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Summary of the risk management plan (RMP) for Dutrebis (lamivudine / raltegravir)

This is a summary of the risk management plan (RMP) for Dutrebis, which details the measures to be taken in order to ensure that Dutrebis 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 Dutrebis, which can be found on Dutrebis's EPAR page.

Overview of disease epidemiology

Dutrebis is a medicine used to treat patients with human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS).

HIV is a virus that attacks the immune system (the body's natural defences) and weakens it by destroying certain white blood cells (called CD4 T cells), which are important for protecting the body against various bacteria, viruses and other germs. If left untreated, the HIV virus multiplies and the body becomes increasingly unable to fight infections 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. Worldwide, 3.4 million children aged below 15 years were living with HIV in 2010 (19,000 children in Europe).

There is no cure for HIV, but early detection and effective treatment with medicines that stop the virus multiplying can reduce the amount of HIV virus in the blood and keep it at a low level, allowing patients to stay healthy and live longer lives.

Summary of treatment benefits

Dutrebis is available as tablets containing the active substances lamivudine and raltegravir, which are already used in the European Union (EU) as single-component medicines for the treatment of HIV infection, since 1996 in the case of lamivudine and 2007 for raltegravir. Because lamivudine and raltegravir are already approved individually to treat HIV infection, the company presented data from the studies used to approve these medicines, including a study involving 160 patients given raltegravir with lamivudine (plus another HIV medicine, tenofovir) for a total of 240 weeks. The main measure of effectiveness was the proportion of patients with a reduction of the levels of virus in the blood (viral load) to fewer than 50 copies of HIV RNA per ml, which was 68.8%.

The company also looked at the way Dutrebis was absorbed in the body in comparison with two separate tablets containing lamivudine and raltegravir. The results of the studies showed that Dutrebis produced similar levels of lamivudine in the body to lamivudine taken separately; although the levels of raltegravir were slightly different, they were considered similarly effective in controlling the virus.

Unknowns relating to treatment benefits

Studies with Dutrebis have included few or no children under 6 years of age, pregnant women, elderly patients (over 65 years of age), and patients with severely reduced liver function. The safety and effectiveness of the medicine are therefore not known in these groups of patients.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Inflammation during recovery of the immune system (immune reconstitution inflammatory syndrome - IRIS)	IRIS is a condition seen in HIV patients whose immune system is recovering, as a result of treatment with HIV medicines. During recovery, there can be a reaction to an existing infection in the body, causing severe inflammation at the site of the infection. IRIS is considered to be an uncommon adverse effect in patients treated with Dutrebis (affecting less than 1 patient in 100).	At present, there does not seem to be a specific way to prevent IRIS. Healthcare professionals and patients should be aware of the possibility of the reaction and the need for treatment of any infection and inflammatory symptoms as appropriate.
Reduced effect of the medicine against HIV (drug resistance)	Drug-resistant viruses can appear during therapy and because they are harder to treat can lead to treatment failure. In addition, drug-resistant viruses can be passed from person to person. There are many reasons that can lead to viruses becoming resistant including not taking the medication as prescribed, such as skipping doses.	Patients should take the medicine as prescribed, which will lower the chance of resistance. Patients are advised to avoid even a short interruption of treatment, as it can lead to resistance.
Effects of other medicines on Dutrebis (interaction with rifampicin and other medicines known as strong UGT1A1 inducers; interaction with magnesium and/or aluminium antacids)	Dutrebis should not be taken with certain medicines such as the antibiotic rifampicin as they can increase the breakdown in the body of raltegravir, one of the active substances in the medicine, and so may lower its effectiveness against HIV. Certain antacids (those containing aluminium or magnesium) are also not recommended with Dutrebis because they can lower the level of raltegravir absorbed into the body.	These effects can be prevented by avoiding the use of such medicines in patients who use Dutrebis. If use with a medicine such as rifampicin is essential, the individual active substances, lamivudine and raltegravir, should be used instead of Dutrebis, and their doses adjusted separately as appropriate.
Variations in levels of active substance	There may be variations in the levels of the active substances in	Variations in the levels of active substances with Dutrebis have not

Risk	What is known	Preventability
in the body and possible impact on safety and effectiveness of the medicine (pharmacokinetic variability and impact, if any, on pharmacodynamics)	the body after a dose of Dutrebis, both in the same patient at different times and in different patients.	currently been shown to affect safety and effectiveness of the medicine. While the risk of such variations cannot be eliminated, it can be minimised by taking the medicine at regular times as instructed by the doctor.
Serious rash	Allergic reactions, including severe and life-threatening skin reactions, have been reported in some patients taking raltegravir, one of the active substances in Dutrebis.	At present, there does not seem to be a specific way to prevent a serious rash, as in general, serious drug-related skin reactions are not predictable. Patients are advised to contact their doctor promptly if they develop a rash.
Build-up of lactic acid in the body (lactic acidosis)	Cases of lactic acidosis, which is a serious and potentially life-threatening side effect, have been reported rarely (in less than 1 patient in 1,000) in those treated with NRTIs (the class of HIV medicines to which lamivudine, one of the active substances in Dutrebis, belongs). Where it has occurred, it has usually developed after a few months of treatment. Symptoms can develop gradually and may include unusual muscle pain and weakness, trouble breathing, fast or uneven heart rate, nausea (feeling sick), vomiting, stomach pain, and numbness or a cold feeling in the arms or legs.	Patients should be monitored for signs of lactic acidosis, especially if at increased risk of developing the condition (such as those with existing liver disease – see below – or who are obese, particularly women). Doctors should exercise extra caution when prescribing Dutrebis to patients at increased risk of developing lactic acidosis. Patients should contact their doctor at once if they experience any of the symptoms of lactic acidosis, even if they are only mild.
Swelling of the liver with fat build-up (severe hepatomegaly with steatosis)	When lactic acidosis (above) occurs in patients given an NRTI it is usually associated with hepatomegaly (swelling of the liver) or steatosis (fatty liver). Liver problems including steatosis have been reported uncommonly (in less than 1 person in 100) in patients taking Dutrebis. Symptoms of liver problems include persistent nausea, stomach/abdominal pain, loss of appetite, dark urine, or yellowing of the eyes/skin.	Patients should contact their doctor if they experience any symptoms of liver problems. Regular blood tests to check for liver damage are usually part of the medical care for patients with HIV. Liver monitoring with Dutrebis is advised in patients who have existing liver disease or are obese, particularly in women. Treatment with Dutrebis should be suspended in any patient who develops symptoms of hepatomegaly.
Inflammation of the pancreas	Pancreatitis has been observed in some patients receiving lamivudine.	Doctors are advised to use Dutrebis with caution in patients previously treated

Risk	What is known	Preventability
(pancreatitis)	Symptoms include severe pain in the upper stomach that spreads to the back, nausea and vomiting, or fast heart rate.	with NRTIs, who have had pancreatitis or have other risk factors for its development. Treatment with Dutrebis should be stopped immediately if symptoms suggestive of pancreatitis occur.

Important potential risks

Risk	What is known
Abnormal body fat distribution (lipodystrophy)	Lipodystrophy is an alteration in distribution of fat on the body that has been seen with many types of HIV medicines, and therefore is considered a potential risk with Dutrebis. It may include loss of fat from legs, arms, and face, and increase in fat around the belly. Patients who have a low body mass index (BMI) when they start HIV medications may develop a form of this condition called lipoatrophy which is a loss of fat. Older patients and those who are already obese or overweight are more likely to have fat accumulation.
Potential for unauthorised (off-label) use in children less than 6 years of age or weighing less than 30 kg; safety concerns related to potentially increased exposure to raltegravir in children 6 to 11 years of age	There is a potential risk that Dutrebis may be given to children below 6 years of age or in children 6 to 11 years of age weighing less than 30 kg. Dutrebis is not authorised in these groups and should not be used in them, as it has not been shown to provide suitable doses of the active substances. It is estimated that children aged 6 to 11 years may be potentially exposed to relatively greater amounts of the raltegravir component for their weight than other patients.
Malignancies	All patients with HIV infection may be at risk for malignancy (cancer) because of a weakened immune system. Experimental results in rats, but not in mice, indicated that raltegravir may be associated with the development of cancers of the nose or throat, so it is considered a potential risk for Dutrebis. However in clinical studies, the number of HIV patients taking raltegravir who developed cancer was similar to that of patients taking other HIV medicines.
Increase in liver enzymes (increase in liver blood tests)	Patients who take raltegravir, one of the active ingredients of Dutrebis, may experience an increase in the level of liver enzymes in their blood tests (a potential sign of liver problems). This risk is increased if patients already have impaired liver function and if patients are also infected with hepatitis B or hepatitis C before they start taking the medicine. Patients are advised to inform their healthcare providers if they have had problems with their liver before, such as hepatitis B or hepatitis C.
Increase in creatine kinase and muscle damage (myopathy, rhabdomyolysis)	Creatine kinase is an enzyme that is released when muscles are damaged or strained, such as by exercise. Muscle problems such as rhabdomyolysis (rapid muscle breakdown) or myopathy (muscle weakness) can occur in association with HIV infection, or following treatment with some medicines, including HIV medicines such as raltegravir (one of the active substances in Dutrebis) and

Risk	What is known
	protease inhibitors, statins, colchinine, antimalaria medicines, clofibrate, and corticosteroids. Because patients with HIV often take a combination of medications, it can be difficult to determine the origin of the problem. Patients are advised to contact their doctor promptly if they experience unexplained muscle pain, tenderness, or weakness while taking Dutrebis.
Depression, suicidal ideation and suicidal behaviours	Depression, suicidal thoughts and actions have been reported in some patients taking raltegravir, particularly in patients with a prior history of depression or psychiatric illness. It is therefore considered a potential risk for Dutrebis. Patients are advised to tell their doctor if they have a history of depression or psychiatric illness.
Use of Dutrebis in pregnancy or while breastfeeding	Use of Dutrebis is not recommended in pregnancy. Although a number of women have taken lamivudine (one of the active substances in the medicine) during pregnancy without apparent harm to the baby, experimental results in rats have suggested that raltegravir, the other active substance, might potentially affect the developing fetus. These effects have not been seen in rabbits, and their relevance for humans is unknown. Breastfeeding is not recommended while taking Dutrebis, but in any case it is recommended that women with HIV should not breastfeed their infants because babies can be infected with HIV through their breast milk. Patients should ask their doctor, pharmacist or nurse for advice before taking any medicine if pregnant or breastfeeding.

Missing information

Risk	What is known
Use during pregnancy	There are no adequate and well-controlled studies of Dutrebis in pregnant women. Use is not recommended in pregnancy.
Long-term safety in older patients	Only a few patients aged 65 and over were involved in clinical studies used to support the licensing of Dutrebis and it is not known whether they could respond differently from younger patients.
Long-term safety in patients also infected with hepatitis B or C (co-infection)	Although raltegravir and lamivudine as separate medicines have proven safe for use in patients co-infected with hepatitis B or C, the safety and effectiveness of Dutrebis has not been established in this population.
Long-term safety in patients with severely reduced liver function (hepatic impairment)	The safety and effectiveness of lamivudine and raltegravir have not been established in patients with existing severe liver disorders. Therefore Dutrebis should be used with caution in patients with severely reduced liver function.

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 Dutrebis can be found on Dutrebis's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Observational post authorization safety study (058)	The overall objective of the analysis is to investigate the incidence of clinically important medical events following treatment with raltegravir.	Malignancy, selected clinically important liver outcomes, lipodystrophy, all-cause mortality, long-term safety data.	Ongoing	The final study report was submitted in June 2014.
Observational post authorization safety study (EPO8025.006)	A medical records database will be used to assess the incidence of pre-specified health outcomes of interest in HIV-infected patients treated with raltegravir under conditions of routine use following approval of the medicine.	Malignancy, selected clinically important liver outcomes, lipodystrophy, all-cause mortality, serious rash, selected clinically important muscle outcomes, long-term safety data.	Ongoing.	The final study report submitted in December 2014.
Collaboration with the D:A:D Cohort Study	Along with other marketing authorisation holders (MAHs), the MAH is currently supporting the D:A:D cohort to monitor the safety of anti-retrovirals in Europe.	Monitored risks include cardiovascular risk; however, the study outcomes are not specific to raltegravir.	Ongoing.	The MAH will support the collaboration until 2017 at which time the D:A:D study will be completed.
Study 022	Evaluation of safety, PK (how the medicine is handled in the body) and efficacy in paediatric patients 4	Long-term safety data in populations studied-paediatric patients aged 4 weeks to 18 years.	Ongoing	Submission 31 Dec 2017 (Final Week 240 CSR).

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	weeks to 18 years of age.			
Study 022- chewable tablet Ctrough substudy (Version 3.0, LOA #4)	Collection of additional Ctrough PK data in paediatric patients 2 to below 6 years of age, receiving the chewable tablet formulation.	PK variability and exposure in paediatric patients aged 2 to under 6 years.	Ongoing.	Submitted in November 2014.
Study 083 (ex-US) (Compassionate access program)	Compassionate use program to provide the raltegravir chewable tablet and granules for suspensions until commercially available.	Long term safety data in populations studied- paediatric patients aged 4 weeks to under 12 years.	Ongoing.	Side effects are monitored on an ongoing basis and reported upon identification of new safety concerns.
Study 135 (US) (Compassionate access program)	Compassionate use program to provide the raltegravir granules for suspensions until commercially available.	Long-term safety data in populations studied- paediatric patients aged 4 weeks to under 12 years.	Ongoing.	Side effects are monitored on an ongoing basis and reported upon identification of new safety concerns.
Antiretroviral Pregnancy Registry (APR) (FDC Registry)	The APR is an international collaborative project to monitor reported exposures to antiretroviral medicines during pregnancy. The Registry is designed to provide an early signal of teratogenicity (malformations) with prenatal use of the medicines monitored through the Registry	Exposure during pregnancy.	Ongoing.	Provided within each regular report required for safety monitoring (PSUR submission)

Studies which are a condition of the marketing authorisation

None of the above studies are a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Not applicable.

This summary was last updated in 03-2015.