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Summary of the risk management plan (RMP) for Rezolsta (darunavir / cobicistat)

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

Overview of disease epidemiology

Rezolsta is an antiviral medicine used to treat adults 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 2011, 34 million people worldwide were living with HIV, including 900,000 in Western and Central Europe and 1.4 million in Eastern Europe and Central Asia. In 2011, 2.5 million people were newly infected with HIV, down by one-fifth (20%) compared with 2001.

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 people to stay healthy and live longer lives. The development of resistance to HIV medicines can be a problem among patients receiving long-term treatment. This means that over time the HIV virus is no longer controlled properly by a particular combination of medicines, and treatment may need to be changed; treatment may also be changed because of side effects.

Summary of treatment benefits

Rezolsta is available as a tablet containing two active substances, darunavir and cobicistat, that are already authorised separately for the treatment of HIV infection. Darunavir is a protease inhibitor. It blocks an enzyme called protease, which is involved in the reproduction of HIV. When the enzyme is blocked, the virus does not reproduce normally, slowing down the rate of replication. Cobicistat acts as a 'booster' to enhance the effects of darunavir, by prolonging the time in which it acts in the body.

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Rezolsta is for use in patients who have not received HIV treatment before or previously treated patients whose disease is not expected to be resistant to darunavir and who are healthy enough and have HIV virus levels below a certain threshold.

Because darunavir and cobicistat have both previously been shown to be effective and are authorised for use in the treatment of HIV infection, studies were mainly carried out to show that Rezolsta produced similar effects and levels of darunavir and cobicistat in the blood to the two active substances given separately, and to darunavir given with a different booster medicine, ritonavir (an established combination).

In addition, one main study was carried out to examine the safety and effectiveness of darunavir and cobicistat, given with other HIV medicines, in 313 adult patients with HIV who had not been previously treated or who had been previously treated and whose infection was not expected to be resistant to darunavir. Effectiveness was measured by reduction in viral load (the amount of HIV-1 virus in the blood) to less than 50 copies/ml. Overall, 258 patients (82%) achieved this response after 24 weeks of treatment, and 253 patients (81%) at 48 weeks.

Unknowns relating to treatment benefits

There is limited information about the long-term use of Rezolsta, and about use in certain subgroups of patients: the elderly (65 years and above), children, pregnant and breastfeeding women and patients with reduced liver or kidney function.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Severe skin reactions	Rash is a very common side effect, seen in more than 1 patient in 10; 16% of patients experienced rash in a study where they were given darunavir and cobicistat. Although severe reactions are possible, in clinical trials where darunavir was given with cobicistat or ritonavir, rash was mostly mild to moderate in severity, often occurring within the first 4 weeks of treatment and resolving despite continued dosing.	Patients should be warned to contact their doctor if rash develops, and healthcare professionals should advise patients on appropriate treatment and whether Rezolsta needs to be stopped.
Adverse effects on the liver (hepatotoxicity)	Side effects that involve the liver (e.g., abnormal liver tests) are seen in up to 1 patient in 10. Inflammation of the liver (hepatitis) is uncommon (reported in less than 1 patient in 100). In clinical trials, these side effects	Rezolsta is contraindicated in patients with severely reduced liver function. Rezolsta should be used with caution in patients with mild or moderate liver impairment: patients should be monitored, and interrupting or stopping treatment considered if there are signs

Risk	What is known	Preventability
	occurred more often in patients who were also infected with hepatitis B or hepatitis C virus than in patients with HIV-1 infection alone.	of new or worsening liver problems.
High blood sugar levels (hyperglycaemia)	Diabetes or increase in blood sugar have been reported in up to 1 patient in 10 given darunavir with cobicistat or ritonavir in studies, but serious problems were infrequent.	The product information includes warnings to doctors and patients on the risk of increased blood sugar. Doctors may consider blood tests where appropriate.
Increased fat in the blood (lipid abnormalities)	Increases in blood levels of various types of fats (lipids), including cholesterol and triglycerides, are common side effects, occurring in up to 1 patient in 10.	The product information includes warnings to doctors and patients of the risk of increased blood fats. Doctors may consider blood tests where appropriate.
Inflammation of the pancreas (pancreatitis)	Inflammation of the pancreas may occur in up to 1 patient in 100.	The product information includes warnings to doctors and patients of the possibility of developing acute pancreatitis.
Fat redistribution	Treatment with combinations of HIV medicines has been associated with redistribution of body fat, including loss of fat on the face and body, increased fat in the abdomen and around the internal organs, breast enlargement, and fat accumulation at the back of the neck and upper back ('buffalo hump'). The long-term significance of these changes is currently unknown. Increasing age and longer duration of HIV treatment also have an influence on redistribution of body fat.	Doctors should evaluate patients regularly for physical signs of fat redistribution.
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, or overactivity of the immune system leading it to attack healthy body tissue (autoimmunity). Such effects may be seen in up to 1	Patients should tell their doctor immediately if they notice any symptoms of infection (for example enlarged lymph nodes and fever) 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. Any inflammatory symptoms should be evaluated by a healthcare professional and appropriate

Risk	What is known	Preventability
	patient in 100 treated with Rezolsta.	treatment started if necessary.
Development of resistance by the virus	In some patients treated with an HIV medicine such as darunavir, the virus may become resistant to it and may be able to continue to reproduce. When the virus becomes resistant to one medicine, some other HIV medicines, particularly those in the same class, may also not be effective, which limits the number of treatment options available to the patient. Studies in patients given darunavir with cobicistat showed that when taken properly the risk of resistance was low.	Before recommending treatment with Rezolsta, the doctor should consider the patient's history of previous HIV treatments and carry out a blood test to find out if the medicine is likely to work ('resistance testing'). Resistance may develop if patients fail to comply with the prescribed treatment; therefore patients should take Rezolsta regularly with food as directed by their doctor and should not stop treatment without discussing it with their doctor.
Taking other medicines with Rezolsta (drug interactions)	Giving Rezolsta with other medicines that are broken down in the body in the same way may interfere with the breakdown of such medicines and increase their blood levels. This can increase the risk of potentially serious side effects. In addition, some other medicines may increase the breakdown of Rezolsta, resulting in loss of effectiveness.	The product information for Rezolsta contains clear recommendations on medicines that should not be taken during treatment or actions to be taken by healthcare professionals such as adjusting doses based on levels of the medicine in the body.

Important potential risks

Risk	What is known
Heart attack (coronary artery events)	High blood sugar and increase in blood fats such as cholesterol, which are considered identified risks, are also risk factors for developing hardening and thickening of the walls of the arteries (arteriosclerosis). If this occurs in the arteries that supply blood to the heart muscle it can cause angina (chest pain) and/or heart attack, which are therefore considered potential risks of Rezolsta.
Alterations in the electrical activity of the heart (cardiac conduction abnormalities)	Alterations in the electrical activity in the heart can result in potentially serious effects on heart rate and rhythm. Such alterations have not been reported in studies in patients given darunavir with cobicistat. However, because they have been reported in patients given darunavir with an alternative booster medicine, ritonavir, they are considered a potential risk with Rezolsta.
Seizures (convulsions)	In animal studies with darunavir, convulsions have been observed in young animals, equivalent to less than 2 years of age in humans. Rezolsta is not authorised for use in children.

Risk	What is known
Effects on the kidneys (renal toxicity)	Cobicistat has been shown to lower the elimination of creatinine from the blood (creatinine clearance), which is normally a sign of reduced kidney function, but without any further effect on the function of the kidneys. Rezolsta should therefore not be used in patients who need to have the dose of another medicine (e.g., emtricitabine, lamivudine, tenofovir disoproxil fumarate, or adefovir dipivoxil) adjusted based upon the creatinine clearance. There is currently not enough information to determine whether taking Rezolsta with tenofovir disoproxil fumarate increases the risk of toxicity to the kidneys, but this is a potential risk. The effects on the kidneys should therefore be monitored when Rezolsta and tenofovir disoproxil fumarate are being given together.
Use in patients for whom Rezolsta is not approved (off-label use)	There is a risk of unapproved or off-label use of Rezolsta, including use in children and adolescents under 18 years old and in adults who have already received treatment with HIV medicines but who have high levels of the virus in their blood (more than 100,000 copies/ml HIV-1 RNA) at the start of treatment. The safety and effectiveness of Rezolsta in such patients has not been shown.

Missing information

Risk	What is known
Use in the elderly (65 years and above)	There is limited information from studies with darunavir and cobicistat in patients over 65 years of age. It is therefore not known whether patients above 65 years of age respond differently to younger patients.
Use in pregnant and breastfeeding women	Darunavir and cobicistat have not been studied in pregnant women. Pregnant women should not take Rezolsta unless it has been agreed with the doctor that the potential benefits outweigh any risks. It is not known whether darunavir or cobicistat pass into human breast milk but in any case it is recommended that mothers with HIV do not breastfeed their infants.
Use in children below 18 years of age	The safety and effectiveness of darunavir and cobicistat in patients aged less than 18 years have not yet been established. Therefore, the use of Rezolsta in this age group is not recommended.
Long-term safety information	The long-term safety effects of Rezolsta will be monitored by ongoing studies and during regular use once it becomes available by prescription.
Use in patients with severely decreased liver function (hepatic impairment)	Darunavir and cobicistat have not been studied in patients with severely decreased liver function and therefore should not be used in these patients. No change in the dose of Rezolsta is required in patients with mildly or moderately decreased liver function.
Use in patients with decreased renal	Rezolsta has not been studied in patients receiving dialysis, and, therefore, no recommendation can be made for these patients.

Risk	What is known
function (renal impairment)	No dose adjustment of Rezolstat is needed in patients with reduced kidney function, including those whose kidney function is severely reduced. An ongoing study will provide additional information about the safety of Rezolsta in HIV-infected adults with mild to moderate kidney impairment. Rezolsta should not be started in patients who have mild kidney impairment and are receiving treatment with certain HIV medicines that require dose adjustment for the kidney impairment.
Use in patients who also have hepatitis B or C infection	Only limited information is available on the use of Rezolsta in patients who also have hepatitis B and/or hepatitis C infection. Patients with pre-existing liver problems, including chronic active hepatitis B or hepatitis C, have an increased risk for abnormalities of liver function including severe and potentially fatal effects. Patients should have their liver function tested before and during treatment, especially during the first few months of treatment and in patients with inflammation of the liver (hepatitis), scarring (cirrhosis) or raised liver enzyme values in the blood. If antiviral therapy for hepatitis B or hepatitis C is given together with Rezolsta, the product information for these medicines should also be consulted.

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 Rezolsta can be found on Rezolsta'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
GS-US-216-0130 (Gilead)	To evaluate the safety and tolerability of darunavir and cobicistat plus 2 fully active	Important potential risk: Kidney toxicity Missing information: Long-term safety of darunavir and cobicistat in adults	Ongoing	Q3 2015 (Final report)

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	'nucleoside reverse transcriptase inhibitors' through 48 weeks of treatment and beyond. After 48 weeks of treatment, subjects are given the option to participate in an open-label extension of the study to receive cobicistat .			
GS-US-216-0128 (Gilead)	To evaluate PK, safety, and efficacy of atazanavir with cobicistat and darunavir with cobicistat in children and adolescents.	Missing information: Children less than 18 years of age	Planned	February 2018 (Week 48 report) February 2022 (Final report)
GS-US-236-0118 (Gilead)	To evaluate the effects (including long-term effects), safety, and tolerability of cobicistat-containing regimens on kidney parameters through 48 weeks of treatment and beyond.	Important potential risk: Kidney toxicity Missing information: Subjects with kidney impairment	Ongoing	Q3 2015 (Final report)
GS-US-236-0140 (Gilead)	To evaluate the effect of tenofovir disoproxil fumarate on kidney function with and without cobicistat.	Important identified risk: Drug interaction Important potential risk: Kidney toxicity	Planned	May 2015 (Final report)

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
TMC114HIV3015	To assess the PK of darunavir/ritonavir in HIV-1-infected pregnant women. This study will be amended to include an evaluation of the pharmacokinetics of darunavir/cobicistat during pregnancy as well.	Missing information: Pregnant and breast-feeding women	Ongoing	Q2 2017
Study of the effect of strong blockers of an enzyme (CYP3A4) on cobicistat levels	To evaluate the potential effect of strong blockers of enzyme (CYP3A4) on cobicistat's levels	Important identified risk: Drug interaction	Planned	Q2 2014 (Final report)
Study of the effect of individual components of Stribild on kidney cells	To evaluate the effect of individual Stribild components (elvitegravir / cobicistat / emtricitabine / tenofovir disoproxil) on kidney cells	Important identified risk: Drug interaction	Ongoing	Q3 2013 (Final report)

Studies which are a condition of the marketing authorisation

None of the above studies are conditions of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 10-2014.