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.

VI.2.2 Summary of treatment benefits

Lopinavir / ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults, adolescents and children above the age of 2 years.

A study was conducted in 653 patients who were not received prior antiretroviral therapy. Three hundred and twenty six (326) patients received lopinavir / ritonavir (400/100 mg twice daily) while three hundred and twenty six (327) patients received nelfinavir (750 mg three times daily) in addition to stavudine and lamivudine. Lopinavir / ritonavir treated patient got good response.

Another study was conducted in 599 patients who were received prior antiretroviral therapy. Three hundred patients were received lopinavir/ritonavir 800/200 mg once daily while remaining 299 patients were received lopinavir/ritonavir 400/100 mg twice daily. Patients were

administered at least two nucleoside/nucleotide reverse transcriptase inhibitors selected by the investigator.

A study was also conducted in 100 paediatric patients. Patients were either received 230 mg lopinavir/57.5 mg ritonavir per m^2 or 300 mg lopinavir/75 mg ritonavir per m^2. Patients were in range of 6 months to 12 years with 14 patients less than 2 years old and 6 patients one year or less. Mean baseline CD4+ T-cell count was 838 cells/mm3 and mean baseline plasma HIV-1 RNA was 4.7 log10 copies/ml.

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

VI.2.3 Unknowns relating to treatment benefits

Data of premature birth in women using a lopinavir/ritonavir-based anti-retroviral regimen during pregnancy and use of lopinavir/ritonavir in elderly patients is not available.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Increase in lipid level (Lipid elevations)	Treatment with Lopinavir / Ritonavir Accord has resulted in increase cholesterol and triglycerides (a form of fat) levels in blood, These may lead to muscle disease (myopathy) and damaged to skeletal muscle	Yes. Patient should inform the physician if taking any drugs to lower blood cholesterol. During treatment, blood cholesterol level should be monitor at the specific interval.

Risk	What is known	Preventability
	tissue (rhabdomyolysis). Large increases in the amount of triglycerides (fats in the blood) have been considered a risk factor for inflammation of the pancreas (pancreatitis). The treatment of Lopinavir / Ritonavir Accord along with the drug used to lower blood cholesterol (HMG-CoA CoA reductase inhibitor: Lovastatin, simvastatin, atorvastatin) is not advisable. Lopinavir / Ritonavir Accord dose should be reduced in case of using with drug used to lower blood cholesterol like rosuvastatin.	Patient should inform the physician for the occurrence of muscle disease (myopathy) and damaged to skeletal muscle tissue (rhabdomyolysis) while on treatment.

Risk	What is known	Preventability
Immune disorders [Immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorder (such as Graves disease)]	Increase of symptoms related to an inactive infection in body (immune reactivation). People taking Lopinavir/ritonavir Accord may still develop infections or other illnesses associated with HIV disease and AIDS. Immune disorders (Graves disease) have also been reported with lopinavir / ritonavir.	Yes. Patients with HIV infection or AIDS remain under the supervision of physician while taking Lopinavir/ritonavir Accord. Patient should inform the physician if they are taking medicine to treat AIDS (HIV-1 integrase inhibitor e.g. raltegravir)

Important potential risks

Risk	What is known
Drug interaction with medicine used to treat hepatitis C (HCV protease inhibitors telaprevir and boceprevir)	Lopinavir / Ritonavir Accord decreases the blood concentration of medicines used to treat hepatitis C (HCV protease inhibitors telaprevir and boceprevir). Patients should not take these drugs together.
Changes in ECG with high dose (QT prolongation with supratherapeutic doses)	Abnormality in electrocardiogram (atrioventricular block) and heart attack (myocardial infarctin) observed uncommonly with the drug. Particular caution must be used when taking Lopinavir/ritonavir Accord and medicinal products known to effect on electrocardiogram

Risk	What is known
	(induce QT interval prolongation) such as: chlorpheniramine, quinidine, erythromycin, clarithromycin. This interaction may cause cardiac events.
Changes in ECG with therapeutic dose (PR prolongation at therapeutic dosing)	Lopinavir/ritonavir Accord caused changed in electrogram (modest asymptomatic prolongation of the PR interval) in some healthy adult. Rare cases of abnormality in electrocardiogram (2^{nd} or 3^{rd} degree atroventricular block) in patients with heart disease are reported.

Missing information

Risk	What is known
Unknown risk of premature birth in women using a lopinavir/ritonavir-based antiviral therapy (anti-retroviral regimen) during pregnancy)	No studies are available for using Lopinavir/ritonavir Accord in pregnant women. However, as per the registry (Antiretroviral Pregnancy Registry), more than 600 women exposed to Lopinavir/ritonavir Accord during pregnancy developed there is increase risk of birth defects. Animal study mentioned increase in drug toxicity.
Use in elderly patients)	Data is not available for using Lopinavir/ritonavir Accord in elderly 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. An abbreviated version of this in lay language is

provided in the form of the package leaflet (PL). 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
2.0	5 Nov 2014	Safety concerns are modified as per the RMS Day 70 Preliminary Assessment Report by The Netherlands dated 02 May 2014. Following are updated safety concerns **Important identified risk**: • Lipid elevations • Immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorder (such as Graves disease) **Important potential risk:** • Drug interaction with HCV	-

Version	Date	Safety Concern	Comment
		protease inhibitors (telaprevir and boceprevir) • QT prolongation with supratherapeutic doses • PR prolongation at therapeutic dosing **Missing information:** • Unknown risk of premature birth in women using a lopinavir/ritonavir-based anti-retroviral regimen during pregnancy • Use in elderly patients	