Product Sheet of Cresemba

Distinctive Name: Cresemba.
Generic Name: Isavuconazole.
Pharmaceutical Form: IV and Capsules.
Presentation: Vial of 200mg (equivalent to 372.6mg of isavuconazonium sulfate). Box with 14 capsules of 100mg (equivalent to 186.3mg of isavuconazonium sulfate).

Indications: CRESEMBA is indicated for adults for the treatment of Invasive Aspergillosis and mucormycosis in patients for whom amphotericin B is inappropriate.

Dosage:

- **Loading dose:** One vial of 200mg every 8 hours during the first 48 hours (6 administrations in total) or 2 capsules of 100mg every 8 hours during the first 48 hours.
- **Maintenance dose:** One vial of 200mg once daily or 2 capsules of 100mg once daily starting between 12 and 24 hours after the last loading dose.

Reconstitution and Dilution of the Vial (IV):
Cresemba IV must be reconstituted by adding 5ml of water for injectable preparations, gently shaking until the powder is completely dissolved. After reconstitution, the entire content must be withdrawn and added to an infusion bag with at least 250ml of Sodium Chloride Injection Solution at 0.9mg/ml (0.9%) or Dextrose Solution at 50mg/ml (5%). The infusion solution contains approximately 1.5mg/ml of isavuconazonium sulfate (equivalent to approximately 0.8mg of Isavuconazole per ml). The infusion solution should be administered intravenously over at least 1 hour through an infusion set with an in-line filter with a microporous membrane made of polyethersulfone (PES) and with a pore size of 0.2µm to 1.2µm.

Mechanism of Action (Pharmacodynamics): Isavuconazole is a prodrug that does not contain cyclodextrin (IV), a moderate CYP3A4/5 inhibitor with high CNS penetration and linear pharmacokinetics.

Customer Profile Questions:

1. How often do you treat cases of Invasive Aspergillosis or Mucormycosis?
2. Have you experienced limitations with amphotericin B or voriconazole in treating these infections?
3. What is your experience with the side effects of current antifungal treatments?
4. How do you evaluate the convenience of administration in the treatment of fungal infections?
5. Have you faced challenges in managing drug interactions with antifungal treatments?

Frequently Asked Questions:

1.- How does Cresemba ensure quality medical care and successful recovery in the treatment of Invasive Aspergillosis and Mucormycosis?

Cresemba (Isavuconazole) is specifically indicated for the treatment of Invasive Aspergillosis and Mucormycosis in adults, conditions for which amphotericin B may be inappropriate. The designation of Cresemba for these infections underscores its effectiveness in combating specific fungal pathogens, thus offering a targeted therapeutic option that contributes to better quality medical care. The efficacy of Cresemba is supported by clinical studies such as the SECURE study, where it demonstrated comparable efficacy with voriconazole, and it is recommended in major international treatment guidelines as a first-line treatment, ensuring successful recovery through effective management of these infections.

2.- How does Cresemba minimize treatment risks of adverse effects and complications compared to other available antifungal options?
Cresemba stands out for its better safety profile compared to antifungal options like voriconazole. Specifically, being a prodrug, its intravenous formulation does not contain cyclodextrin, thereby eliminating the risk of renal toxicity associated with other antifungal therapies. Moreover, Isavuconazole has the characteristic of shortening the QTc interval, unlike other azoles, reducing the risk of cardiac complications. These aspects significantly contribute to minimizing the risks of adverse effects and complications, offering a safer treatment option for patients.

3.- How do the linear pharmacokinetics and low drug interaction profile of Cresemba improve the management of patients with complex medical conditions?
The linear pharmacokinetics of Cresemba ensures less inter- and intra-patient variability, meaning that dosing can be more predictable and stable without the need for routine monitoring of plasma levels. This is particularly beneficial for patients with complex medical conditions as it simplifies the treatment regimen and reduces the risk of dose-dependent complications. Additionally, Cresemba has a favorable drug interaction profile, being a moderate inhibitor of CYP3A4/5, allowing its use with a wider range of medications without the risk of significant interactions. This is crucial for patients already on complex treatments for other conditions, enhancing the safety and efficacy of antifungal treatment.

4.- What are the advantages of Cresemba compared to Voriconazole in terms of EFFICACY?
Cresemba demonstrated comparable efficacy with voriconazole in the Secure Study and real-world evidence and is recommended as a first-line treatment for Invasive Aspergillosis and Mucormycosis in major international treatment guidelines. Isavuconazole is the only azole indicated for mucormycosis.

5.- What are the advantages of Cresemba compared to Voriconazole in terms of SAFETY?
Isavuconazole has a better safety profile with fewer drug-related adverse events compared to voriconazole. As a prodrug, the IV formulation does not contain cyclodextrin, eliminating the risk of renal toxicity. Isavuconazole shortens the QTc interval, unlike other azoles, decreasing cardiac complications.

6.- What are the advantages of Cresemba compared to Voriconazole in terms of DRUG INTERACTIONS?
Isavuconazole has fewer drug interactions with immunosuppressants and new hematological drugs.

7.- What are the advantages of Cresemba compared to Voriconazole in terms of CONVENIENCE?
Cresemba is more convenient as the IV and oral formulations are interchangeable. No dose adjustment is needed in patients with obesity or mild to moderate hepatic or renal impairment. The dosage is once a day without food restrictions. Unlike voriconazole, Cresemba has a predictable pharmacokinetic profile, not requiring routine plasma level monitoring.

8.- What are the indications for Cresemba?
CRESEMBA is indicated for adults for the treatment of Invasive Aspergillosis and mucormycosis in patients for whom amphotericin B is inappropriate.

9.- What is the posology of Cresemba?
CRESEMBA is initiated with a loading dose of 200mg every 8 hours during the first 48 hours (1 vial every 8 hours or 2 capsules every 8 hours) followed by a maintenance dose of 200mg once a day (1 vial per day or 2 capsules per day). The IV and oral presentations are interchangeable.

10.- How is Cresemba IV reconstituted, diluted, and infused?
Cresemba IV must be reconstituted by adding 5 ml of water for injectable preparations, gently shaking until the powder is completely dissolved. After reconstitution, the entire content must be withdrawn and added to an infusion bag with at least 250 ml of Sodium Chloride Injection Solution at 0.9mg/ml (0.9%) or Dextrose Solution at 50 mg/ml (5%). The infusion solution contains approximately 1.5mg/ml of isavuconazonium sulfate (equivalent to approximately 0.8mg of Isavuconazole per ml). The infusion solution should be administered intravenously over at least 1 hour through an infusion set with an in-line filter with a microporous membrane made of polyethersulfone (PES) and with a pore size of 0.2µm to 1.2µm.

11.- What advantages does Cresemba have as a prodrug?
It is activated in the body only after administration, is water-soluble, and therefore does not contain cyclodextrin, eliminating the risk of renal toxicity.

12.- How is Cresemba metabolized?
It is a moderate inhibitor of CYP3A4/5, allowing a more favorable drug interaction profile.

13.- What does it mean that Cresemba has linear pharmacokinetics?
The molecule has less inter-patient and intra-patient variability, so routine plasma level monitoring is not required.

KNOWLEDGE OF PIVOTAL STUDIES

14.- What is the pivotal study of Cresemba in Aspergillosis and what were the efficacy results?
The SECURE study. The results showed that Isavuconazole is not inferior to voriconazole concerning all-cause mortality up to day 42 = Survival rate of 81% with Isavuconazole vs 80% with voriconazole.

15.- What did the SECURE study evaluate, how long was the follow-up, and how many ITT patients were included?
The non-inferiority of Isavuconazole compared to voriconazole in the primary treatment of

patients with invasive fungal infection caused by Aspergillus spp or other filamentous fungi, lasted 84 days, and 516 patients received at least one dose of medication (ITT).

16.- In the SECURE study, what were the results regarding drug-related adverse events?
Cresemba showed significantly better tolerability with 42% of drug-related adverse events with Isavuconazole vs 60% with Voriconazole, such as skin, eye, psychiatric, and hepatobiliary disorders.

17.- What is the pivotal study of Cresemba in Mucormycosis, how many ITT patients were included, and how many patients had proven or probable mucormycosis?
In the VITAL study, 146 patients received at least one dose of Isavuconazole (ITT), and 37 patients had proven or probable mucormycosis.

18.- With which molecule was Cresemba compared in the VITAL study and what were the results?
The VITAL study was a single-arm study. A comparative analysis was performed with a control group of FungiScope™ patients treated with Amphotericin B (N=33) and compared as controls to the 21 patients in the VITAL study who received isavuconazole as primary treatment. The probability of survival up to day 84 was similar between patients treated with Isavuconazole (57%) and FungiScope controls (50%).

TREATMENT GUIDELINES

19.- In which Treatment Guidelines is Cresemba recommended and what is the grade of recommendation?
In the Guidelines of the European Society of Microbiology and Infectious Diseases (ESCMID), Isavuconazole is recommended as A-I in the treatment of 1st-line invasive pulmonary aspergillosis. The ECIL-6 2017 guidelines recommend A-I isavuconazole as the first-line treatment of invasive aspergillosis in patients with leukemia and stem cell transplantation. Isavuconazole is recommended as an alternative 1st-line treatment for invasive aspergillosis in the US IDSA treatment guidelines.

DRUG INTERACTIONS

20.- What do you mean by saying that Cresemba has fewer drug interactions?
Isavuconazole can be administered together with proton pump inhibitors, antacids, statins, and immunosuppressants (it is not contraindicated with Sirolimus). Cresemba has fewer interactions with drugs metabolized by CYP3A, such as new drugs to treat hematological malignancies of B cells, including BTK inhibitors, P13K, and BCL-2 like Ibrutinib and Venetoclax.

PHYSICIAN ADOPTION PROFILE

21.- If I use Cresemba only in patients who cannot use or do not respond to voriconazole, why should I prescribe Cresemba in 1st-line?
Cresemba is as effective as voriconazole and has a better safety profile. Cresemba is recommended as 1st-line in major international treatment guidelines. Isavuconazole has fewer drug interactions with immunosuppressants and new hematological drugs.

22.- If I only use Cresemba for very complicated patients like CAPA patients, for example, for other patients I use voriconazole.

You can give all your 1st-line patients the benefit of a product as effective as voriconazole but with fewer adverse events. Cresemba is recommended as 1st-line in major international treatment guidelines. Isavuconazole has fewer drug interactions with immunosuppressants and new hematological drugs.

23.- Does Cresemba work for prophylaxis?
Cresemba is not indicated for prophylaxis.

24.- Can I use Cresemba in children?
Cresemba is only indicated for adults. I can contact you with the medical department to provide information about Cresemba in pediatric populations.

25.- Can I use Cresemba to treat other fungal infections such as Candida or Cryptococcus?
Cresemba is not indicated for other fungal infections. If you need information on this, I can contact you with the medical department.