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Summary of the risk management plan (RMP) for Cresemba (isavuconazole)

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

Overview of disease epidemiology

Cresemba is an azole anti-fungal medicine used to treat adults with either of two life-threatening fungal infections: invasive aspergillosis or mucormycosis.

Aspergillosis is an infection caused by the fungus *Aspergillus*. Invasive aspergillosis usually affects people with weakened immune systems, such as those who have had a bone marrow transplant or a solid organ transplant, people receiving chemotherapy for cancer, those who are taking high doses of corticosteroids, intensive care unit and surgical patients, and people with advanced human immunodeficiency virus (HIV) infection. Invasive aspergillosis occurs rarely in the general population. In the United States, up to 3.6 per 100,000 persons are infected annually. People infected with invasive aspergillosis can become very sick and even die.

Mucormycosis (also called zygomycosis) is a rare infection caused by organisms that belong to a group of fungi called *Mucoromycotina*. Mucormycosis infection occurs more commonly among people with weakened immune systems, but, rarely, it can occur in people who are otherwise healthy. Risk factors for developing mucormycosis include: uncontrolled diabetes, cancer, organ transplantation, neutropenia (low white blood cell count), and skin trauma (cuts, scrapes, punctures or burns). Invasive mucormycosis is rare in Europe; a study in Italy found that only 0.1% of cases of invasive fungal infection were due to mucormycosis. A study in the United States showed that 1.7 persons per million of the population develop mucormycosis every year. Invasive mucormycosis can be fatal; approximately 64% of those who develop it die from it.

Summary of treatment benefits

Studies show that survival following treatment with Cresemba is similar to that seen with other treatments.

In a main study of 516 patients with invasive aspergillosis, the mortality rate at 42 days was similar in patients treated with Cresemba (19%) and those treated with another antifungal medicine voriconazole (20%).

Another study included 146 patients, among which 37 patients had mucormycosis and were treated with Cresemba; in patients with mucormycosis the mortality rate after 84 days was 43%, which is similar to rates seen in the published literature for standard treatments with amphotericin-B. In addition, Cresemba has the advantage that it can be used in patients with reduced kidney function.

Unknowns relating to treatment benefits

Among Cresemba-treated patients in phase 3 studies, 79.2% were white, 78.9% were aged up to 65 years, and 60.8% were male. There is no evidence that treatment benefit would be different based on gender or age.

Treatment benefit has not been assessed in patients with severely reduced liver function or in patients aged under 18 years.

In one study in Asian patients, overall, fewer patients responded in the Cresemba group than in the voriconazole treatment group. The differences in response rates between Asian and non-Asian patients cannot be explained by exposure or by resistance to Cresemba. A potential ethnicity effect can neither be excluded nor confirmed.

The clinical data for Cresemba in the treatment of mucormycosis are limited, comprising data from only one clinical study in 37 patients with mucormycosis who received Cresemba as first treatment, or because other anti-fungal treatments (mainly amphotericin B) were inappropriate. In *Mucorales* species other than *Rhizopus spp.*, the clinical efficacy data are limited to very small numbers of patients, with susceptibility data only available in a subset of cases.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Changes in blood levels of liver enzymes (elevated liver transaminases) and hepatitis	Changes in blood levels of liver enzymes were reported in Cresemba-treated patients in clinical studies, but rarely required stopping the treatment. These changes were not associated with liver failure.	The doctor should consider monitoring liver enzymes levels during treatment with Cresemba.
Side effects during the Cresemba infusion (infusion-related reactions)	Low blood pressure, shortness of breath, dizziness, tingling sensation, nausea, and headache were reported in Cresemba-treated patients during the intravenous infusion in clinical studies.	Intravenous infusion of Cresemba must be given over a minimum of 1 hour. The healthcare professional should stop the infusion if these symptoms occur. The patient should immediately report to the healthcare professional any side effects such as shortness of breath, dizziness, tingling sensation, , nausea, and headache, or suspected low blood pressure.
Severe skin reactions (severe cutaneous adverse reactions)	In clinical trials, very few Cresemba-treated patients experienced severe skin reactions; none of the cases required stopping the medicine.	Cresemba should be discontinued if a patient develops severe skin reactions.

Risk	What is known	Preventability
	Severe skin reactions, such as severe blistering of the skin, mouth, eyes and genitals, have been reported during treatment with other anti-fungal medicines belonging to the 'azole' class.	
Abnormal heart rhythm caused by shortened QT interval (arrhythmia due to QT shortening)	Some healthy subjects treated with Cresemba experienced shortening of their QT interval (an interval measured on an electrocardiogram). It is unknown whether QT shortening caused by medicines can lead to abnormal heart rhythms.	Cresemba must not be given to patients with a specific genetic condition called 'familial short QT syndrome'. The doctor should use caution when prescribing Cresemba to patients who are concurrently taking other medicines known to shorten the QT interval.

Important potential risks

Risk	What is known
Harm to the unborn baby (teratogenicity)	Based on studies in animals, Cresemba may harm an unborn baby when given to a pregnant woman. Bone abnormalities consistent with those observed for other azole anti-fungal agents were reported in rats and rabbits. Cresemba has not been studied in pregnant women. Treatment with Cresemba is not recommended during pregnancy, except in patients with severe or potentially life-threatening fungal infections when the anticipated benefit would outweigh the risk to the unborn baby. Women who become pregnant during treatment with Cresemba should contact their doctor.
Effect on children exposed to Cresemba via breast milk	In animal studies, Cresemba was detected in the milk of rats following intravenous administration. It is not known whether Cresemba passes to human breast milk. Women should not breastfeed while taking Cresemba.
Development of resistant strains	Similar to other azole anti-fungal agents, Cresemba may become less effective due to the development of resistance. During clinical studies, the emergence of Cresemba resistance among infecting pathogens was not identified. When administering Cresemba for long periods (beyond 6 months), the doctor should consider the possibility of fungus becoming resistant to Cresemba.
Off-label use (use outside approved indication)	No information is available regarding off-label uses for Cresemba. However, off-label use (e.g., treatment to prevent fungal infections, combination anti-fungal treatment, or high-dose treatment) occurs in over one-third of patients treated with voriconazole, another anti-fungal

Risk	What is known
	medicine. Cresemba should only be used in the approved indications (treatment in adults for invasive aspergillosis and treatment in adults for mucormycosis), and at the dosing regimens recommended in the product information.

Missing information

Risk	What is known
Use in patients below 18 years	To date, Cresemba has not been studied in juvenile animals, or in humans aged under 18 years.
Use in patients with severely reduced liver function (use in patients with severe hepatic impairment)	Based on clinical studies, no dose adjustment of Cresemba is necessary in patients with mildly or moderately reduced liver function. Cresemba has not been studied in patients with severely reduced liver function; Cresemba should only be used in patients with severe hepatic impairment if the benefit outweighs the risk. These patients should be carefully monitored for potential drug toxicity.
Efficacy in invasive aspergillosis in Asian patients	It is unknown why Asian patients enrolled in the aspergillosis study had a lower success rate in the Cresemba group than in the voriconazole treatment group. A potential ethnicity effect can neither be excluded nor confirmed.
Efficacy and safety in patients infected with *Mucorales* species	The clinical data for Cresemba in the treatment of mucormycosis are limited to data from one prospective non-controlled clinical study in 37 patients who received Cresemba as a first treatment, or because other anti-fungal treatments (mostly amphotericin B) were inappropriate.

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 Cresemba can be found on Cresemba’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
Registry	To collect data on efficiency in the treatment of *Mucorales* species.	The clinical data for Cresemba in the treatment of mucormycosis are based on one non-controlled clinical study in 37 patients. For individual *Mucorales* species, the clinical efficacy data are very limited, often to one or two patients. Susceptibility data were available in only a small subset of cases.	Synopsis	Q2 2016 (Protocol submission)

Studies which are a condition of the marketing authorisation

There are no studies that 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 08-2015.