VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

The human immunodeficiency virus type 1 (HIV-1) is the primary cause of the acquired immunodeficiency syndrome (AIDS), which is a slow, advancing and deteriorative disease of the human immune system.

The global proportion of a population found to have HIV-1 has stabilized at 0.8%, with 33 million people living with HIV/AIDS, 2.7 million new infections, and 2.0 million AIDS deaths in 2007. Heterosexual spread in the general population is the main mode of transmission in sub-Saharan Africa, which remains the most heavily affected region, with 67% of the global burden. Male-male sex, injection drug use, and sex work are the predominant risk factors in most other regions. Infection rates are declining in some regions, including some of the most heavily affected countries in Africa, but climbing elsewhere such as in eastern Europe and central Asia.

VI.2.2 Summary of treatment benefits

Based on the available data from clinical studies and clinical experience of several years, atazanavir represents an effective drug in the treatment of HIV-1 infection.

Infection with HIV is not considered a curable condition because eradication of HIV has not been achieved with available antiretroviral therapy (ART). Treatment is directed toward decreasing the impact of HIV infection on morbidity and mortality, improving quality of life, preventing transmission of the virus, and maintaining immune function by effective suppression of the viral load.

If administered as indicated in the Summary of Product Characteristics and taking into account the contra-indications, the warnings and precautions, atazanavir can be considered effective in the approved indications and generally well tolerated.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
PR interval prolongation *(Irregular heart beat)*	Atazanavir should not be taken with certain medicines: medicines to lower blood pressure, to slow heart rate, or to correct heart rhythm (e.g. bepridil, diltiazem, verapamil). Palpitation (fast or irregular heart beat) may affect up to 1 in 1000 people. There have been reports of unusual heart beat in both adult and paediatric patients using atazanavir.	Patients should inform the doctor if they are taking any medicines for blood pressure or heart disorders (e.g. bepridil, diltiazem, verapamil). Children receiving atazanavir may require their heart to be monitored. Unusual heart beat should be reported to the doctor. Double dose should not be taken.
Hyperbilirubinaemia *(Increase in the level of bilirubin in the blood)*	Hyperbilirubinaemia has occurred in patients receiving atazanavir. The signs may be a mild yellowing of the skin or eyes.	Patients should inform the doctor if they notice mild yellowing of the skin or eyes, especially if they also have hepatitis B or C. Patients should inform the doctor if they are also taking other medicines to treat HIV infection (e.g. indinavir).
Nephrolithiasis *(Formation of kidney stones)*	Kidney stones have been reported in patients taking atazanavir. Nephrolithiasis may affect up to 1 in 100 people.	Patients should inform the doctor if they develop signs or symptoms of kidney stones (pain in the side, blood in urine, pain when urinating).
Severe skin reactions	Serious skin rash, including Stevens-Johnson syndrome, has been reported in patients taking atazanavir. Up to 1 in 100 people may experience serious skin rashes (allergic reactions including rash, a	Patients with known allergy to atazanavir or any of the other ingredients of this medicine must not take this product. Doctor should be informed immediately in case a patient develops a rash.

Risk	What is known	Preventability
	high temperature, increased levels of liver enzymes seen in blood tests, an increase in a type of white blood cell [esosinophilia], and/or enlarged lymph nodes). Up to 1 in 1000 people may experience allergic reactions including serious skin rash, a high temperature and enlarged lymph nodes (Stevens-Johnson syndrome).	
Cholelithiasis *(Gallstones)*	Up to 1 in 100 people may experience gallstones.	Patients should inform the doctor, pharmacist or nurse if they develop any side effects.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
QT prolongation *(Irregular heart beat)*	QT prolongation may affect up to 1 in 1000 people. There have been reports of unusual heart beat in both adult and paediatric patients using atazanavir.
Kernicterus *(Bilirubin-induced brain dysfunction)*	No cases of kernicterus in neonates were reported, however, it is considered a potential risk for neonates and infants.
Acute renal failure (adults) *(Acute kidney injury (adults))*	Acute kidney injury is an abrupt loss of kidney function. This safety concern was added based on the RMP of the reference product Reyataz hard capsules.
Angioedema *(Severe swelling)*	Up to 1 in 100 people may experience angioedema (severe swelling of the skin and other tissues most often the lips or the eyes).
Interstitial nephritis *(Kidney inflammation)*	Interstitial nephritis is a form of inflammation of kidneys which affects the interstitium (support tissue in kidneys) of the kidneys surrounding the tubules (functional part of the kidney). Up to 1 in 100 people may experience kidney inflammation.
Immune reconstitution inflammatory syndrome (IRIS) *(immune recovery syndrome)*	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. Doctor should be immediately informed about any symptoms of infection. 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 any symptoms of infection or other

Risk	What is known (Including reason why it is considered a potential risk)
	symptoms are noticed, such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, the doctor should be informed immediately to start necessary treatment.
Lack of efficacy due to unboosted ATV "off-label use"	Atazanavir should be taken together with ritonavir in order to insure sufficient drug levels for suppression of the virus. Therefore strict recommendations exist regarding this drug association and the withdrawal of ritonavir. This medicine should be taken exactly as the doctor has prescribed it. This way, it is sure the drug is fully effective and the risk of the virus developing resistance to the treatment is reduced.

Missing information

Risk	What is known
Pregnancy	Only moderate amount of data is available on use in pregnant women. Patients should inform the doctor if they are pregnant or planning to become pregnant. They should talk to the doctor about pregnancy.
Hepatic impairment *(Liver failure)*	Patients should not take atazanavir if they have moderate to severe liver problems (this is evaluated by the doctor).
Paediatric patients <3 months of age	Atazanavir should not be not be used in children less than 3 months because of risk of serious complications.
Geriatrics	No specific information is available for this group of patients.
Women who are breastfeeding	It is unknown whether atazanavir or atazanavir metabolites are excreted in human milk. Therefore HIV infected women should not breast-feed their infants in order to avoid transmission of HIV.

VI.2.5 Summary of risk minimisation measures by safety concern

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

Table 3. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	03 March 2014	**Important identified risks** • Cardiac conduction abnormalities • Hyperbilirubinaemia • Nephrolithiasis **Important potential risks** • QT prolongation • Kernicterus **Missing information** • Pregnancy and lactation • Renal impairment • Hepatic impairment • Paediatric population: o Safety data in paediatric patients < 6 years (<15 kg) o Limited safety data in children 6 years to less than 18 years of age	Not applicable.
1.1	18 Nov 2014	**Important identified risks** • PR interval prolongation • Hyperbilirubinaemia • Nephrolithiasis • Severe skin reactions • Cholelithiasis **Important potential risks** • QT prolongation • Kernicterus • Acute renal failure (adults) • Angioedema • Interstitial nephritis • Immune reconstitution inflammatory syndrome (IRIS) **Missing information** • Pregnancy • Hepatic impairment • Paediatric population: o Safety data in paediatric patients < 6 years (<15 kg) o Limited safety data in children 6 years to less than 18 years of age	Safety concerns have been updated based on RMS Day 70 Preliminary Assessment Report (SE/H/1398/01-03/DC)
1.2	29 Jul 2015	No changes	New SPC and PIL added to Annex 2.
1.3	25 Nov 2016	**Important identified risks** • PR interval prolongation (both paediatric	Align the PI and RMP with the reference

Version	Date	Safety Concerns	Comment
		and adult populations) • Hyperbilirubinaemia • Nephrolithiasis with or without alteration of the renal function • Severe skin reactions • Cholelithiasis **Important potential risks** • QT prolongation • Kernicterus • Acute renal failure (adults) • Angioedema • Interstitial nephritis • Immune reconstitution inflammatory syndrome (IRIS) • Lack of efficacy due to unboosted ATV "off-label use" **Missing information** • Pregnancy • Hepatic impairment • Paediatric patients <3 months of age • Geriatrics • Women who are breastfeeding	product information and RMP.