VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Since the beginning of the epidemic, more than 70 million people have been infected with the HIV virus and about 35 million people have died of HIV. Globally, 36.7 million [34.0–39.8 million] people were living with HIV at the end of 2015. An estimated 0.8% [0.7-0.9%] of adults aged 15–49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions.[1]

Sub-Saharan Africa remains most severely affected, with nearly 1 in every 25 adults (4.4%) living with HIV and accounting for nearly 70% of the people living with HIV worldwide. South & South East Asia has an estimated 4 million cases, with about 250,000 deaths in 2010.[2] In 2008 approximately 1.2 million people in the United States had HIV. Over the 10-year period from 1999–2008 it resulted in about 17,500 deaths per year.[3] In the United Kingdom, as of 2009, there were approximately 86,500 cases and 516 deaths.[4] In Australia, as of 2009, there were about 21,171 cases and around 23 deaths.[5] In Canada as of 2008 there were about 65,000 cases and 53 deaths.[6]

VI.2.2 Summary of treatment benefits

An international randomised, open-label, multicenter, prospective trial of treatment naïve patients comparing atazanavir/ritonavir (300 mg/100 mg once daily) to lopinavir/ritonavir (400 mg/100 mg twice daily), each in combination with fixed dose tenofovir disoproxil fumarate/emtricitabine (300 mg/200 mg tablets once daily). The atazanavir/ritonavir arm showed similar (non-inferior) antiviral efficacy compared to the lopinavir/ritonavir arm. Analyses of data through 96 weeks of treatment demonstrated durability of antiviral activity.

In an open-label, randomised, comparative study following a 26- to 30-week induction phase with atazanavir 300 mg + ritonavir 100 mg once daily and two NRTIs, unboosted atazanavir 400 mg once daily and two NRTIs administered during a 48-week maintenance phase (n=87) had similar antiviral efficacy compared with atazanavir + ritonavir and two NRTIs (n=85) in HIV infected subjects with fully suppressed HIV replication, 78% of subjects on unboosted atazanavir and two NRTIs compared with 75% on atazanavir + ritonavir and two NRTIs.

A randomised, multicenter trial comparing atazanavir/ritonavir (300/100 mg once daily) and atazanavir/saquinavir (400/1,200 mg once daily), to lopinavir + ritonavir (400/100 mg fixed dose combination twice daily), each in combination with tenofovir disoproxil fumarate and one NRTI, in patients with virologic failure on two or more prior regimens containing at least one PI, NRTI, and NNRTI, showed that through 48 weeks of treatment, the mean changes from baseline in HIV RNA levels for atazanavir + ritonavir and lopinavir + ritonavir were similar (non-inferior). Through 96 weeks of treatment, mean HIV RNA changes from baseline for atazanavir + ritonavir and lopinavir + ritonavir met criteria for non-inferiority based on observed cases.

VI.2.3 Unknowns relating to treatment benefits

There are insufficient data in patients with hepatic impairment. Atazanavir with ritonavir should be used with caution in patients with mild hepatic impairment. Atazanavir with ritonavir must not be used in patients with moderate to severe hepatic impairment.

The safety and efficacy of atazanavir have not been demonstrated in children less than 3 months of age. Atazanavir should not be used in pediatric patients less than 3 months due to safety concerns.

There are limited data for the use of atazanavir in the elderly patient population.

There are inadequate data to support the safety and efficacy of the use of atazanavir during pregnancy and breastfeeding.

VI.2.4 Summary of safety concerns

Important identified risks:

Risk	**What is known**	**Preventability**
Changes in heart beat rhythm (both pediatric and adult populations) ***(PR interval prolongation)***	• Dose related asymptomatic changes in heart beat rhythm with atazanavir have been observed in clinical studies.	• Caution should be used with medicinal products known to induce changes in heart beat rhythm. In patients with pre-existing conduction

Risk	What is known	Preventability
	• Asymptomatic changes in heart beat rhythm were more frequent in children than adults. Asymptomatic first- and second-degree AV block was reported in children.	problems (second degree or higher atrioventricular or complex bundle-branch block), atazanavir should be used with caution and only if the benefits exceed the risk. • In children with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), atazanavir should be used with caution and only if the benefits exceed the risk. • Cardiac monitoring is recommended based on the presence of clinical findings (e.g. slower heart beat).
Kidney stones with or without alteration of the renal function (Nephrolithiasis)	• Kidney stones have been reported in patients receiving atazanavir. Some patients required hospitalization for additional management and some had complications. In some cases, kidney stones have been associated with acute renal failure or renal insufficiency.	• If signs or symptoms of kidney stones occur, temporary interruption or discontinuation of treatment may be considered.
Increased level of bilirubin in the blood (Hyperbilirubinemia)	• Reversible elevations in bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving atazanavir. • Indinavir is also associated with increased level of bilirubin in the blood due to inhibition of UGT.	• Hepatic transaminase elevations that occur with elevated bilirubin in patients receiving atazanavir should be evaluated for alternative causes. Alternative antiretroviral therapy to atazanavir may be considered if jaundice or scleral icterus is unacceptable to a patient. • Dose reduction of atazanavir

Risk	What is known	Preventability
		is not recommended because it may result in a loss of therapeutic effect and development of resistance. • Combinations of atazanavir and indinavir have not been studied and co-administration of these medicinal products is not recommended.
Severe skin reactions	• 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 in patients receiving atazanavir.	• Patients should be advised of the signs and symptoms and monitored closely for skin reactions. 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 atazanavir, atazanavir may not be restarted.
Stones in the gallbladder (Cholelithiasis)	Stones in the gallbladder have been reported in patients receiving atazanavir. Some patients required hospitalization for additional management and some had complications.	• If signs or symptoms of stones in the gallbladder occur, temporary interruption or discontinuation of treatment may be considered.
Allergic swelling of the skin around the lips and eyes (Angioedema)	Severe swelling of the skin and other tissues was identified through post-marketing surveillance. However, the frequencies were estimated from a statistical calculation based on the total number of patients exposed to atazanavir in	If there is swelling of the skin around the lips and eyes, it is important to get medical help immediately so that atazanavir can be discontinued if suspected to be the cause of the allergic reaction.

Risk	What is known	Preventability
	randomised controlled and other available clinical trials.	
Inflammation from previous infections ***[Immune reconstitution inflammatory syndrome (IRIS)]***	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) 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 occurs many months after initiation of treatment.	IRIS is not preventable; there is no known way to prevent IRIS and no known way that IRIS develops.
Chronic kidney problems (***Chronic kidney disease)***	Chronic kidney disease in HIV-infected patients treated with atazanavir, with or without ritonavir, has been reported during postmarketing surveillance. A large prospective observational study has shown an association between an	Regular monitoring of the renal function of patients should be maintained throughout the treatment duration.

Risk	What is known	Preventability
	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.	

Important potential risks:

Risk	What is known (Including reason why it is considered a potential risk)
Changes in heart beat rhythm (QT prolongation)	Dose related changes in heart beat rhythm with atazanavir have been observed in clinical studies. Caution should be used with medicinal products known to induce changes in heartbeat. In patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), atazanavir should be used with caution and only if the benefits exceed the risk. Particular caution should be used when prescribing Atazanavir in association with medicinal products which have the potential to cause changes in heart beat rhythm and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances).
Bilirubin-induced brain dysfunction (Kernicterus)	It is not known whether atazanavir with ritonavir administered to the mother during pregnancy will exacerbate physiological hyperbilirubinaemia and lead to kernicterus in neonates and infants. In the prepartum period, additional monitoring should be considered.
Acute renal failure (adults)	In some cases, nephrolithiasis has been associated with acute renal failure or renal insufficiency.
Kidney inflammation (Interstitial nephritis)	Kidney inflammation has been reported for patients treated with atazanavir. The frequency is defined as uncommon.
Lack of efficacy due to unboosted ATV "off-label use"	Use of ATV (400 mg) without RTV in certain populations can lead to lower exposures; geometric mean ATV AUC is approximately 66% lower and ATV Cmin is approximately 82% lower than ATV with RTV. These reduced exposures may lead to loss of efficacy and the potential for development of drug resistance to the PI class and reduced therapeutic options. Lack of efficacy could lead to vertical transmission from mother to child in the case of pregnancy.

Missing information:

Risk	What is known
Liver dysfunction (Hepatic impairment)	Atazanavir with ritonavir has not been studied in patients with liver dysfunction. Atazanavir with ritonavir should be used with caution in patients with mild liver dysfunction. Atazanavir with ritonavir must not be used in patients with moderate to severe liver dysfunction. In case of withdrawal of ritonavir from the initial recommended ritonavir boosted regimen, unboosted atazanavir could be maintained in patients with mild liver dysfunction at a dose of 400 mg, and in patients with moderate liver dysfunction with a reduced dose of 300 mg once daily with food. Unboosted Atazanavir must not be used in patients with severe liver dysfunction.
Pregnancy	During the second and third trimesters of pregnancy: atazanavir 300 mg with ritonavir 100 mg may not provide sufficient exposure to atazanavir, especially when the activity of atazanavir or the whole regimen may be compromised due to drug resistance. Since there are limited data available and due to inter-patient variability during pregnancy, Therapeutic Drug Monitoring (TDM) may be considered to ensure adequate exposure. The risk of a further decrease in atazanavir exposure is expected when atazanavir is given with medicinal products known to reduce its exposure (e.g., tenofovir or H2-receptor antagonists). If tenofovir or an H2-receptor antagonist is needed, a dose increase to atazanavir 400 mg with ritonavir 100 mg with TDM may be considered. It is not recommended to use atazanavir with ritonavir for pregnant patients who are receiving both tenofovir and an H2-receptor antagonist. A moderate amount of data in pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative toxicity of atazanavir. Animal studies do not indicate reproductive toxicity. The use of Atazanavir with ritonavir may be considered during pregnancy only if the potential benefit justifies the potential risk. It is not known whether atazanavir with ritonavir administered to the mother during pregnancy will exacerbate physiological increase of the level of bilirubin in the blood and lead to bilirubin-induced brain dysfunction in neonates and infants.
Pediatric patients <3 months of age	Atazanavir should not be used in children less than 3 months because of safety concerns especially taking into account the potential risk of kernicterus.

Risk	What is known
Geriatric patients	A study of the pharmacokinetics of atazanavir was performed in 59 healthy male and female subjects (29 young, 30 elderly). There were no clinically important pharmacokinetic differences based on age.
Women who are breastfeeding	Atazanavir is excreted in human milk. Patients should not breast-feed while taking atazanavir. It is recommended that women infected with HIV do not breast-feed because the virus might be transmitted through the breast milk.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for atazanavir 100 mg, 150 mg, 200 mg & 300 mg hard capsules can be found as Annex 2.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable

VI.2.7 Summary of changes to the risk management plan over time

Not applicable