EVOTAZ and cisapride is contraindicated (see section 4.3).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

EVOTAZ is not recommended during pregnancy nor should it be initiated in pregnant patients; an alternative regimen is recommended (see sections 4.2 and 4.4). 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.

Animal studies with EVOTAZ are insufficient with respect to reproductive toxicity (see section 5.3).

Breast-feeding

Atazanavir, an active component of EVOTAZ, has been detected in human milk. It is unknown if cobicistat/metabolites are excreted in human milk. Studies in animals have been shown excretion of cobicistat/metabolites in milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in breast-feeding infants, women should be instructed not to breast-feed if they are receiving EVOTAZ.

Fertility

The effect of EVOTAZ on fertility in humans has not been studied. In a nonclinical fertility and early embryonic development study in rats, atazanavir altered oestrus cycling with no effects on mating or fertility (see section 5.3). No human data on the effect of cobicistat on fertility are available. Animal studies do not indicate harmful effects of cobicistat on fertility.

4.7 Effects on ability to drive and use machines

EVOTAZ has a minor influence on the ability to drive or use machines. Dizziness may occur following administration of regimens containing atazanavir and cobicistat (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of EVOTAZ is based on available data from clinical trials conducted with atazanavir, atazanavir boosted with either cobicistat or ritonavir, and post-marketing data.

As EVOTAZ contains atazanavir and cobicistat, the adverse reactions associated with each of the individual components may be expected.

In a Phase III study (GS-US-216-0114), the most frequently reported adverse reactions in the atazanavir boosted with cobicistat group were associated with elevated bilirubin levels (see Table 2).

In two controlled clinical trials, where subjects received atazanavir alone (400 mg once daily) or atazanavir (300mg daily) boosted with ritonavir (100mg daily), the most frequently reported adverse reactions were nausea, diarrhoea and jaundice. In the majority of cases, jaundice was reported within a few days to a few months after the initiation of treatment (see section 4.4).

Chronic kidney disease in HIV-infected patients treated with atazanavir, with or without ritonavir, has been reported during postmarketing surveillance (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions are listed by system organ class and frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to 1/1,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2: Tabulated summary of adverse reactions

System Organ Class Frequency	Adverse Reactions
Immune system disorders	
uncommon	hypersensitivity
Metabolism and nutrition disorders	
common	increased appetite
uncommon	weight decreased, weight gain, anorexia
Psychiatric disorders	
common	insomnia, abnormal dreams
uncommon	depression, sleep disorder, disorientation, anxiety
Nervous system disorders	
common	headache, dizziness, somnolence, dysgeusia
uncommon	peripheral neuropathy, syncope, amnesia
Eye disorders	
very common	ocular icterus
Cardiac disorders	
uncommon	torsades de pointes[a]
rare	QTc prolongation[a], oedema, palpitation
Vascular disorders	
uncommon	hypertension
Respiratory, thoracic and mediastinal disorders	
uncommon	dyspnoea
Gastrointestinal disorders	
very common	nausea
common	vomiting, diarrhoea, dyspepsia, abdominal pain, abdominal distension, flatulence, dry mouth
uncommon	pancreatitis, gastritis, stomatitis aphthous
Hepatobiliary disorders	
very common	jaundice
common	hyperbilirubinaemia
uncommon	hepatitis, cholelithiasis[a], cholestasis[a]
rare	hepatosplenomegaly, cholecystitis[a]
Skin and subcutaneous tissue disorders	
common	rash
uncommon	pruritus, erythema multiforme[a,b], toxic skin eruptions[a,b], drug rash with eosinophilia and systemic symptoms (DRESS) syndrome[a,b], angioedema[a], urticaria, alopecia
rare	Stevens-Johnson syndrome[a,b], vesiculobullous rash, eczema, vasodilatation
Musculoskeletal and connective tissue disorders	
uncommon	myalgia, muscle atrophy, arthralgia
rare	myopathy
Renal and urinary disorders	
uncommon	nephrolithiasis[a], haematuria, proteinuria, pollakiuria, interstitial nephritis, chronic kidney disease[a]
rare	kidney pain
Reproductive system and breast disorders	
uncommon	gynaecomastia

System Organ Class Frequency	Adverse Reactions
General disorders and administration site conditions	
common	fatigue
uncommon	pyrexia, asthenia, chest pain, malaise
rare	gait disturbance

[a] These adverse reactions were identified through post-marketing surveillance; however, the frequencies were estimated from a statistical calculation based on the total number of patients exposed to atazanavir (with and without ritonavir) in randomised controlled and other available clinical trials (n = 2321).
[b] See section Description of selected adverse reactions for more details.

Description of selected adverse reactions

Immune reactivation syndrome and autoimmune disorders
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Osteonecrosis
Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Metabolic parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Rash and associated syndromes
Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 3 weeks of starting therapy with atazanavir.

Stevens-Johnson syndrome (SJS), erythema multiforme, toxic skin eruptions and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome have been reported with the use of atazanavir (see section 4.4).

Renal impairment
Cobicistat, a component of EVOTAZ, has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine. An increase from baseline in serum creatinine solely due to cobicistat's inhibitory effect generally does not exceed 0.4 mg/dl.

In study GS-US-216-0114, decreases in estimated creatinine clearance occurred early in treatment with cobicistat, after which they stabilised. The mean (± SD) change in estimated glomerular filtration rate (eGFR) by Cockcroft-Gault method after 144 weeks of treatment was -15.1 ± 16.5 ml/min in the atazanavir boosted with cobicistat plus emtricitabine and tenofovir DF fixed-dose combination group and -8.0 ± 16.8 ml/min in the atazanavir boosted with ritonavir plus emtricitabine and tenofovir DF fixed-dose combination group.

Effects on the liver
In study GS-US-216-0114, through 144 weeks of treatment hyperbilirubinaemia (> 1 x ULN) was common: 97.7% in the atazanavir boosted with cobicistat plus emtricitabine and tenofovir DF fixed-dose combination group, and 97.4% in the atazanavir boosted with ritonavir plus emtricitabine and tenofovir DF fixed-dose combination group. However, a higher percentage of subjects in the atazanavir boosted with cobicistat group had increases in total bilirubin > 2 x ULN than those in the

atazanavir boosted with ritonavir group (88.0% versus 80.9%). The rates of study drug discontinuation due to bilirubin-related adverse events were low and similar in both groups (4.9% in the cobicistat-boosted group and 4.0% in the ritonavir-boosted group). An increase of > 3 x ULN in alanine aminotransferase or aspartate aminotransferase was recorded in 12.8% of subjects in the cobicistat-boosted group and 9.0% in the ritonavir-boosted group.

Laboratory abnormalities
The most frequently reported laboratory abnormality in patients receiving regimens containing atazanavir 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). Among experienced patients treated with atazanavir 300 mg once daily with 100 mg ritonavir once daily for a median duration of 95 weeks, 53% had Grade 3-4 total bilirubin elevations. Among naïve patients treated with atazanavir 300 mg once daily with 100 mg ritonavir once daily for a median duration of 96 weeks, 48% had Grade 3-4 total bilirubin elevations (see section 4.4).

Other marked clinical laboratory abnormalities (Grade 3 or 4) reported in ≥ 2% of patients receiving regimens containing atazanavir and one or more NRTIs included: elevated creatine kinase (7%), elevated alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) (5%), low neutrophils (5%), elevated aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) (3%), and elevated lipase (3%).

Two percent of patients treated with atazanavir experienced concurrent Grade 3-4 ALT/AST and Grade 3-4 total bilirubin elevations.

Paediatric population

Paediatric patients aged 3 months to <12 years
In clinical studies, paediatric patients 3 months to less than 18 years of age had a mean duration of treatment with atazanavir of 115 weeks. The safety profile in these studies was overall comparable to that seen in adults. Both asymptomatic first-degree (23%) and second-degree (1%) atrioventricular block were reported in paediatric patients. The most frequently reported laboratory abnormality in paediatric patients receiving atazanavir was elevation of total bilirubin (≥ 2.6 times ULN, Grade 3-4) which occurred in 45% of patients.

Paediatric patients aged 12 to <18 years and weighing more than 35 kg
The safety of atazanavir administered with cobicistat plus two NRTIs (N = 14) was evaluated in HIV-1 infected virologically suppressed paediatric patients between the ages of 12 to < 18 years through 48 weeks in an open-label clinical study (GS-US-216-0128). In this study, the safety profile of atazanavir and cobicistat was similar to that in adults.

Other special populations

Patients co-infected with hepatitis B and/or hepatitis C virus
Co-infected patients with hepatitis B and/or C were more likely to have baseline hepatic transaminase elevations than those without chronic viral hepatitis. No differences in frequency of bilirubin elevations were observed between these patients and those without viral hepatitis. The frequency of treatment emergent hepatitis or transaminase elevations in co-infected patients was comparable between atazanavir and comparator regimens (see section 4.4).

Patients with chronic hepatitis B or hepatitis C virus co-infection:

In GS-US-216-0114, 3.6% of subjects were hepatitis B virus surface antigen positive and 5.3% were hepatitis C virus seropositive. Subjects with significant liver function test abnormalities generally had abnormal baseline transaminases (AST or ALT), underlying chronic or acute hepatitis B or C co-infection, concomitant hepatotoxic medicinal products (e.g., isoniazid), or a medical history of alcoholism or alcohol abuse.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Human experience of acute overdose with EVOTAZ is limited.

There is no specific antidote for overdose with EVOTAZ. 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. Since atazanavir and cobicistat are extensively metabolised by the liver and highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicinal product.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use; antivirals for treatment of HIV infections, combinations. ATC code: J05AR15

Mechanism of action

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

Atazanavir
Atazanavir is an azapeptide HIV-1 protease inhibitor (PI). 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
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, where bioavailability is limited and half-life is shortened by CYP3A-dependent metabolism.

Antiviral activity *in vitro*

Atazanavir
Atazanavir exhibits anti-HIV-1 (including all clades tested) and anti-HIV-2 activity in cell culture.

Cobicistat
Cobicistat has no antiviral activity.

Pharmacodynamic effects

Effect of cobicistat on atazanavir pharmacokinetics
The antiretroviral effect of EVOTAZ is due to the atazanavir component. The activity of cobicistat as a pharmacokinetic enhancer to atazanavir has been demonstrated in pharmacokinetic trials. In these pharmacokinetic trials, the exposure of atazanavir 300 mg with cobicistat 150 mg was consistent with that observed when boosted with ritonavir 100 mg. EVOTAZ is bioequivalent to atazanavir 300 mg once daily in combination with cobicistat 150 mg once daily coadministered as single agents (see section 5.2).

Clinical efficacy and safety

In treatment-naïve HIV-1 infected patients
The safety and efficacy of atazanavir with cobicistat in HIV-1 infected patients were evaluated in the randomised, double-blind, active-controlled phase 3 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).

Patients were randomised in a 1:1 ratio to receive either atazanavir 300 mg with cobicistat 150 mg once daily or atazanavir 300 mg with ritonavir 100 mg once daily, each administered with a fixed background regimen containing tenofovir DF 300 mg and emtricitabine 200 mg administered as a fixed-dose combination tablet. Randomisation was stratified by screening HIV-1 RNA level (≤100,000 copies/ml or >100,000 copies/ml). Virologic response rate was evaluated in both treatment arms and virologic response was defined as achieving an undetectable viral load (<50 HIV-1 RNA copies/ml). Viruses were known to be susceptible to atazanavir, emtricitabine and tenofovir DF at baseline.

The demographic and baseline characteristics were similar between the atazanavir with cobicistat and atazanavir with ritonavir groups. The median age of subjects was 36 years (range: 19-70). The median baseline plasma HIV-1 RNA was 4.81 $\log_{10}$ copies/ml (range: 3.21-6.44). The median baseline CD4+ cell count was 352 cells/mm^3 (range: 1-1455) and 16.9% had CD4+ cell counts ≤200 cells/mm^3. The percentage of subjects with baseline viral loads >100,000 copies/ml was 39.7%. Treatment outcomes at weeks 48 and 144 for study GS-US-216-0114 are presented in Table 3.

Table 3: Virologic outcome of randomised treatment of study GS-US-216-0114 at weeks 48[a] and 144[b]

	Week 48		**Week 144**	
	Atazanavir with cobicistat[f] (n = 344)	**Atazanavir with ritonavir[f] (n = 348)**	**Atazanavir with cobicistat[f] (n = 344)**	**Atazanavir with ritonavir[f] (n = 348)**
Virologic success HIV-1 RNA <50 copies/ml	85%	87%	72%	74%
Treatment difference	-2.2% (95% CI = -7.4%, 3.0%)		-2.1% (95% CI = -8.7%, 4.5%)	
Virologic failure[e]	6%	4%	8%	5%
No virologic data in week 48 or week 144 window	9%	9%	20%	21%
Discontinued study drug due to AE or death[d]	6%	7%	11%	11%
Discontinued study drug due to other reasons and last available HIV-1 RNA <50 copies/ml[e]	3%	2%	8%	10%

Missing data during window but on study drug	0%	0%	< 1%	< 1%

[a] Week 48 window is between day 309 and 378 (inclusive)

[b] Week 144 window is between day 967 and 1,050 (inclusive)

[c] Includes subjects who had ≥50 copies/ml in the week 48 or 144 windows, 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.

[d] Includes patients who discontinued due to adverse event (AE) 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 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.

[f] Plus background regimen of emtricitabine 200 mg and tenofovir DF 300 mg fixed-dose combination.

Atazanavir with cobicistat and emtricitabine and tenofovir DF fixed-dose combination was non-inferior in achieving HIV-1 RNA <50 copies/ml when compared to atazanavir with ritonavir and emtricitabine and tenofovir DF fixed-dose combination.

In study GS-US-216-0114, the mean increase from baseline in CD4+ cell count at weeks 48 and 144 were 213 and 310 cells/mm^3 in patients receiving atazanavir boosted with cobicistat and 219 and 332 cells/mm^3 in patients receiving atazanavir boosted with ritonavir, respectively.

Resistance

The resistance profile of EVOTAZ is driven by atazanavir. Cobicistat does not select any HIV resistance mutations, due to its lack of antiviral activity.

Atazanavir
In clinical trials of antiretroviral treatment naive patients treated with unboosted atazanavir, the I50L substitution, sometimes in combination with an A71V change, is the signature resistance substitution for atazanavir. Resistance levels to atazanavir ranged from 3.5- to 29-fold without evidence of phenotypic cross resistance to other PIs. For more information consult the REYATAZ Summary of Product Characteristics.

Atazanavir with cobicistat
Limited data are available on the development of resistance to atazanavir boosted with cobicistat.

In an analysis of treatment-failure subjects who received atazanavir 300 mg co-administered with cobicistat 150 mg in study GS-US-216-0114 through Week 144, evaluable genotypic data from paired baseline and treatment-failure isolates were available for all 21 virologic failures in this group (6%, 21/344). Among the 21 subjects, 3 developed the emtricitabine-associated resistance substitution M184V. No subject developed the tenofovir-associated resistance substitution K65R or K70E or any primary resistance substitution associated with protease inhibitors. In the group receiving atazanavir 300 mg co-administered with ritonavir 100 mg, evaluable genotypic data was available for all 19 virologic failures (5%, 19/348). Among the 19 patients, 1 developed the emtricitabine-associated resistance substitution M184V with no tenofovir or protease inhibitor associated resistance substitutions.

Paediatric population

Paediatric patients aged 3 months to <12 years or weighing less than 35 kg
The European Medicines Agency has deferred the obligation to submit the results of studies with EVOTAZ in the treatment of HIV-1 infection (see section 4.2 for information on paediatric use).

Paediatric patients aged 12 to <18 years and weighing more than 35 kg
The safety and efficacy of atazanavir with cobicistat were evaluated in an open-label phase 2/3 Study GS-US-216-0128 in HIV-1 infected virologically suppressed paediatric patients between the ages of

12 and < 18 years with baseline estimated creatinine clearance ≥ 90 mL/min. Fourteen patients received atazanavir 300 mg once daily with cobicistat 150 mg once daily administered with a background regimen containing two NRTIs.

The median age of patients was 14 years (range: 12 to 17); median weight of patients was 52,7 kg (range: 46,5 to 63,3); 71% were male; 57% were Asian, 29% were White, and 14% were Black. At baseline, 13/14 subjects had plasma HIV-1 RNA < 50 copies/mL and 1 subject had plasma HIV-1 RNA = 50 copies/mL.

In patients treated with atazanavir + cobicistat, the median baseline CD4+ cell count and CD4+% was 770 cells/mm^3 (range: 486 to 1765) and 33% (range: 23% to 45%), respectively. At Week 48, 93% (13/14) of patients retained HIV-1 RNA < 50 copies/mL and the median change from baseline in CD4+ cell count and CD4+% was -60 cells/mm^3 and -0.3%, respectively. Three out of 14 patients qualified for resistance analysis: 1 patient showed no resistance in protease or reverse transcriptase and 2 had missing data due to assay failure.

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 following statements reflect the pharmacokinetic properties of atazanavir in combination with cobicistat or the individual components of EVOTAZ.

Absorption

In a trial where HIV-infected subjects (n=22) were instructed to take atazanavir 300 mg with cobicistat 150 mg once daily with food, the steady-state atazanavir C_{max}, AUC_{tau} and C_{tau} (mean ± SD) values were 3.9 ± 1.9 μg/ml, 46.1 ± 26.2 μg•hr/ml and 0.80 ± 0.72 μg/ml, respectively. 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 approximately 23% due to delayed absorption; the median T_{max} increased from 2.0 to 3.5 hours. C_{max} and AUCs after a high fat meal decreased 36% and 25% in comparison to a light meal, respectively; however, the 24-hour atazanavir concentration was similar when EVOTAZ was given with a light meal and a high fat meal. To enhance bioavailability, EVOTAZ is to be taken with food.

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). In a multiple-dose study in HIV-infected patients dosed with 400 mg of atazanavir once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid and semen.

Cobicistat

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

Biotransformation

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. Metabolites are then excreted in the bile as either free or glucuronidated metabolites. Additional minor metabolic pathways consist of N-dealkylation and hydrolysis. Two minor metabolites of atazanavir in plasma have been characterised. Neither metabolite demonstrated *in vitro* antiviral activity.

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

Elimination

Atazanavir
Following a single 400 mg dose of [^{14}C]atazanavir, 79% and 13% of the total radioactivity was recovered in the faeces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the faeces and urine, respectively. Mean urinary excretion of unchanged drug was 7% following 2 weeks of dosing at 800 mg once daily. In HIV-infected adult patients (n=33, combined studies), the mean half-life within a dosing interval for atazanavir was 12 hours at steady state following a dose of 300 mg daily with ritonavir 100 mg once daily with a light meal.

Cobicistat
Following oral administration of [^{14}C]cobicistat, 86% 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 3-4 hours.

Linearity/non-linearity

Atazanavir
Atazanavir demonstrates nonlinear pharmacokinetics with greater than dose-proportional increases in AUC and C_{max} values over the dose range of 200 mg to 800 mg once daily.

Cobicistat
Cobicistat exposures are non-linear and greater than dose-proportional over the range of 50 mg to 400 mg, consistent with a mechanism-based CYP3A inhibitor.

Special populations

Renal impairment
Atazanavir
In healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. There are no pharmacokinetic data available for atazanavir in combination with cobicistat in patients with renal insufficiency. Atazanavir has been studied in adult patients with severe renal impairment (n=20), including those on haemodialysis, at multiple doses of 400 mg once daily. Although this study presented some limitations (i.e., unbound drug concentrations not studied), results suggested that the atazanavir pharmacokinetic parameters were decreased by 30% to 50% in patients undergoing haemodialysis compared to patients with normal renal function. The mechanism of this decrease is unknown (see sections 4.2 and 4.4.)

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.

Hepatic impairment
Atazanavir
Atazanavir is metabolised and eliminated primarily by the liver. The effects of hepatic impairment on the pharmacokinetics of atazanavir given with cobicistat have not been studied. Concentrations of atazanavir given with cobicistat are expected to be increased in patients with impaired hepatic function (see sections 4.2 and 4.4).

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 moderate impairment and healthy subjects. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of cobicistat has not been studied.

Elderly
The pharmacokinetics of atazanavir and cobicistat, alone or in combination, have not been evaluated in an elderly population (65 years of age and older).

Paediatric population

Paediatric Patients aged 3 months to <12 years
For paediatric patients aged 3 months to $\leq$ 12 years, no data are available on the pharmacokinetics of atazanavir and cobicistat in combination.

Paediatric Patients aged 12 to <18 years and weighing more than 35 kg
In paediatric patients aged 12 to < 18 years who received cobicistat-boosted atazanavir (n = 14) in Study GS-US-216-0128, exposures of atazanavir and cobicistat (AUC_{tau}, C_{max}, and C_{trough}) were higher (24% to 180%) than in adults; however, the increases were not considered clinically significant as the safety profiles were similar in adult and paediatric patients.

Gender
No clinically relevant pharmacokinetic differences due to gender have been identified for atazanavir or cobicistat.

Race
No clinically relevant pharmacokinetic differences due to ethnicity have been identified for atazanavir or cobicistat.

5.3 Preclinical safety data

In a 3-month combination oral toxicity study of atazanavir and cobicistat in rats, there were no toxicologic interactions apparent as no additive or synergistic toxicities were observed. When compared to their single-agent profiles all findings could be attributed to either atazanavir or cobicistat.

In an *ex vivo* rabbit pharmacology study, isolated hearts were exposed to atazanavir, cobicistat, or atazanavir and cobicistat in combination. Each single agent produced effects on left ventricular contractility and PR prolongation at concentrations at least 35-fold higher than the free atazanavir and cobicistat concentrations at the recommended human dose (RHD) C_{max}. When administered in

combination, no clear additive or synergistic cardiovascular effects were observed at atazanavir and cobicistat concentrations at least 2-fold higher than the free atazanavir and cobicistat concentrations at the RHD C_{max}.

The following statements reflect the preclinical safety results of the individual active substances of EVOTAZ.

Atazanavir

In repeat-dose toxicity studies, conducted in mice, rats, and dogs, atazanavir-related findings were generally confined to the liver and included generally minimal to mild increases in serum bilirubin and liver enzymes, hepatocellular vacuolation and hypertrophy, and, in female mice only, hepatic single-cell necrosis. Systemic exposures of atazanavir in mice (males), rats, and dogs at doses associated with hepatic changes were at least equal to that observed in humans given 400 mg once daily. In female mice, atazanavir exposure at a dose that produced single-cell necrosis was 12 times the exposure in humans given 400 mg once daily. Serum cholesterol and glucose were minimally to mildly increased in rats but not in mice or dogs.

During *in vitro* studies, cloned human cardiac potassium channel (hERG), was inhibited by 15% at a concentration (30 μM) of atazanavir corresponding to 30 fold the free drug concentration at C_{max} in humans. Similar concentrations of atazanavir increased by 13% the action potential duration (APD_{90}) in rabbit Purkinje fibres study. Electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prolongation of QT interval, and prolongation of QRS complex) were observed only in an initial 2 week oral toxicity study performed in dogs. Subsequent 9 month oral toxicity studies in dogs showed no drug-related electrocardiographic changes. The clinical relevance of these non-clinical data is unknown. Potential cardiac effects of this product in humans cannot be ruled out (see sections 4.4 and 4.8). The potential for PR prolongation should be considered in cases of overdose (see section 4.9).

In a fertility and early embryonic development study in rats, atazanavir altered oestrus cycling with no effects on mating or fertility. No teratogenic effects were observed in rats or rabbits at maternally toxic doses. In pregnant rabbits, gross lesions of the stomach and intestines were observed in dead or moribund does at maternal doses 2 and 4 times the highest dose administered in the definitive embryo-development study. In the pre- and postnatal development assessment in rats, atazanavir produced a transient reduction in body weight in the offspring at a maternally toxic dose. Systemic exposure to atazanavir at doses that resulted in maternal toxicity was at least equal to or slightly greater than that observed in humans given 400 mg once daily.

Atazanavir was negative in an Ames reverse-mutation assay but did induce chromosomal aberrations *in vitro* in both the absence and presence of metabolic activation. 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*.

In long-term carcinogenicity studies of atazanavir in mice and rats, an increased incidence of benign hepatic adenomas was seen in female mice only. The increased incidence of benign hepatic adenomas in female mice was likely secondary to cytotoxic liver changes manifested by single-cell necrosis and is considered to have no relevance for humans at intended therapeutic exposures. There were no tumorigenic findings in male mice or in rats.

Atazanavir increased opacity of bovine corneas in an *in vitro* ocular irritation study, indicating it may be an ocular irritant upon direct contact with the eye.

Cobicistat

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction and development. No teratogenic effects were observed in rats and rabbit developmental toxicity studies. In rats, ossification changes in the spinal column and sternebra of foetuses occurred at a dose that produced significant maternal toxicity.

Ex vivo rabbit studies and *in vivo* dog studies suggest that cobicistat has a low potential for QT prolongation, and may slightly prolong the PR interval and decrease left ventricular function at mean concentrations at least 10-fold higher than the human exposure at the recommended 150 mg daily dose.

A long-term carcinogenicity study of cobicistat in rats revealed tumourigenic potential specific for this species that is regarded as of no relevance for humans. A long-term carcinogenicity study in mice did not show any carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

cellulose, microcrystalline (E460(i))
croscarmellose sodium (E468)
sodium starch glycolate
crospovidone (E1202)
stearic acid (E570)
magnesium stearate (E470b)
hydroxypropylcellulose (E463)
silica (E551)

Film-coating

hypromellose (hydroxypropyl methyl cellulose, E464)
titanium dioxide (E171)
talc (E553b)
triacetin (E1518)
red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a child-resistant polypropylene closure. Each bottle contains 30 film-coated tablets and a silica gel dessicant.

The following pack sizes are available: outer cartons containing 1 bottle of 30 film-coated tablets and outer cartons containing 90 (3 bottles of 30) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1025/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2015
Date of latest renewal: 27 March 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Pharmaceutical Operations, External Manufacturing
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

CATALENT ANAGNI S.R.L.
Loc. Fontana del Ceraso snc
Strada Provinciale 12 Casilina, 41
03012 - Anagni (FR)
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

EVOTAZ 300 mg/150 mg film-coated tablets
atazanavir/cobicistat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg of atazanavir (as sulphate) and 150 mg of cobicistat.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 (3 bottles of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1025/001 30 film-coated tablets
EU/1/15/1025/002 90 (3 bottles of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

evotaz

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

B. PACKAGE LEAFLET

Package leaflet: Information for the user

EVOTAZ 300 mg/150 mg film-coated tablets
atazanavir/cobicistat

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What EVOTAZ is and what it is used for
2. What you need to know before you take EVOTAZ
3. How to take EVOTAZ
4. Possible side effects
5. How to store EVOTAZ
6. Contents of the pack and other information

1. What EVOTAZ is and what it is used for

EVOTAZ contains two active substances:
- **atazanavir, an antiviral (or antiretroviral) medicine.** It is one of a group called *protease inhibitors*. These medicines control human immunodeficiency virus (HIV) infection by stopping production of a protein that HIV needs for its multiplication. They work by reducing the amount of HIV in your body and this in turn, strengthens your immune system. In this way atazanavir reduces the risk of developing illnesses linked to HIV infection.
- **cobicistat, a booster (pharmacokinetic enhancer) to help improve the effects of atazanavir**. Cobicistat, does not directly treat your HIV, but boosts the levels of atazanavir in the blood. It does this by slowing down the breakdown of atazanavir which will make it stay in the body for longer.

EVOTAZ may be used by adults and adolescents (aged 12 years and older weighing at least 35 kg), who are infected with HIV, the virus that causes acquired immunodeficiency syndrome (AIDS). It is used in combination with other anti-HIV medicines to help control your HIV infection. Your doctor will discuss with you which combination of these medicines with EVOTAZ is best for you.

2. What you need to know before you take EVOTAZ

Do not take EVOTAZ
- **if you are allergic** to atazanavir, cobicistat or any of the other ingredients of this medicine (listed in section 6)
- **if you have moderate to severe liver problems**
- **if you are taking any of these medicines**: see also *Other medicines and EVOTAZ*
  - rifampicin (an antibiotic used to treat tuberculosis)
  - carbamazepine, phenobarbital and phenytoin (antiepileptics used to prevent seizures)
  - astemizole or terfenadine (commonly used to treat allergy symptoms, these medicines may be available without prescription); cisapride (used to treat gastric reflux, sometimes called heartburn); pimozide (used to treat schizophrenia); amiodarone, dronedarone, quinidine,

lidocaine (injectable) or bepridil (used to correct heart rhythm); ergotamine, dihydroergotamine, ergonovine, ergometrine and methylergonovine (used to treat headaches); and alfuzosin (used to treat enlarged prostatic gland)
- quetiapine (used to treat schizophrenia, bipolar disorder and major depressive disorder); lurasidone (used to treat schizophrenia)
- medicines containing St. John's wort (*Hypericum perforatum*, a herbal preparation).
- triazolam and oral (taken by mouth) midazolam (used to help you sleep and/or to relieve anxiety)
- simvastatin, lovastatin, and lomitapide (used to lower blood cholesterol)
- avanafil (used to treat erectile dysfunction)
- colchicine (used to treat gout), if you have kidney and/or liver problems
- dabigatran and ticagrelor (used to prevent and reduce the blood clots)
- grazoprevir-containing products, including elbasvir/grazoprevir fixed dose combination, and glecaprevir/pibrentasvir fixed dose combination (used to treat chronic hepatitis C infection)

Do not take sildenafil with EVOTAZ when sildenafil is used for the treatment of pulmonary arterial hypertension. Sildenafil is also used for the treatment of erectile dysfunction. Tell your doctor if you are using sildenafil for the treatment of erectile dysfunction.

Tell your doctor at once if any of these apply to you.

Warnings and precautions

Some people will need special care before or while taking EVOTAZ. Talk to your doctor or pharmacist before taking EVOTAZ.

EVOTAZ is not a cure for HIV infection. You may continue to develop infections or other illnesses linked to HIV infection. You can still pass on HIV to other people when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.

Make sure your doctor knows:
- if you have liver problems
- if you develop signs or symptoms of gall stones (pain in your right side). Gall stones have been reported in patients taking atazanavir, a component of EVOTAZ.
- if you have type A or B haemophilia. You may notice increased bleeding.
- if you have problems with your kidneys or require haemodialysis. Kidney stones have been reported in patients taking atazanavir, a component of EVOTAZ. If you develop signs or symptoms of kidney stones (pain in your side, blood in your urine, pain when you urinate), please inform your doctor immediately
- if you are taking oral contraceptives **("the Pill")** to prevent pregnancy. If you are currently using an oral contraceptive or using a patch contraceptive to prevent pregnancy, you should use an additional or different type of contraception (e.g. condom)

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately. In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Hyperbilirubinaemia (an increase in the level of bilirubin in the blood) has occurred in patients receiving EVOTAZ. The signs may be a mild yellowing of the skin or eyes. If you notice any of these symptoms please inform your doctor.

Serious skin rash, including Stevens-Johnson syndrome, may develop in patients taking EVOTAZ. If you develop a rash inform your doctor immediately.

EVOTAZ may affect how well your kidneys work.

If you notice a change in the way your heart beats (heart rhythm changes), please inform your doctor.

Children
Do not give this medicine to children under 12 years of age or who weigh less than 35 kg, as the use of EVOTAZ was not studied in this population.

Other medicines and EVOTAZ

You must not take EVOTAZ with certain medicines. These are listed under Do not take EVOTAZ, at the start of section 2.

There are other medicines that may not be taken together or may require a change in their mode of administration when taken with EVOTAZ. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. It is especially important to mention these:
- medicines containing ritonavir or cobicistat (booster agents)
- other medicines to treat HIV infection (e.g. indinavir, didanosine, tenofovir disoproxil, tenofovir alafenamide, efavirenz, etravirine, nevirapine and maraviroc)
- sofosbuvir/velpatasvir/voxilaprevir (used to treat hepatitis C)
- sildenafil, vardenafil and tadalafil (used by men to treat impotence [erectile dysfunction])
- if you are taking an oral contraceptive ("the Pill"). You should also use an additional or different type of contraception (eg. condom).
- any medicines used to treat diseases related to the acid in the stomach (“heartburn”) (e.g. antacids, H_2-blockers like famotidine and proton pump inhibitors like omeprazole)
- disopyramide, flecainide, mexiletine, propafenone, digoxin, bosentan, amlodipine, felodipine, nicardipine, nifedipine, verapamil, diltiazem, metoprolol and timolol (medicines to lower blood pressure, to slow heart rate or to correct heart rhythm)
- atorvastatin, pravastatin, fluvastatin, pitavastatin and rosuvastatin (used to lower blood cholesterol)
- salmeterol (used to treat asthma)
- ciclosporin, tacrolimus and sirolimus (medicines to decrease the effects of body's immune system)
- certain antibiotics (rifabutin, clarithromycin)
- ketoconazole, itraconazole, voriconazole and fluconazole (antifungals)
- metformin (used to treat type 2 diabetes)
- warfarin, apixaban, edoxaban and rivaroxaban (used to reduce blood clots)
- irinotecan, dasatinib, nilotinib, vinblastine and vincristine (used to treat cancer)
- trazodone (used to treat depression)
- perphenazine, risperidone, thioridazine, midazolam (given by injection), buspirone, clorazepate, diazepam, estazolam, flurazepam and zolpidem (used to treat nevous system disorders)
- buprenorphine (used to treat opioid addiction and pain)

It is important to tell your doctor if you are taking: Corticosteroids including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of the eyes, joints and muscles and other inflammatory conditions. If alternatives cannot be used, its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.

Pregnancy and breast-feeding

EVOTAZ should not be used during pregancy, because the drug levels in your blood may be lower during pregancy and may no longer be high enough to control HIV. Your doctor may prescribe different medicines if you become pregnant while taking EVOTAZ.

Atazanavir, a component of EVOTAZ is excreted in human milk. It is unknown if cobicistat, the other component of EVOTAZ, is excreted in human milk but it has been shown in animals that it is excreted in milk. Talk to your doctor about breast-feeding if you are taking EVOTAZ. Patients should not breast-feed while taking EVOTAZ. It is recommended that women infected with HIV do not breast-feed because the virus might be transmitted through the breast milk.

Driving and using machines
Some patients have reported dizziness when taking atazanavir or cobicistat, active substances of EVOTAZ. If you feel dizzy or lightheaded, do not drive, use any tools or use machines and contact your doctor immediately.

3. How to take EVOTAZ

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. This way, you can be sure your medicine is fully effective and you reduce the risk of the HIV-virus developing resistance to the treatment.

The recommended adult and adolescent (aged 12 years and older weighing at least 35 kg) dose of EVOTAZ is one tablet daily by mouth and with food, in combination with other anti-HIV medicines. The tablets have a poor taste, therefore swallow the tablet whole; do not crush or chew the tablets. This will help ensure you get the full dose.

If you take more EVOTAZ than you should
If you accidentally take more EVOTAZ than your doctor recommended, contact your doctor at once or contact the nearest hospital for advice.

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

If you stop taking EVOTAZ
Do not stop taking EVOTAZ before talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor if you notice anything unusual about your health.

The following side effects may occur when taking EVOTAZ

Very common (may affect more than 1 in 10 people)
- yellowing of the skin or the white part of your eyes
- nausea

Common (may affect up to 1 in 10 people)
- increased levels of bilirubin in the blood
- vomiting, diarrhoea, stomach pain or discomfort, indigestion, bloated or distended tummy (abdomen), wind (flatulence)
- headache, dizziness
- extreme tiredness
- increased appetite, impairment of the sense of taste, dry mouth
- difficulty sleeping, abnormal dreams, sleepiness
- rash

Uncommon (may affect up to 1 in 100 people)
- life threatening irregular heart beat (torsade de pointes)
- allergic reaction (hypersensitivity)
- inflammation of the liver
- inflammation of the pancreas, inflammation of the stomach
- allergic reactions including rash, a high temperature, increased levels of liver enzymes seen in blood tests, an increase in a type of white blood cell [eosinophilia] and/or enlarged lymph nodes (see section 2)
- severe swelling of the skin and other tissues most often the lips or the eyes
- fainting, high blood pressure
- chest pain, generally feeling unwell, fever
- shortness of breath
- formation of kidney stones, kidney inflammation, blood in the urine, excess protein in the urine, increased frequency of urination, chronic kidney disease (how well your kidneys work)
- gallstones
- muscle shrinkage, joint pain, aching muscles
- breast enlargement in men
- depression, anxiety, sleep disorder
- unusual tiredness or weakness
- loss of appetite, weight loss, weight gain
- disorientation, loss of memory
- numbness, weakness, tingling or pain in the arms and legs
- mouth ulcers and cold sores
- itchy rash, unusual hair loss or thinning, itching

Rare (may affect up to 1 in 1,000 people)
- allergic reactions including serious skin rash, a high temperature and enlarged lymph nodes (Stevens-Johnson syndrome, see section 2).
- fast or irregular heartbeat (QTc prolongation)
- enlargement of the liver and spleen
- gallbladder inflammation
- kidney pain
- swelling

- visible accumulation of fluid under the skin, skin rash, widening of blood vessels
- abnormal manner of walking
- aching muscles, muscle tenderness or weakness not caused by exercise

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store EVOTAZ

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What EVOTAZ contains
- The active substances are atazanavir and cobicistat. Each film-coated tablet contains 300 mg of atazanavir (as sulphate), and 150 mg cobicistat.
- The other ingredients are:
  Tablet core - cellulose, microcrystalline (E460(i)), croscarmellose sodium (E468), sodium starch glycolate, crospovidone (E1202), stearic acid (E570), magnesium stearate (E470b), hydroxypropyl cellulose (E463), silica (E551)
  Film-coating - hypromellose (hydroxypropyl methyl cellulose, E464), titanium dioxide (E171), talc (E553b), triacetin (E1518), red iron oxide (E172)

What EVOTAZ looks like and contents of the pack
EVOTAZ film-coated tablets are pink, oval, biconvex, of approximate dimensions of 19 mm x 10.4 mm, debossed on one side with "3641" and plain-faced on the other side of the tablet.

EVOTAZ film-coated tablets are supplied in bottles of 30 tablets. The following pack sizes are available: outer cartons containing 1 bottle of 30 film-coated tablets and outer cartons containing 90 (3 bottles of 30) film-coated tablets.

Not all packages may be marketed in your country.

Marketing Authorisation Holder
Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867

Manufacturer
CATALENT ANAGNI S.R.L.
Loc. Fontana del Ceraso snc
Strada Provinciale 12 Casilina, 41
03012 Anagni (FR)

Ireland	Italy
	Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Pharmaceutical Operations, External Manufacturing Plaza 254 Blanchardstown Corporate Park 2 Dublin 15, D15 T867 Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.