VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

In 1981, the Centers for Disease Control and Prevention reported unusual clusters of pneumonia caused by fungus (*Pneumocystis carinii*pneumonia) and cancer (Kaposi's sarcoma) in gay men in parts of the US. These were the first reported cases of Acquired Immune Deficiency Syndrome (AIDS). Twenty years later, the global HIV/AIDS epidemic has killed an estimated 21.8 million people and another 36.1 million are living with HIV infection. Around 95% of these people live in non-industrialised countries with few financial resources to deal with the HIV/AIDS epidemic. Over 90% of people living with HIV/AIDS do not know they are infected and even if they did antiretroviral therapies (ART) are not at present an option for them. Most people living with HIV/AIDS are in the economically productive age-group supporting children and elderly relatives and most will receive minimal

care when they finally develop AIDS-related illness. From many aspects the global HIV/AIDS epidemic is an enormous tragedy for humankind. [4]

VI.2.2 Summary of treatment benefits

Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infected patients (adults and children of 2 years of age and older).

In a study ritonavir was used as add-on therapy with other drug (i.e. zidovudine, stavudine, didanosine and zalcitabine etc.) in HIV-1 infected patients. The results indicated decrease in mortality and AIDS related events.

In another study, HIV-1 infected patients without previous anti-viral therapy were treated with ritonavir in combination with zidovudine or alone and showed beneficial effect.

In one study, HIV infected children showed good response in favour of a triple drug therapy of ritonavir, zidovudine and lamivudine for 48 weeks.

In a study 50 HIV-1 infected children age 4 weeks to 2 years received ritonavir 350 or 450 mg/m^2 every 12 hours along with zidovudine 160 mg/m^2 every 8 hours and lamivudine 4 mg/kg every 12 hours. Response was similar in both dosing regimens and across patient age.

In a study, 76 HIV-1 infected children aged 6 months to 12 years who were received ritonavir 350 or 450 mg/m^2 every 12 hours co-administered with lamivudine and stavudine. Favorable response was achieved at week 48.

However, these studies were conducted for the reference product (Norvir, AbbVie Ltd., UK) and no studies were performed for Accord ritonavir to evaluate the expected benefit, considering its similarity to the reference product.

VI.2.3 Unknowns relating to treatment benefits

Data on use of ritonavir 100 mg tabletin liver disease patients, kidney disease patients, use during pregnancy and breast feeding as well as use in elderly patients andchildren below 2 years of age is not available.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Toxicity of ritonavir oral solution in preterm neonates	None	None
Abnormal ECG (PR interval prolongation)	Ritonavir has been shown to cause abnormal ECG (modest asymptomatic prolongation of the PR interval) in some healthy adult subjects. Rare reports heart block (2^{nd} or 3^{rd} degree atrioventricular block) in patients with underlying heart disease or in patients receiving medicinal products for abnormal ECG (known to prolong the PR interval) have been reported when receiving ritonavir.	Yes. During the treatment, doctor should monitor the patient's ECG on regular interval.
Disorder in which a person's immune system attacks parts of his or her own body (Immune Reconstitution Inflammatory Syndrome (IRIS) manifesting as autoimmune disorders (such as	Disorder in which a person's immune system attacks parts of his or her own body (Graves disease) has been reported.	Yes. Patients should inform to their doctor for occurrenceof any immune disorder during the treatment.

Risk	What is known	Preventability
Graves' disease))		

Important potential risks

Risk	What is known
Drug-drug interactions with HCV products	Patients with hepatitis and treated with combination antiviral therapy are at an increased risk of life-threateningliver disease.
Risk of bleeding	There have been reports of increased bleeding in patients with impaired ability to control blood clotting or coagulation (haemophilia) who are taking this protease inhibitors medicine.
Destruction of bone (Osteonecrosis)	Cases for destruction of bone (osteonecrosis) have been reported in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy.

Missing information

Risk	What is known
Severe liver disease (hepatic impairment)	The safety of ritonavir has not been studied in the patient with severe liver disease (hepatic impairment).
Severe kidney disease (renal impairment)	Kidney disease (acute renal failure) has been reported in patient taking ritonavir.
Use during pregnancy and breast feeding (lactation)	There is a limited data on use of ritonavir in pregnant and breast feeding (lactating) women.
Limited experience with the 100 mg Tablet in HIV-1-	The safety or efficacy of ritonavir has not been studied in the

Risk	What is known
infected childrenless than 2 years of age	patient less than 2 years of age.
Elderly (Geriatric) population	Data on study of what the body does to the drug indicated that no dose adjustment is necessary for older patients.

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 health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No studies planned

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

Version	Date	Safety Concern	Comment
3.0	18-Aug-2015	Following safety concerns are added: **Important identified risk**: • Toxicity of ritonavir oral solution in preterm neonates **Missing information:** • Geriatric population	Safety concerns have been updated based on RMS Day 120 Draft Preliminary Assessment Report of Ritonavir 100 mg tablets (NL/H/3149/01-02/DC and NL/H/3150/01-02/DC) by The Netherland,

Version	Date	Safety Concern	Comment
			dated 10 July 2015.
2.0	25-Jun-2015	Following safety concerns are added: **Important identified risk**: • Immune Reconstitution Inflammatory Syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease) **Important potential risk:** • Drug-drug interactions with HCV products Following safety concerns are removed: **Important identified risk**: • Pancreatitis • Diabetes/Hyperglycemia **Important potential risk:** • Lipodystrophy • Nephrolithiasis with combination with other protease inhibitors and ritonavir	Safety concerns have been updated based on RMS Day 70 PreliminaryAssessment Report of Ritonavir Accord/Sandoz 100 mg tablets (NL/H/3149/01-02/DC and NL/H/3150/01-02/DC) by The Netherland, dated 05 August 2014.

Version	Date	Safety Concern	Comment
		• Stevens Johnson syndrome • Drug interaction between ritonavir and quetiapine • Drug interaction between ritonavir and fluticasonepropionate The important potential risk PR interval prolongation has been upgraded to important identified risk.	