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Summary of the risk management plan (RMP) for Evotaz (atazanavir/cobicistat)

This is a summary of the risk management plan (RMP) for Evotaz, which details the measures to be taken in order to ensure that Evotaz is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Evotaz, which can be found on Evotaz's EPAR page.

Overview of disease epidemiology

Evotaz is an antiviral medicine used in combination with other medicines to treat adults infected with human immunodeficiency virus type 1 (HIV-1), a virus that causes acquired immune deficiency syndrome (AIDS). HIV attacks the immune system (the body's natural defences against infection) and weakens it by destroying a type of white blood cells called CD4 T-cells, which protect the body against infection caused by bacteria, viruses and other germs. If left untreated, the HIV virus multiplies and the body starts losing its ability to fight infection and disease.

In 2012 over 35 million people were living with HIV, increased from 34 million in 2011 (including 900,000 in Western and Central Europe and 1.4 million in Eastern Europe and Central Asia). In 2012, about 2.3 million people were newly infected with HIV. In 2011, 1.7 million people died of AIDS, including 7,900 in Western and Central Europe and 92,000 in Eastern Europe and Central Asia.

There is no cure for HIV, but early and effective treatment can reduce HIV in the blood and keep it at a low level. This allows people to stay healthier and live longer. Resistance to HIV medicines can be a problem. So, over time, a particular combination of medicines may not be able to control the HIV virus properly, and treatment may need to be changed; treatment may also be changed because of side effects.

Summary of treatment benefits

Evotaz is available as a tablet containing the two active substances atazanavir and cobicistat. Evotaz is for use, in combination with other medicines, to treat HIV-1 infection in patients whose infection is not expected to be resistant to atazanavir.

Because atazanavir and cobicistat have both previously been shown to be effective and are authorised for use in the treatment of HIV infection, studies were mainly carried out to show that Evotaz produced similar levels of atazanavir in the blood to the two active substances taken together, and to atazanavir given with a different booster medicine, ritonavir (an established combination).

In addition, the use of atazanavir with cobicistat has been evaluated in one main study in 698 HIV patients who had not been treated previously. Atazanavir and cobicistat were compared with atazanavir and ritonavir; all patients also received the HIV medicines emtricitabine and tenofovir disoproxil. The main measure of effectiveness was the proportion of patients in whom the HIV-1 count in the blood was reduced to less than 50 copies/ml after 48 weeks of treatment. Overall, 85% of

patients (293 out of 344) treated with atazanavir and cobicistat achieved this reduction. This was comparable to a reduction in 87% of patients (304 of 348) treated with atazanavir and ritonavir.

Unknowns relating to treatment benefits

There is limited information from clinical studies on the use of Evotaz in elderly patients or pregnant women.

Evotaz has not been studied in children or patients with liver disease, and it is not recommended in patients with liver problems.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
The electrical activity that controls the heart is affected (PR interval prolongation)	Electrocardiography (ECG) is a technique for recording the electrical activity of the heart. Sometimes people with changes to the heart's electrical activity have symptoms that include feeling dizzy, a slow pulse, getting tired easily, shortness of breath with exercise, and fainting. Laboratory and animal studies have suggested that both atazanavir and cobicistat might affect the electrical activity of the heart in humans. In studies of atazanavir (without cobicistat), about 1 in 20 adults and 1 in 4 children had ECG changes. These changes were not associated with any symptoms. In three other clinical trials, the electrical activity of the heart was not affected in any individual receiving atazanavir and cobicistat (either separately or together as a single tablet).	Evotaz should be used with caution in patients who already have problems with electrical activity in the heart. Evotaz should be used cautiously with medicines that affect the electrical activity of the heart. The patient can be monitored with ECG if Evotaz is given with other medicines that affect heart rhythm.
Increased bilirubin level in the blood (hyperbilirubinaemia)	Bilirubin is a breakdown product of red blood cells and high levels of bilirubin (hyperbilirubinaemia) can cause yellowing of the skin and the eyes (jaundice) in a few people. Raised bilirubin is the most common blood abnormality among patients taking atazanavir. Any yellowing of the eyes and the skin rapidly	If yellowing of the skin or eyes is troublesome, a different medication can be considered instead of Evotaz. Women being treated with Evotaz should not breastfeed. Atazanavir is not recommended for children aged less than 3 months because it could possibly raise

Risk	What is known	Preventability
	disappears when atazanavir treatment is stopped. In studies with atazanavir alone, bilirubin was raised in around 8 patients in 10, but few developed jaundice. In 3 clinical trials with atazanavir and cobicistat (given separately or together as a single tablet), bilirubin level was raised in between 1 and 5 patients in 10. No evidence has been discovered to link cobicistat alone with raised bilirubin. See below for potential risk of kernicterus (brain damage resulting from excessive bilirubin levels).	bilirubin to harmful levels.
Kidney stones (nephrolithiasis)	If the kidney stones are large, they may cause symptoms like flank pain, frequent urination, blood in the urine, and even block the flow of urine and lead to kidney failure. People treated with HIV medicines get kidney stones slightly more often than people without HIV. Kidney stones have been reported in people taking atazanavir, and some of these stones are composed partly or entirely of atazanavir. The risk of kidney stones while taking atazanavir may be increased in people who drink less water or who had kidney stones previously. In 3 clinical studies of patients receiving atazanavir and cobicistat (either separately or together as a single tablet), no kidney stones had been reported. One patient had pain in the flank area but there was no evidence of a kidney stone. There is no evidence to link the use of cobicistat alone with the occurrence of kidney stones.	If the patient has any signs or symptoms of kidney stones, the doctor may consider either temporary interruption or discontinuation of Evotaz. The management of kidney stones in people taking atazanavir is the same as for any other kidney stones, and medical care or surgery may be involved.

Risk	What is known	Preventability
Severe skin reactions	Skin reactions are among the most common side effects of HIV medicines. The severity of reactions can range from mild to serious and life threatening. HIV patients are at higher risk of skin reactions because of their lower immunity. In 3 clinical studies, up to 1 patient in 5 receiving atazanavir and cobicistat (either separately or together as a single tablet), had a rash or skin irritation. Severe skin reactions were not reported.. There is no evidence of a link between cobicistat alone and severe skin reactions.	It is important to watch for a skin reaction and to identify it early. Patients who develop a rash should contact their doctor promptly. An allergy medicine (antihistamine) with or without a steroid can be recommended by the doctor if necessary to help relieve the symptoms.
Gallstones (cholelithiasis)	Gallstones may occur in patients not taking atazanavir and in those on atazanavir. Symptoms include pain in the right or middle upper abdomen, fever, nausea, vomiting, yellowing of the skin and of the eyes. Some patients who developed gallstones on atazanavir were in hospital for a long time and required surgery to remove the gallstones. Other complications including pancreatitis and death have been reported. In 3 clinical studies of atazanavir and cobicistat (either separately or together as a single tablet), no patient had gallstones. There is no evidence of a link between cobicistat alone and gallstones.	If the patient has any signs or symptoms of gallstones, the doctor may consider either temporarily interrupting treatment with Evotaz or discontinuing it.

Important potential risks

Risk	What is known
A change in the electrical activity of the heart (Prolonged QT interval)	Prolonged QT interval can cause events like sudden death, death from heart disorders and torsades de pointes (an irregular heartbeat that can lead to death), and all have been reported rarely with atazanavir. Prolonged QT interval and complications

Risk	What is known
	can occur in people on other medicines or no medicines. In studies on atazanavir involving 1,793 HIV patients, the QT interval was prolonged very infrequently, and at rates similar to patients receiving other HIV medicines. In 3 clinical studies on patients receiving atazanavir and cobicistat (either separately or together as a single tablet), QT interval prolongation was recorded in one subject but this did not affect the patient in any other way. In 2 studies with atazanavir and cobicistat given separately, the QT interval was not prolonged in any patient. In some people the QT interval is prolonged for unknown reasons and atazanavir may not be the best HIV medicine for these people. In patients already with problems with the heart's electrical activity, Evotaz should be used cautiously with medicines that prolong the QT interval. Evotaz should also be used with caution in patients who are prone to QT interval prolongation (such as those with abnormal levels of substances such as sodium, potassium and calcium in their blood).
Brain damage resulting from excessive bilirubin in the blood (kernicterus)	Bilirubin is a breakdown product of red blood cells. Because bilirubin is removed more slowly in newborn babies than in adults and it is produced faster than in adults, newborn babies are at higher risk of increased bilirubin. Breastfeeding may also increase the baby's bilirubin level. The high level of bilirubin in babies with or without HIV infection can cause mild jaundice (called physiological jaundice of the newborn). Kernicterus, a serious and life-threatening condition in infants may develop if the bilirubin level is very high. Although no case of kernicterus has been identified from clinical trials on atazanavir, kernicterus is a potential risk because of the effects of atazanavir on bilirubin levels. Atazanavir affects an enzyme involved with the removal of bilirubin. Atazanavir given to the mother during pregnancy has not been reported to cause kernicterus in the newborn baby. There is no evidence of a link between cobicistat alone and kernicterus. It is not known if either atazanavir or cobicistat gets into human milk. It is recommended that a mother being treated with Evotaz not breastfeed her infant.
Rapid decline in the kidneys' ability to work properly (acute renal failure)	In clinical trials on adults receiving atazanavir, acute renal failure was rarely seen (occurring in less than 10 patients in every 10,000).

Risk	What is known
	One large study reported that the HIV medicines tenofovir disoproxil, atazanavir (with ritonavir as a booster), and lopinavir (with ritonavir as a booster) were associated with rapidly worsening kidney function. Most cases of patients with kidney failure had additional reasons for kidney failure other than the use of atazanavir. Risk factors for acute kidney failure in HIV patients receiving atazanavir include older age, therapy with tenofovir disoproxil, and HIV-associated kidney disease. Other protease inhibitors are also associated with deteriorating renal function. Cobicistat can increase creatinine in the blood. Creatinine level is commonly measured to check how well the kidneys are working and an increase can indicate worsening health of the kidneys. However, this may not be the case in patients taking cobicistat. Close monitoring of renal function is recommended in patients on Evotaz, especially if given with tenofovir disoproxil. Evotaz should not be started in patients with creatinine clearance (a measure of kidney function) of less than 70 mL/minute. The effect of cobicistat on creatinine measurement should be considered when creatinine is used to measure kidney function of patients on Evotaz to guide management and dose adjustment of other medications.
Rapid swelling of deeper skin tissues, mostly around the eyes and lips, and also in the throat (angioedema)	Angioedema can be life threatening and affect a person's ability to breathe properly. In 3 clinical studies of patients receiving atazanavir and cobicistat (either separately or together as a single tablet), one patient had angioedema. In clinical trials on adults receiving atazanavir, angioedema occurred uncommonly (in less than 10 patients in 1,000). Since atazanavir has been on the market, there have been 2 cases of angioedema that are most likely associated with atazanavir. Skin rash occurred in both cases but there were no effects on breathing and the reaction was not life threatening. Symptoms of angioedema resolved when atazanavir was stopped. In a further 15 cases, angioedema may have been associated with atazanavir. There is no evidence of a link between cobicistat and angioedema. If there is swelling around the lips and eyes, it is important to get medical help immediately so that Evotaz can be stopped if it is suspected to have caused an allergic reaction.
Kidney inflammation (interstitial nephritis)	Interstitial nephritis can lead to kidney failure and possibly the need for dialysis. In clinical trials on adults receiving atazanavir, interstitial

Risk	What is known
	nephritis occurred uncommonly (in less than 10 patients in 1,000). Two cases of adults with interstitial nephritis and long-term kidney failure potentially associated with atazanavir have been reported. There is no evidence of a link between cobicistat alone and interstitial nephritis. Close monitoring of renal function is recommended in patients on Evotaz.
Symptoms of infection caused by the recovering immune system (immune reconstitution inflammatory syndrome)	Immune reconstitution inflammatory syndrome occurs when HIV patients are treated with HIV medicines. As the immunity recovers, the patient's body can start fighting infections, such as tuberculosis, that the patient may have had before starting HIV treatment. This recovery of immunity makes the symptoms of infection much more severe. Autoimmune disorders (when the immune system attacks the body's own tissue, such as in Graves' disease) have also been reported as part of the syndrome. The symptoms can occur months after the start of treatment. In 3 clinical studies of patients receiving atazanavir and cobicistat (either separately or together as a single tablet), no patient suffered immune reconstitution inflammatory syndrome. In clinical trials on atazanavir, immune reconstitution inflammatory syndrome occurred rarely (in less than10 cases in 10,000). No case of the syndrome has been reported in patients taking atazanavir since atazanavir entered the market. At present no measure is available to prevent immune reconstitution inflammatory syndrome. In the short term, doctors may need to watch patients more closely and patients may have more invasive procedures, such as a needle in the back to check for infection in the spinal cord and brain. In the longer term, there may be an increased risk of autoimmune disorders (such as Graves' disease).
Concurrent use of medicines whose use with cobicistat is contraindicated	Some medicines and herbal remedies taken during treatment with cobicistat may decrease the amount of cobicistat in the blood and reduce its boosting effect on atazanavir, thereby risking ineffective HIV treatment and promoting the development of resistance. Alternatively, cobicistat may increase the level of certain medicines and increase the risk of side effects. A number of medicines can interact with cobicistat and therefore must not be used together with Evotaz. Warnings on interactions have been included in the Evotaz

Risk	What is known
	summary of product characteristics (information for health professionals) and in the package leaflet (information for patients) to inform the doctor and patient.
Unintentional use of other medicines that contain atazanavir or cobicistat while on Evotaz leading to overdose (Medication error leading to overdose in case of concurrent use of Evotaz with any components including atazanavir, cobicistat or with fixed-dose combination products that contain cobicistat)	Information from clinical trials on overdose of atazanavir and cobicistat is limited. The main risks arise from excessive amount of atazanavir and include prolongation of PR interval (see above) or of QT interval (see above), and high bilirubin levels (see above). Warnings about inadvertent use of atazanavir products while taking Evotaz have been included in the Evotaz summary of product characteristics (information for health professionals) and in the package leaflets (information for patients) to inform the doctor and patient.

Missing information

Risk	What is known
Long term safety of Evotaz	There is no long-term safety data for Evotaz.
Elderly people	Clinical studies of cobicistat did not include enough patients aged over 65 years to determine if elderly patients respond differently than younger patients.
Women who are breastfeeding	It is not known whether atazanavir or cobicistat are found in human milk. In animal studies, both atazanavir and cobicistat were found in milk. Mothers should not breast feed if they are receiving Evotaz because of the risk of passing on HIV to the breastfeeding infant and the risk of serious reactions in the infant.
Hepatic impairment (severely decreased liver function)	Evotaz has not been studied in people with moderate to severe liver disease and it is not recommended for such people. Atazanavir has been studied in adults with moderate to severe liver disease using a single 400-mg dose. Increased blood concentrations of atazanavir are expected in patients with moderate or severe liver disease. Cobicistat has not been studied in patients with severe liver disease.
Pregnancy	Evotaz has not been studied in pregnant women. Evotaz should only be used during pregnancy if the potential benefit outweighs the risk. An ongoing study to collect information about birth defects in children of women who were exposed to HIV medicines during pregnancy has a large enough group of women who have taken atazanavir to detect a 2-fold increase in birth defects. No such

Risk	What is known
	increase has been detected to date. The use of atazanavir may be considered during pregnancy only if the potential benefit justifies the potential risk. There is limited information about cobicistat in pregnant women.
Limited safety data in children and adolescents aged under 18 years	The safety of Evotaz and its effectiveness against HIV infection has not been established in patients aged less than 18 years. The safety of cobicistat and its effectiveness against HIV has not been established in children aged less than 18 years.
Limited information on use in patients with kidney impairment	Evotaz should not be started in patients with creatinine clearance (a measure of kidney function) of less than 70 mL/minute and it should also not be used in patients on kidney dialysis. Evotaz should not be used with medicines that contain emtricitabine, lamivudine, tenofovir disoproxil, or adefovir in patients with severe kidney disease.
Limited information on use in patients with heart rhythm problems	Evotaz should be used with caution in patients with disorders in the electrical activity in the heart. Caution should be used when giving Evotaz with medicines that affect the electrical activity of the heart, such as verapamil or most medicines known as beta-blockers. Disorders with the electrical activity of the heart are a known risk with atazanavir (see above). Cobicistat has not been studied in patients who had significant heart-rhythm problems.
Limited information on drug-drug interactions	Drug interactions have not been specifically studied with Evotaz. However, drug interactions are anticipated with Evotaz on the basis of drug-interaction studies with the individual components (atazanavir and cobicistat), as well as the known effect of atazanavir and cobicistat on enzymes. Atazanavir has many drug interactions; the levels of medicines in the blood can be affected by atazanavir and levels of atazanavir can be affected by other medicines. More information is included in the summary of product characteristics and the package leaflet. Cobicistat has the potential to affect the levels in the blood of some other medicines and levels of cobicistat can be affected by other medicines. Studies are ongoing to provide further information on various drug interactions with cobicistat.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks

and recommendations for minimising them. Information for patients is available in plain language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The summary of product information and the package leaflet are part of the medicine's product information. The product information for Evotaz can be found on Evotaz's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	**Objectives**	**Safety concerns / efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
GS-US-216-0105: A Phase 2, randomized, double-blinded study of the safety and efficacy of GS-9350-boosted atazanavir (ATV/GS-9350) compared to ritonavir-boosted atazanavir (ATV/r) in combination with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in HIV-1 infected, antiretroviral treatment naïve adults	To evaluate the efficacy, safety and tolerability of ATV/COBI+TVD versus ATV/RTV+TVD	Missing information Long-term safety of ATV/COBI in HIV-1 infected patients	Ongoing	Final report (Week 192) Q1 2016
GS-US-216-0114: A Phase 3, randomized, double-blind study to evaluate the safety and efficacy of GS-9350-boosted atazanavir versus ritonavir-boosted atazanavir each administered with emtricitabine/tenofovir disoproxil fumarate in HIV-1 infected,	To evaluate the efficacy, safety and tolerability of ATV/COBI+TVD versus ATV/RTV+TVD	Missing information Long-term safety of ATV/COBI in HIV-1 infected patients	Ongoing	Final report (Week 192) Q1 2016

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
antiretroviral treatment-naive adults				
Antiretroviral Pregnancy Registry: (to detect any major teratogenic effects involving any of the Registry drugs, including ATV/COBI, to which pregnant women are exposed)	To detect any major teratogenic effects involving any of the Registry drugs, including ATV/COBI, to which pregnant women are exposed)	Missing information Pregnancy (ATV and COBI)	Ongoing	Interim reports are issued by the APR in June and December each year and the most current data available are included in PSUR/PBRER submissions

Studies which are a condition of the marketing authorisation

None of the studies above are conditions of the marketing authorisation

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in MM-YYYY.