EMA/449395/2015

Summary of the risk management plan (RMP) for Respreeza (human alpha$_1$-proteinase inhibitor)

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

Overview of disease epidemiology

Respreeza is a medicine used in adults with severe alpha$_1$-proteinase inhibitor deficiency. This is a genetic condition caused by lack of alpha 1-proteinase inhibitor (also called alpha 1- antitrypsin), a component of the blood whose function is to protect the lung tissue from damage. People who have alpha 1-proteinase inhibitor deficiency do not make enough alpha 1-proteinase inhibitor and are susceptible to lung disease.

There are different forms of the condition, some more severe than others, and not all people with the gene changes (mutations) that can lead to the condition will develop clinically significant symptoms.

There are approximately 3.5 million individuals worldwide affected by one of the mutations that can lead to severe disease; however, an additional 117 million individuals are carriers for one of the mutations and might or might not be diagnosed. In Europe, alpha$_1$-proteinase inhibitor deficiency affects more frequently individuals with Northern European ancestry and is equally seen in males and females. The diagnosis generally occurs during the third to fourth decade of life after patients develop symptoms such as emphysema (a type of lung disease characterised by difficulty breathing).

Summary of treatment benefits

Respreeza is used to slow down damage to the lungs in patients with severe disease. The active substance in Respreeza, human alpha$_1$-proteinase inhibitor, is obtained from human blood and works by replacing the protein that is lacking in patients with alpha$_1$-proteinase inhibitor deficiency. Respreeza is available as a powder and solvent to be made into a solution for infusion (drip) into a vein.

Respreeza has been shown to slow down lung damage in one main study involving 180 patients with lung damage due to alpha$_1$-proteinase inhibitor deficiency. In the study, Respreeza was compared with placebo (a dummy treatment) and the main measure of effectiveness was the decrease in lung density. Lung density is an indicator of the extent of lung damage: the bigger the decrease in lung density, the greater is the damage to the lung. The decrease in lung density after 24 months was around 2.6 g/l in patients who received Respreeza, compared with a decrease of around 4.2 g/l in patients receiving placebo.

Unknowns relating to treatment benefits

All patients treated with Respreeza in clinical studies were white of both sexes below the age of 65. Experience in older people and paediatric populations, in patients with kidney or liver disease, other races and patients with severe emphysema remains limited. Patients who were pregnant or breastfeeding, who have had a lung transplant or volume reduction surgery were not included in the clinical studies, so no experience with treatment in these groups is available. However, the limited data did not show a safety concern in these populations.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reactions including anaphylaxis	Patients may experience an allergic reaction that can range from mild to serious, and may result in death. This may occur after the first or any dose. Symptoms may include: hot flush, rash, itching, dizziness, increased heart rate, and trouble with breathing or swallowing as well as any swelling of hands, face or mouth.	Respreeza must not be used in patients who have ever had an allergic reaction to $alpha_1$-proteinase inhibitor or any of the other ingredients of this medicine, or in patients who are lacking a protein in the blood called IgA and who have developed antibodies against it, as these patients are more prone to allergic reactions. Immediate discontinuation of the infusion may be required, depending on the severity of the allergic reaction. Patients should call their doctor right away if they have any symptoms of an allergic reaction after they receive Respreeza. Patients should tell their doctor if they had an allergic reaction to Respreeza in the past or to any alpha 1-proteinase inhibitor.

Important potential risks

Risk	What is known
Transmission of infectious agents	Respreeza is made from donated human blood; therefore, the risk of transmitting infectious agents, including viruses and, theoretically, Creutzfeldt-Jakob disease, cannot be completely eliminated. The risk of getting a virus from Respreeza is very low. This is the result of required testing of human donors for certain viruses, and inclusion of effective manufacturing steps to inactivate/remove viruses. Although the risk is low, patients should talk with their doctor if they have concerns. The doctor may give hepatitis A and B vaccines to patients who

Risk	What is known
	receive plasma-derived medicines regularly.
Increased or unknown risks with home-based self-administration	There are limited data regarding the use of Respreeza in a home setting and when the medicine is given by the patient or a caregiver. Patients who home-treat and/or self-administer may be at risk of using the wrong dose, or handling the medication, device, sterile water or intravenous tubing incorrectly. There is also a potential for side effects, such as allergic reactions, to occur at home and be managed incorrectly without the aid of a healthcare professional. The decision whether a patient is suitable for home treatment and self-administration is made by the treating doctor, who should ensure that appropriate training is provided to the patient.
Medication error	Errors can occur when the product is administered either by a healthcare professional or a patient, and include incorrect dosage, possibility of incorrect medicine due to name confusion, errors in use of device, filter or tubing for the infusion into a vein.

Missing information

Risk	What is known
Limited information on use in older patients (above 65 years old)	In clinical trials Respreeza has only been tested in few older patients, but post-marketing data do not indicate that the safety in older people differs from that of adults aged below 65 years.
Limited information on use in pregnant or breastfeeding women	Respreeza has not been tested in women who are pregnant or breastfeeding. Since human alpha$_1$-proteinase inhibitor is a normal constituent of human blood, it is considered unlikely that Respreeza will cause harm to the fetus or present a risk to the breastfed newborn/infant when given at the recommended doses. Patients should talk to their doctor if they are planning to become pregnant or think they may be pregnant. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with Respreeza should be made, taking into account the benefit of breastfeeding to the child and the benefit of human alpha$_1$-proteinase inhibitor therapy to the woman.
No experience in patients who have undergone lung transplantation or volume reduction surgery	Patients who had undergone lung transplantation or volume reduction surgery were not enrolled in clinical trials. It is not known if patients who have had this surgery will benefit or if they have the same risks as patients who have not had surgery. Patients who have previously had lung surgery of any type should discuss with their doctor the possible benefits and risks of treatments with Respreeza.
No experience in patients with liver (hepatic) disease	Some patients with alpha$_1$-proteinase inhibitor deficiency may have both lung and liver disease. Patients with significant liver disease were not enrolled in clinical trials. It is not expected that liver disease will respond to treatment with Respreeza. The risks of giving Respreeza to patients with lung disease who also have liver abnormalities are unknown.
Limited experience in	Low numbers of patients with severe emphysema (or obstructive lung

Risk	What is known
patients with severe emphysema (a type of lung disease characterised by reduced breathing)	disease) as measured by lung function tests (FEV_1 less than 35%) were enrolled in clinical trials. It is not known if patients with severe lung disease would benefit from treatment. It is expected, but not known, that they have similar risks as patients with higher lung functions (FEV_1 between 35% and 70%).
Limited information on long-term safety.	65.6% of subjects received Respreeza for over a year, 46.6% of subjects for over 2 years, and 9% for over 4 years.

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 Respreeza can be found on Respreeza'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
CE1226_3001: An open, non-controlled, multicenter, multinational study to evaluate the efficacy and safety of CE1226 administration in chronic augmentation and maintenance therapy in subjects with emphysema due to alpha1-proteinase inhibitor deficiency who completed clinical study CE1226_4001	To collect long-term data for the safety and efficacy of treatment with Respreeza given as an infusion into a vein at a dose of 60 mg/kg once a week in subjects with emphysema due to $alpha_1$-proteinase inhibitor deficiency.	To assess safety by adverse effects, laboratory results and periodic physical exams. To assess the clinical efficacy of therapy in reducing progression of emphysema, assessed by decline in lung density.	Ongoing	Final Results: September 2015

Studies which are a condition of the marketing authorisation

There are no safety studies which are a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 07-2015.