CRESEMBA®
(isavuconazonium sulfate)
372 mg for injection • 186 mg capsules

ABOUT CRESEMBA®

CRESEMBA® (isavuconazonium sulfate) is the prodrug containing the active antifungal agent isavuconazole, an azole antifungal indicated for patients 18 years of age and older in the treatment of invasive aspergillosis and invasive mucormycosis.

Data from two Phase 3 studies have demonstrated CRESEMBA's positive outcomes:

- In the SECURE study (a randomized, double-blind, active-control study of 516 adult patients with invasive aspergillosis), CRESEMBA demonstrated non-inferiority to voriconazole on the primary endpoint of all-cause mortality at Day 42 for the treatment of adult patients with invasive aspergillosis or other filamentous fungi. All-cause mortality through Day 42 was 18.6 percent in the CRESEMBA treatment group and 20.2 percent in the voriconazole treatment group.

- The VITAL study (an open-label non-comparative study of CRESEMBA in adult patients with invasive aspergillosis and renal impairment or in patients with invasive fungal disease caused by other rare fungi) included a subpopulation of 37 patients with invasive mucormycosis treated with CRESEMBA. All-cause mortality in CRESEMBA-treated patients was 38 percent. The efficacy of CRESEMBA for the treatment of invasive mucormycosis has not been evaluated in concurrent, controlled clinical trials.

- In the SECURE study, the overall safety profile for CRESEMBA demonstrated similar rates of mortality and non-fatal adverse events as the comparator, voriconazole. The most frequent adverse events for patients treated with CRESEMBA in the two Phase 3 clinical trials were: nausea (26%), vomiting (25%), diarrhea (22%), headache (17%), elevated liver chemistry tests (17%), hypokalemia (14%), constipation (13%), dyspnea (12%), cough (12%), peripheral edema (11%), and back pain (10%).

Like other azoles, isavuconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14α-demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane thus weakening the structure and function of the fungal cell membrane.

IMPORTANT SAFETY INFORMATION FOR CRESEMBA

CRESEMBA is contraindicated in persons with known hypersensitivity to isavuconazole.

Coadministration of strong CYP3A4 inhibitors, such as ketoconazole or high-dose ritonavir (400 mg every 12 hours), with CRESEMBA is contraindicated because strong CYP3A4 inhibitors can significantly increase the plasma concentration of isavuconazole.

Coadministration of strong CYP3A4 inducers, such as rifampin, carbamazepine, St. John's wort, or long acting barbiturates with CRESEMBA is contraindicated because strong CYP3A4 inducers can significantly decrease the plasma concentration of isavuconazole.

CRESEMBA shortened the QTc interval in a concentration-related manner. CRESEMBA is contraindicated in patients with familial short QT syndrome.

Hepatic Adverse Drug Reactions (e.g., elevations in ALT, AST, alkaline phosphatase, total bilirubin) have been reported in clinical trials and were generally reversible and did not require discontinuation of CRESEMBA. Cases of severe hepatic adverse drug reactions including hepatitis, cholestasis or hepatic failure including death have been reported in patients with serious underlying medical conditions (e.g., hematologic malignancy) during treatment with azole antifungal agents, including CRESEMBA. Evaluate liver tests at the start and during therapy. Monitor patients who develop liver abnormalities during CRESEMBA therapy for severe hepatic injury. Discontinue if clinical signs and symptoms consistent with liver disease develop that may be attributable to CRESEMBA.

Infusion-related reactions including hypotension, dyspnea, chills, dizziness, paresthesia, and hypoesthesia were reported during intravenous administration of CRESEMBA. Discontinue the infusion of CRESEMBA if these reactions occur.

Serious hypersensitivity and severe skin reactions, such as anaphylaxis or Stevens Johnson syndrome, have been reported during treatment with other azole antifungal agents. Discontinue CRESEMBA if a patient develops a severe cutaneous adverse reaction. Caution should be used when prescribing CRESEMBA to patients with hypersensitivity to other azoles.

During pregnancy, CRESEMBA may cause fetal harm when administered, and should be used during pregnancy

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only if the potential benefit to the patient outweighs the risk to the fetus. Women who become pregnant while receiving CRESEMBA are encouraged to contact their physician.

Following dilution, CRESEMBA intravenous formulation may form precipitate from the insoluble isavuconazole. Administer CRESEMBA through an in-line filter.

The most frequent adverse events among CRESEMBA-treated patients were: nausea (26%), vomiting (25%), diarrhea (22%), headache (17%), elevated liver chemistry tests (16%), hypokalemia (14%), constipation (13%), dyspnea (12%), cough (12%), peripheral edema (11%), and back pain (10%).

The adverse reactions which most often led to permanent discontinuation of CRESEMBA therapy during the clinical trials were: confusional state (0.7%), acute renal failure (0.7%), increased blood bilirubin (0.5%), convulsion (0.5%), dyspnea (0.5%), epilepsy (0.5%), respiratory failure (0.5%), and vomiting (0.5%).

For Full Prescribing Information, please visit here.

DOSING INFORMATION

The recommended loading dose of CRESEMBA is one reconstituted vial or two capsules (372 mg isavuconazonium sulfate equivalent to 200 mg of isavuconazole) every eight hours for six doses (48 hours) via oral or intravenous administration. The recommended maintenance dose is one reconstituted vial or two capsules (372 mg isavuconazonium sulfate equivalent to 200 mg of isavuconazole) once per day via oral or intravenous administration, starting 12 to 24 hours after the last loading dose. Capsules can be taken with or without food. CRESEMBA for injection must be administered through an in-line filter over a minimum of one hour.

ABOUT INVASIVE ASPERGILLOSIS

Invasive aspergillosis (IA) is a life-threatening invasive infection that is seen predominantly in patients with prolonged neutropenia related to antineoplastic chemotherapy and/or hematopoietic stem cell transplantation (HSCT), patients receiving immunosuppressants following solid organ transplants and patients given high doses of corticosteroids.[1]

Mortality rates approaching 30 percent have been reported in patients with invasive aspergillosis.[2,3]

ABOUT INVASIVE MUCORMYCOSIS

Invasive mucormycosis (IM) is a rare, but potentially fatal fungal infection caused by the filamentous fungi of the Mucorales order from the phylum of Zygomycota.[4] Many of the conditions predisposing patients to invasive mycormycosis are the same as for invasive aspergillosis and include hematological malignancy with or without stem cell transplantation and prolonged neutropenia. Other groups of patients at risk are diabetics with uncontrolled hyperglycemia as well as dialysis patients with iron overload. The presentation of IM often resembles that of IA or other invasive fungal infections. Clinical forms include: rhinocerebral, pulmonary, gastrointestinal, cutaneous and disseminated disease.[5]

QIPD/ORPHAN DRUG STATUS

The FDA designated CRESEMBA as a Qualified Infectious Disease Product (QIDP) for both invasive aspergillosis and invasive mucormycosis. QIDP status provides priority review and a five-year extension of market exclusivity in the United States. QIDP incentives were granted under the 2012 U.S. Generating Antibiotic Incentives Now (GAIN) Act as a part of the FDA Safety and Innovation Act.

Also, in 2013, CRESEMBA was granted Orphan Drug status for invasive aspergillosis and invasive mucormycosis which will result in the product having seven years of market exclusivity in addition to that provided under the GAIN Act.

CRESEMBA is being co-developed with Basilea Pharmaceutica International Ltd. Basilea submitted a European Marketing Authorization Application on July 16, 2014 for the treatment of invasive aspergillosis and mucormycosis in adults. In addition, CRESEMBA has European Union orphan drug status for invasive aspergillosis and mucormycosis. The regulatory review of the European Marketing Authorization Application is anticipated to be completed by the fourth quarter of 2015.

Information regarding CRESEMBA ongoing clinical trials is available at clinicaltrials.gov.

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