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Summary of the risk management plan (RMP) for Lopinavir/Ritonavir Mylan (lopinavir / ritonavir)

This is a summary of the risk management plan (RMP) for Lopinavir/Ritonavir Mylan, which details the measures to be taken in order to ensure that Lopinavir/Ritonavir Mylan is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Lopinavir/Ritonavir Mylan, which can be found on Lopinavir/Ritonavir Mylan's EPAR page.

Overview of disease epidemiology

Lopinavir/Ritonavir Mylan is an antiviral medicine used in combination with other medicines to treat adults infected with human immunodeficiency virus type 1 (HIV-1), a virus that causes acquired immune deficiency syndrome (AIDS). HIV attacks the immune system (the body's natural defences against infection) and weakens it by destroying a type of white blood cells called CD4 T-cells, which protect the body against infection caused by bacteria, viruses and other germs. If left untreated, the HIV virus multiplies and the body starts losing its ability to fight infection and disease.

In 2012 over 35 million people were living with HIV, increased from 34 million in 2011 (including 900,000 in Western and Central Europe and 1.4 million in Eastern Europe and Central Asia). In 2012, about 2.3 million people were newly infected with HIV. In 2011, 1.7 million people died of AIDS, including 7,900 in Western and Central Europe and 92,000 in Eastern Europe and Central Asia.

There is no cure for HIV, but early and effective treatment can reduce HIV in the blood and keep it at a low level. This allows people to stay healthier and live longer. Resistance to HIV medicines can be a problem. So, over time, a particular combination of medicines may not be able to control the HIV virus properly, and treatment may need to be changed; treatment may also be changed because of side effects.

Summary of treatment benefits

Lopinavir/Ritonavir Mylan contains the active substances lopinavir and ritonavir. Lopinavir/Ritonavir Mylan is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU) called Kaletra.

Because Lopinavir/Ritonavir Mylan is a generic medicine, its benefits and risks are taken as being the same as those of the reference medicine. Studies in people have been limited to tests to determine that it is bioequivalent to the reference medicine, Kaletra. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

Unknowns relating to treatment benefits

The efficacy of lopinavir/ritonavir has not been demonstrated in patients under the age of 2 years and in older people infected with HIV.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Use in patients with pre-existing liver disease (liver disorder)	Patients with a history of liver disease, including chronic hepatitis B or C, are at increased risk of severe and potentially fatal liver side effects during treatment with lopinavir/ritonavir. Patients with pre-existing liver disease have an increased frequency of some liver disorders such as increased liver enzymes associated with inflammation of the liver, fatty liver, liver enlargement, cholangitis (biliary duct infection), hyperbilirubinemia (increase in bilirubin) and jaundice.	Lopinavir/Ritonavir Mylan must not be used in patients with severely reduced liver function. Appropriate laboratory tests should be performed before starting therapy, and close monitoring is recommended during treatment with Lopinavir/Ritonavir Mylan. Patients should tell their doctor if they have a history of liver problems. Treatment should be stopped if liver disease worsens in these patients. Clarithromycin and colchicine should not be taken along with Lopinavir/Ritonavir Mylan.
Increased risk of bleeding in patient with haemophilia (haemorrhage)	Patients suffering from the blood disorder haemophilia, if treated with Lopinavir/Ritonavir Mylan may have increased bleeding, including spontaneous skin haematomas and bleeding into joint spaces. In some patients additional factor VIII was given. Giving rivaroxaban with lopinavir/ritonavir may increase the risk of bleeding.	Patients should tell their doctor if they have haemophilia type A or B. Doctors should inform patients with haemophilia of the increased risk of bleeding during treatment with Lopinavir/Ritonavir Mylan. The medicine rivaroxaban should not be used along with Lopinavir/Ritonavir Mylan.
Increase blood levels of triglycerides (fats) and cholesterol (hypertriglyceridaemia and hypercholesterolaemia)	Treatment with lopinavir/ ritonavir may result in increases in cholesterol and triglyceride (a type of fat) levels in the blood. Patients with advanced HIV disease may be at risk of increased triglycerides. A large increase in the amount of triglycerides in the blood is a risk factor for pancreas inflammation (see below). Giving fosamprenavir with lopinavir/ ritonavir may lead to an increase in triglyceride level.	Before starting therapy with Lopinavir/Ritonavir Mylan and at periodic intervals during therapy, triglycerides and cholesterol blood levels should be monitored, especially in patients with high values and with history of lipid diseases. Patients should tell their doctor if they have/had large increases in the amount of triglycerides in the blood. The medicine fosamprenavir should not be taken along with Lopinavir/Ritonavir Mylan.
Inflammation of the pancreas (pancreatitis)	Patients with increased level of triglycerides are at risk of	Patients should tell their doctor if they experience nausea, vomiting or

Risk	What is known	Preventability
	developing inflammation of the pancreas. Patients with advanced HIV disease may be at risk of inflammation of the pancreas. Between about 1 and 10 in 100 patients treated with lopinavir/ritonavir may have this risk. Clinical symptoms or abnormalities in laboratory values suggestive of pancreatitis are nausea, vomiting, abdominal pain, and increased serum lipase or amylase values.	abdominal pain as these may be suggestive of inflammation of the pancreas. If pancreatitis is diagnosed, Lopinavir/Ritonavir Mylan should be stopped.
High blood sugar levels (hyperglycaemia)	Between about 1 and 10 in 100 patients treated with lopinavir/ritonavir may suffer from decreased ability of the body to handle sugar, including diabetes and weight loss.	Patients should tell their doctor if they have diabetes, as increased blood sugar levels have been reported in patients receiving lopinavir/ritonavir. Patients should also tell their doctor if they experience thirst, frequent urination, blurred vision or weight loss as this may indicate raised blood sugar levels.
A flare-up of symptoms related to an inactive infection in the body (immune reactivation syndrome)	In some patients with advanced HIV infection and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. In addition to the opportunistic infections, autoimmune disorders (conditions that occur when the immune system attacks healthy body tissue) may also occur after starting HIV medicines. Autoimmune disorders may occur many months after the start of treatment. Between about 1 and 10 patients in 1,000 may be affected by this event.	Patients should inform their doctor immediately and seek necessary treatment if they notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity.
Death of bone tissue (osteonecrosis)	Between about 1 and 10 in 1,000 patients receiving lopinavir/ritonavir may develop osteonecrosis. Risk factors for developing the condition include long-term use of combination anti-HIV therapy, corticosteroid	Patients should tell their doctor if they experience joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement.

Risk	What is known	Preventability
	use, alcohol consumption, severe immunosuppression (reduction in the activity of the immune system) and higher body mass index.	
Interaction with CYP3A metabolized medicines	The active substances lopinavir and ritonavir are 'CYP3A inhibitors': they slow down the break-down of some other medicines, thereby increasing their levels in the body and potentially causing serious and/or life-threatening side effects. Affected medicines include certain medicines used to treat allergy symptoms, schizophrenia, bipolar disorder, major depressive disorder, erectile dysfunction, high blood pressure in the pulmonary artery, high blood cholesterol, an enlarged prostate, skin infections, headaches, abnormal heart beat, or the medicines used to relieve anxiety and/or trouble sleeping, certain stomach problems, and anti-gout medicine. The herbal remedy St. John's wort may in turn accelerate the break-down of lopinavir and therefore reduce the effectiveness of Lopinavir/Ritonavir Mylan.	Patients should tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines. Lopinavir/Ritonavir Mylan must not be given with the medicines alfuzosin, amiodarone, fusidic acid, astemizole, terfenadine, pimozide, quetiapine, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, lovastatin, simvastatin, avanafil, sildenafil, vardenafil, midazolam (given by mouth), triazolam, and St. John's wort (*Hypericum perforatum*, a herbal remedy).
Interaction with St John's wort	St. John's wort acts as a CYP3A inducer and may accelerate the break-down of lopinavir, therefore reducing the effectiveness of Lopinavir/Ritonavir Mylan.	Products containing St John's wort must not be taken along with Lopinavir/Ritonavir Mylan. Patients should tell their doctor if they are taking or had recently taken products containing St John's wort If a patient is already taking St John's wort, this should be stopped viral levels should be checked if possible. Lopinavir/Ritonavir Mylan can be started safely 2 weeks after stopping of St John's wort.

Important potential risks

Risk	What is known
Abnormal body fat distribution (lipodystrophy)	Combination anti-HIV therapy can cause redistribution of body fat (lipodystrophy) in HIV patients. Old age patients, long-term use of anti-HIV therapy and related metabolic disorder in a patient are risk factors for lipodystrophy. The cause and long-term health effects of this condition are not known at this time. Clinical examination should include evaluation for physical signs of fat redistribution; consideration should be given to measurement of fasting serum lipids and blood glucose. Patients should tell their doctor if they experience changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck ('buffalo hump').
QT prolongation with supratherapeutic doses and PR prolongation at therapeutic dosing (electrocardiogram QT prolonged and electrocardiogram PR prolongation)	Lopinavir/ritonavir may cause changes in the heart rhythm and the electrical activity of the heart. These changes may be seen on an ECG. Caution should be exercised in patients with heart disease and pre-existing abnormalities in the heart's electrical activity, or in patients taking medicines used to correct heart rhythm or salmeterol, verapamil or atazanavir along with lopinavir/ritonavir. Patients should tell their doctor if they experience symptoms of dizziness, light-headedness, fainting or sensation of abnormal heartbeats.

Missing information

Risk	What is known
Limited information on use in elderly patients	No data on the use of lopinavir/ritonavir in elderly patients is available.
Risk of premature birth in women using lopinavir/ritonavir during pregnancy	Studies with lopinavir/ritonavir in animals have shown reproductive toxicity. Women using an oral contraceptive or using a patch contraceptive to prevent pregnancy should use an additional or different type of contraception (e.g. condom) during treatment with Lopinavir/Ritonavir Mylan, as lopinavir/ritonavir may reduce the effectiveness of oral and patch contraceptives. Women should tell their doctor immediately if they are planning to have a baby, are pregnant, or think they may be pregnant.

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, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Lopinavir/Ritonavir Mylan can be found on Lopinavir/Ritonavir Mylan's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

No studies are planned.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 1-2016.