PDL DRUG REVIEW

Proprietary Name: Cresemba®
Common Name: isavuconazonium sulfate
PDL Category: Antifungals

Comparable Products	Preferred Drug List Status
Itraconazole	Non-Preferred with Conditions
Noxafil	Non-Preferred with Conditions
Voriconazole	Preferred with Conditions

Summary

Pharmacology/Usage: Isavuconazonium sulfate, the active ingredient of Cresemba®, is the prodrug of isavuconazole. Isavuconazole is an azole antifungal that inhibits the synthesis of ergosterol, which is a main part of the fungal cell membrane.

Indications: For patients ≥18 years of age for the treatment of invasive aspergillosis AND for the treatment of invasive mucormycosis. *Per the prescribing information*: Specimens for fungal culture and other relevant laboratory studies (including histopathology) to isolate and identify causative organism(s) should be obtained prior to initiating antifungal therapy. Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

This is a pregnancy category C medication. The safety and efficacy of use in children under the age of 18 years have not been established.

Dosage Forms: Capsules: 186mg isavuconazonium sulfate (equivalent to 100mg of isavuconazole); Also available as a single-dose vial as a sterile lyophilized powder for injection: 372mg isavuconazonium sulfate (equivalent to 200mg of isavuconazole)

Recommended Dosage: Take 2 capsules PO Q8H for 6 doses as the loading dose (48 hours) and then 2 capsules PO QD as the maintenance dose. For injection, administer 1 reconstituted vial IV Q8H for 6 doses as loading dose and then 1 reconstituted vial IV QD as the maintenance dose. Bioequivalence of IV and oral formulations has been shown and thus switching between formulations is acceptable. A loading dose is not needed when switching between formulations.

Dose adjustments are not required in those with renal impairment or in those with mild or moderate hepatic impairment. Use has not been studied in those with severe hepatic impairment and thus should only be used in this population if the benefit outweighs the risk. It is recommended to monitor for Cresemba®-related adverse events if used in this population.

Drug Interactions: Please refer to the contraindications section for a list of drugs that are contraindicated with Cresemba®. Use the following drugs with caution if given concomitantly with Cresemba®, monitoring and adjusting the dose if needed: lopinavir 400mg in combination with ritonavir 100mg, atorvastatin, cyclosporine, sirolimus, tacrolimus, midazolam, bupropion, mycophenolate mofetil, and digoxin.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Cresemba®) minus reported % incidence for voriconazole. Please note that an incidence of 0% means the incidence of Cresemba® was the same as or less than comparators.* The most frequently reported adverse events included nausea (0%), vomiting (0%), diarrhea (0.5%), abdominal pain (0%), constipation (0%), dyspepsia (0.8%), peripheral edema (0%), fatigue (3.6%), chest pain (2.7%), injection site reaction (4.7%), elevated liver lab tests (0%), hypokalemia (0%), decreased appetite (0%), hypomagnesemia (0%), back pain (2.8%), headache (2%), insomnia (0.8%), delirium (0%), anxiety (1.3%), renal failure (2%), dyspnea (3.6%), acute respiratory failure (0%), rash (0%), pruritus (2.4%), and hypotension (0%).

Elevations in liver-related laboratory tests have been reported with Cresemba® use; however, the elevations were generally reversible and did not require discontinuation of treatment. It is recommended to obtain liver-related lab tests prior to starting therapy and during treatment.

Contraindications: In those with familial short QT syndrome; Co-administration of strong CYP3A4 inhibitors (such as ketoconazole or high-dose ritonavir of 400mg BID); Co-administration of strong CYP3A4 inducers (such as rifampin, carbamazepine, St. John's wort, or long-acting barbiturates); and with known hypersensitivity to isavuconazole.

Manufacturer: Astellas

Analysis: Study 1 was a randomized, double-blind, non-inferiority active-controlled study that assessed the safety and efficacy of Cresemba® as compared to voriconazole in adults with invasive fungal disease caused by *Aspergillus* species or other filamentous fungi. Patients received IV loading dose in both treatment arms; thereafter, patients could be switched to oral therapy. The protocol-defined maximum treatment duration was 84 days. The mean treatment duration was 47 days for both groups, of which 8-9 days was by IV administration. All-cause mortality was assessed through day 42 and results are illustrated in the table below.

	Cresemba®	**Voriconazole**
All-cause mortality in ITT population	18.6% (N=48/258)	20.2% (N=52/258)
All-cause mortality in Proven/probable Invasive Aspergillosis	18.7% (N=23/123)	22.2% (N=24/108)

In the subgroup of adults with proven/probable invasive aspergillosis confirmed by serology, culture, or histology, overall success at end-of-treatment (EOT) was assessed. Results suggested that overall success at EOT was seen in 35% (N=43/123) of the Cresemba® group vs 38.9% (N=42/108) of the voriconazole group.

Study 2 was an open-label, non-comparative study that assessed the safety and efficacy of a subset of patients (N=37) with probable or proven invasive mucormycosis. Cresemba® was administered as either IV or oral. Patients were classified as being treated as primary therapy or as those refractory to or intolerant of other antifungal therapies. The median treatment duration was 102 days for patients classified as primary, 33 days for refractory, and 85 days for intolerant. All-cause mortality through day 42 and success in overall response at the end of treatment (EOT) were assessed. Results suggested that Cresemba® was effective for the treatment of mucormycosis; however, its efficacy for the treatment for invasive mucormycosis has not been assessed in concurrent controlled clinical trials. The table below, adapted from the prescribing information, illustrates the results.

	Primary (N=21)	Refractory (N=11)	Intolerant (N=5)	Total (N=37)
All-cause mortality through day 42	33% (N=7)	46% (N=5)	40% (N=2)	38% (N=14)
Overall response success rate at EOT	32% (N=6/19)[1]	36% (N=4)	20% (N=1)	31% (N=11/35)[1]

[1] Two primary adults were not assessed due to ongoing treatment

Place in Therapy: One noted reference source recommends voriconazole-based regimens for initial therapy of those with confirmed invasive aspergillosis.[2] Cresemba® was found to be comparable to voriconazole in one non-inferiority study in regards to all-cause mortality, as well as with overall success in a subgroup with proven or probable invasive aspergillosis. Guidelines from the Infectious Disease Society of America regarding aspergillosis were published prior to the availability of Cresemba®.[3]

Cresemba® is also approved for the treatment of invasive mucormycosis based on results from a non-comparative study. Guidelines from the European Society for Clinical Microbiology and Infectious Diseases and the European Confederation of Medical Mycology regarding the treatment of mucormycosis were also published prior to the approval of Cresemba®. Recommended treatment in this guideline is with amphotericin B or, as an alternative, posaconazole for mucormycosis.[4]

There is no evidence at this time to support that Cresemba® is more efficacious or safer than the currently available, more cost effective medications. It is therefore recommended that Cresemba® remain non-preferred and require prior authorization and be available to the few who are unable to tolerate or have failed on any preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Cresemba [package insert]. Northbrook, IL: Astellas Pharma US, Inc; 2015.

[2] UpToDate desktop version. Treatment and prevention of invasive aspergillosis. Accessed January 2016.

[3] Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2008; 46(3):327-360.

[4] Cornely OA, Arikan-Akdagli S, Dannaoui E, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. *Clin Microbiol Infect*. 2014; 20 Suppl 3: 5-26.