astellas

Committed to Infectious Diseases

Astellas is actively committed to the infectious disease field. Our infectious disease portfolio includes three classes of drugs: AmBisome® (amphotericin B) liposome for injection, CRESEMBA® (isavuconazonium sulfate), and MYCAMINE® (micafungin sodium) for injection.

We continue to expand the knowledge base of this therapeutic area and empower physicians to make evidence-based clinical decisions. Our proud history of collaborating with clinical investigators has provided opportunities around the world to study compounds that have the potential to be significant breakthroughs and allows us to generate and publish key information about these advances. In fact, Astellas pioneered the empiric antifungal clinical trial and has performed some of the world's largest clinical trials in fungal infections.

AmBisome®
(amphotericin B) liposome for injection

AmBisome® is indicated for the following:

- Empirical therapy for presumed fungal infection in febrile neutropenic patients
- Treatment of Cryptococcal Meningitis in HIV-infected patients
- Treatment of *Aspergillus* species, *Candida* species and/or *Cryptococcus* species infections refractory to amphotericin B deoxycholate, or in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate
- Treatment of visceral leishmaniasis; in immunocompromised patients with visceral leishmaniasis treated with AmBisome, relapse rates were high following initial clearance of parasites

In a clinical study, AmBisome® delivered significantly less nephrotoxicity than Abelcet® (amphotericin B lipid complex injection)[1]

- 2/3 less nephrotoxicity with AmBisome than Abelcet[2,3]
  - 14.1% of patients treated with AmBisome 3 mg/kg/day (n=85) and 14.8% of those treated with AmBisome 5 mg/kg/day (n=81) experienced nephrotoxicity compared with 42.3% of patients treated with Abelcet 5 mg/kg/day (n=78) ($p \leq 0.001$)
- Significantly fewer infusion-related reactions with AmBisome than Abelcet[2,3]
  - 51.8% of patients treated with AmBisome 3 mg/kg/day (n=85) and 48.1% of those treated with AmBisome 5 mg/kg/day (n=81) experienced infusion-related reactions compared with 88.5% of patients treated with Abelcet 5 mg/kg/day (n=78) ($p \leq 0.001$)
- The incidence of some common adverse events was greater in patients taking AmBisome compared to patients taking Abelcet in the clinical study noted above including: chest pain, hypocalcemia, hypomagnesemia, confusion, headache, and rash

Important Safety Information

Despite significantly less nephrotoxicity observed at a dose range of 1.5–6.0 mg/kg/day compared to amphotericin B deoxycholate at a dose range of 0.3–1.2 mg/kg/day in a randomized clinical trial, dose-limiting renal toxicity may still be observed with AmBisome.

Dose-limiting renal toxicity may still be observed with AmBisome even though significantly less nephrotoxicity was observed at dosages of 3 mg/kg/day and 5 mg/kg/day compared to Abelcet at a dosage of 5 mg/kg/day.

The toxicity of AmBisome due to overdose has not been defined. Repeated daily doses up to 10 mg/kg in pediatric patients and 15 mg/kg in adult patients have been administered in clinical trials with no reported dose-related toxicity.

There have been a few reports of flushing, back pain with or without chest tightness, and chest pain associated with AmBisome administration; on occasion this has been severe.

Anaphylaxis has been reported with amphotericin B formulations including AmBisome.

Please see full prescribing Information for AmBisome.

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

CRESEMBA® (isavuconazonium sulfate) is the prodrug containing the active antifungal agent isavuconazole, an azole antifungal drug 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%)

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.

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 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.

MYCAMINE®
(micafungin sodium) for injection

MYCAMINE® is indicated in adult and pediatric patients 4 months and older for:

- Treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis, and abscesses
  - MYCAMINE has not been adequately studied in patients with endocarditis, osteomyelitis, and meningitis due to *Candida* infections
- Treatment of patients with esophageal candidiasis
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation

NOTE: The efficacy of MYCAMINE against infections caused by fungi other than *Candida* has not been established.

Effective across a range of *Candida* species with once-daily dosing MYCAMINE can deliver:

- Power in treating candidemia and other *Candida* infections
  - 70.7% of adult patients with invasive candidiasis or candidemia treated with MYCAMINE (n=191) achieved treatment success at the end of IV therapy vs 63.3% of patients treated with caspofungin (n=188)[4]
- Efficacy across a range of *Candida* species
  - Treatment success against *C. albicans* 70.4% (57/81), *C. glabrata* 69.6% (16/23), *C. tropicalis* 63% (17/27), *C. parapsilosis* 75% (21/28), and *C. krusei* 62.5% (5/8)
- Once-daily dosing considerations
  - No loading dose[5]
  - No dose adjustment required based on:
    - Race, gender, or in the elderly
    - Severe renal dysfunction
    - Mild-to-severe hepatic insufficiency
    - Room temperature storage

Important Safety Information

MYCAMINE is contraindicated in patients with known hypersensitivity to micafungin, any component of MYCAMINE, or other echinocandins.

Isolated cases of serious hypersensitivity (anaphylaxis and anaphylactoid) reactions (including shock) have been reported in patients receiving MYCAMINE. In these cases, MYCAMINE should be discontinued and appropriate treatment administered.

Elevations in BUN and creatinine, and isolated cases of clinically significant hepatic dysfunction, hepatitis, hepatic failure, renal dysfunction, acute renal failure, hemolysis, or hemolytic anemia have occurred in some patients who have received MYCAMINE. Patients who develop these conditions, or abnormal liver or renal function tests, should be monitored closely for worsening function and evaluated for risk/benefit of continuing MYCAMINE therapy.

In clinical trials, possible histamine-mediated symptoms have been reported with MYCAMINE (including rash, pruritus, facial swelling, and vasodilatation).

In clinical trials, the most common treatment-emergent adverse reactions in adults for all indications included diarrhea, nausea, vomiting, pyrexia, thrombocytopenia, and headache. The most common treatment-emergent adverse reactions observed in pediatric patients 4 months and older included vomiting, diarrhea, pyrexia, nausea, abdominal pain, and thrombocytopenia.

Please see full prescribing information for MYCAMINE.

1. Abelcet® is a registered trademark of Sigma-Tau Pharmaceuticals, Inc.
2. Wingard JR, White MH, Anaissie E, et al; and the L Amph/ABLC Collaborative Study Group. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. Clin Infect Dis. 2000;64:1155-1163.
3. AmBisome (amphotericin B) liposome for injection [package insert]. Northbrook, IL: Astellas Pharma US, Inc.
4. MYCAMINE® (microfungin sodium) for injection [package insert]. Northbrook, IL: Astellas Pharma US, Inc.
5. Hiemenz J, Cagnoni P, Simpson D, et al. Pharmacokinetic and maximum tolerated dose study of micafungin in combination with fluconazole versus fluconazole alone for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. Antimicrob Agents Chemother. 2005;49(4):1331-1336