Part VI: Summary of the Risk Management Plan

Summary of risk management plan for Kaletra/Aluvia (lopinavir/ritonavir)

This is a summary of the risk management plan (RMP) for lopinavir/ritonavir (Kaletra/Aluvia). The RMP details important risks of lopinavir/ritonavir, how these risks can be minimized, and how more information will be obtained about lopinavir/ritonavir's risks and uncertainties (missing information).

lopinavir/ritonavir's summary of product characteristics (SmPCs) and its package leaflets (PLs) give essential information to health care professionals and patients on how lopinavir/ritonavir should be used.

This summary of the RMP for lopinavir/ritonavir should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which are part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of lopinavir/ritonavir's RMP.

I The Medicine and What it Is Used For

Lopinavir/ritonavir oral solution is indicated for treatment of HIV-1 infected adults, adolescents and children 14 days of age and older (see SmPC for the full indication). Lopinavir/ritonavir 200 mg/100 mg film-coated tablets and Lopinavir/ritonavir 100 mg/25 mg film-coated tablets are indicated for treatment of HIV-1 infected adults, adolescents, and children above the age of 2 years (see SmPC for the full indication). Lopinavir/ritonavir contains lopinavir/ritonavir as the active substance and it is given by mouth.

Further information about the evaluation of lopinavir/ritonavir benefits can be found in lopinavir/ritonavir's EPAR, including in its plain-language summary, available on the EMA website.

II Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of lopinavir/ritonavir, together with measures to minimize such risks and the proposed studies for learning more about lopinavir/ritonavir's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and health care professionals;
- Important advice on the medicine's packaging;
- The authorized pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine PV activities.

If important information that may affect the safe use of lopinavir/ritonavir is not yet available, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of lopinavir/ritonavir are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of lopinavir/ritonavir. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• Toxicity in preterm neonates of lopinavir/ritonavir oral solution. • Immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease). • Lipid elevations.
Important potential risks	• QT prolongation with supratherapeutic doses. • PR prolongation at therapeutic dosing. • Risks of overdose resulting from medication errors with lopinavir/ritonavir oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg
Missing information	• Not applicable

II.B Summary of Important Risks

Important identified risk: Harm from the alcohol and propylene glycol contained in lopinavir/ritonavir oral solution in pre-mature newborn babies. **(Toxicity in preterm neonates of lopinavir/ritonavir oral solution)**	
Evidence for linking the risk to the medicine	Lopinavir/ritonavir oral solution contains: • alcohol – 42%, which is 356.3 mg per mL. • propylene glycol – 15%, which is 152.7 mg per mL. These can cause serious and life threatening side effects in premature newborn babies.
Risk factors and risk groups	Preterm neonates (neonates before a postmenstrual age [first day of the mother's last menstrual period to birth plus the time elapsed after birth] of 42 weeks and before a postnatal age of at least 14 days).
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.2 - Posology and method of administration, including dosing instruction for oral solution based on infant's BSA and body weight for accurate dosing to avoid toxicity from excipients SmPC Section 4.4 - Special warnings and precautions for use, regarding particular risk of toxicity in relation to the amount of alcohol and propylene glycol contained in lopinavir/ritonavir oral solution Close monitoring instruction for infants for toxicity related to lopinavir/ritonavir oral solution is provided in Section 4.4 of SmPC Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists

Important identified risk: Immune Reconstitution Inflammatory Syndrome (IRIS) manifesting as autoimmune disorders – such as Graves' disease

Evidence for linking the risk to the medicine	HIV treatment usually improves the ability of the immune system to fight infections. This improvement can make the body over-respond to infections in the body which have previously been hidden infections. • This is called IRIS or 'Immune Reconstitution Inflammatory Syndrome.' • Patients with IRIS could be at a higher risk of getting some illnesses called 'auto-immune disorders:' • This is where your immune system attacks healthy parts of your body • This includes hyperthyroidism (Graves' disease).
Risk factors and risk groups	Patients with pre-existing infections and low baseline CD4 cell counts.
Risk minimization measures	Routine risk minimization: SmPC Section 4.4 - Special warnings and precautions for use, regarding patients at risk of immune reconstitution informatory syndrome (IRIS), inflammatory reaction to asymptomatic or residual opportunistic infections with relevant examples of these conditions. Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist

Important identified risk: Increase in fat (lipid) levels in the blood (Lipid elevations)	
Evidence for linking the risk to the medicine	Increased fats (lipids) in the blood have been linked with 'PI' HIV medicines like lopinavir/ritonavir. There are several causes of this: • the HIV infection itself • infections because of the body's immune system being less able to fight infections • treatments for HIV • the stage of the HIV

	• any heart problems
Risk factors and risk groups	Particular caution should be paid to patients with high values at baseline and with history of lipid disorders.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 - Special warnings and precautions for use, regarding: • increase blood levels of lipids during antiretroviral therapy. • Information to monitor blood lipids during treatment using HIV guideline. Lipid disorders should be managed as clinically appropriate. Information on the appropriate lipid-lowering agents and lopinavir/ritonavir and important DDIs - lipid-lowering agents interactions are provided in Section 4.5 Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists
Important potential risk: QT prolongations with supratherapeutic doses	
Evidence for linking the risk to the medicine	QTcF interval was evaluated in a study in 39 healthy adults taking either 400/100 mg lopinavir/ritonavir twice daily or 800/200 mg lopinavir/ritonavir twice daily. No subject experienced an increase in QTcF of ≥ 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec. As noted in the prescribing information, through drug-drug interactions lopinavir/ritonavir can increase concentrations of certain co-administered medicinal products, come of which are known to cause QT prolongation, and this may result in an increase of their associated cardiac adverse reactions. Health care professionals should take care when prescribing lopinavir/ritonavir and medicines that can cause QT prolongation. These include: • chlorpheniramine – for allergies • quinidine – for heart beat problems • antibiotics such as erythromycin and

	clarithromycin • antibacterials called 'fluoroquinolones' such as moxifloxacin and ciprofloxacin
Risk factors and risk groups	Individuals with congenital long QT syndrome, hypokalemia, or who may be taking concomitant drugs that have associated QTc prolongation as an adverse event.
Risk minimization measures	Routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists

Important potential risk: PR prolongation at therapeutic dosing	
Evidence for linking the risk to the medicine	Lopinavir/ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some patients (text in CCDS). Rare reports of second- or third-degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving drugs known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving lopinavir/ritonavir. Lopinavir/ritonavir should be used with caution in such patients.
Risk factors and risk groups	Individuals with pre-existing structural heart disease and pre-existing conduction system abnormalities or who are taking concomitant drugs that have PR prolongation as an associated adverse event. First-degree AV block, defined as prolongation of the PR interval on the surface electrocardiogram, is not an uncommon finding on electrocardiographic screening of asymptomatic young individuals. Prevalences of 0.65% to 1.1% have been reported. In the majority of cases the PR prolongation may be rendered normal by autonomic intervention. Long-term follow-up studies have indicated that although the risk of subsequent coronary artery disease (CAD) may be slightly increased, the risk of sudden death, syncope, or advanced AV block is not (Bexton 1984).
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 - Special warnings and

	precautions for use, regarding patients' pre-existing conditions for PR prolongation while taking lopinavir/ritonavir Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists
Important potential risk: Errors with dosing that cause too much lopinavir/ritonavir oral solution to be swallowed by infants. (Risk of overdose resulting from medication errors with lopinavir/ritonavir oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg)	
Evidence for linking the risk to the medicine	As with all liquid medicines administered with a syringe, it is possible to draw up too much medicine into the syringe and administer an overdose of medicine. Lopinavir/ritonavir oral solution contains ingredients called ethanol and propylene glycol, which may be harmful when given in excessive amounts to young children. It is extremely important that the correct dose of lopinavir/ritonavir oral solution is given to young children. Children should attend all of their HIV clinic appointments so that the dose of HIV medication can be adjusted as they grow and gain weight.
Risk factors and risk groups	Infants from 2 to 9 weeks of age and weighing less than 3.8 kg
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.2 - Posology and method of administration, including dosing instruction for oral solution based on infant's BSA and body weight for accurate dosing SmPC Section 4.9 – overdose including general information on unintended overdoses in preterm neonates and treatment of overdose Instruction on accurate dosing based on BSA and body weight for infants and children is provided in Section 4.2 Instructions to minimize medication errors and overdose leading to potential propylene glycol and ethanol toxicity during dosing and dispensing for infants and children are provided in Section 4.4 Close monitoring instruction for infants for toxicity related to lopinavir/ritonavir oral solution is provided

	in Section 4.4 Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • A smaller volume (2 mL/2.5 mL) oral dosing syringe is available to measure lower doses.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorization

Not applicable.

II.C.2 Other studies in post-authorisation development plan

Not applicable.