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Date of Request: 08/31/2016
NCCN Guidelines Panel: Prevention and Treatment of Cancer-Related Infections 2017

Astellas Pharma Global Development, Inc. requests your consideration to review data that demonstrates the appropriateness of CRESEMBA (isavuconazonium sulfate) as a treatment option in patients with cancer-related invasive *Aspergillus* spp. and other filamentous fungi, including mucormycosis.

Specific changes: Recommend isavuconazonium sulfate as an appropriate systemic therapy for adult cancer patients and hematopoietic stem cell transplant (HSCT) recipients with invasive aspergillosis and invasive mucormycosis.

FDA clearance: FDA granted the following designations to isavuconazonium sulfate:[1]

- May 2013: Orphan Drug Designation for the treatment of invasive aspergillosis.
- October 2013: Orphan Drug Designation for the treatment of invasive mucormycosis.
- November 2013: Qualified Infectious Disease Product (QIDP) for invasive mucormycosis
- February 2014: QIDP for the treatment of invasive mucormycosis.
- March 2015: approval of CRESEMBA (isavuconazonium sulfate) for the treatment of invasive aspergillosis and invasive mucormycosis.

Isavuconazonium sulfate is the water-soluble prodrug of the active triazole isavuconazole.[2] For the remainder of this document, isavuconazonium sulfate will be referred to as isavuconazole (ISAV) when referring to the compound.

Rationale: The published data below support efficacy and safety of isavuconazole as primary treatment, for refractory disease, or as an alternate treatment to current therapies described in the NCCN guidelines for cancer-related invasive aspergillosis and mucormycosis.

SECURE was a phase 3, double-blind, global multicenter, comparative-group study. Patients with suspected invasive fungal disease were randomized in a 1:1 ratio and stratified by geographical region, allogeneic hematopoietic stem cell transplantation, and active malignant disease at baseline.[3] The authors assessed non-inferiority of the primary efficacy endpoint of all-cause mortality from first dose of study drug to day 42 in patients who received at least one dose of the study drug (intention-to-treat [ITT] population) using a 10% non-inferiority margin. Safety was assessed in patients who received the first dose of study drug.

There were 527 adult patients randomly assigned (n=58 for both groups).[3] All-cause mortality from first dose of study drug to day 42 for the ITT population was 19% with isavuconazole (n=48) and 20% with voriconazole (n = 52), with an adjusted treatment difference of –1.0% (95% CI −7.8 to 5.7). Because the upper bound of the 95% CI (5.7%) did not exceed 10%, non-inferiority was shown. Most patients (n = 247 [96%]) receiving isavuconazole and (n = 255 [98%]) receiving voriconazole had treatment emergent adverse events (p = 0.122); the most common were gastrointestinal disorders (n = 174 [68%] vs n = 180 [69%]) and infections and infestations (n = 152 [59%] vs n = 158 [61%]). Proportions of patients with treatment-emergent adverse events by system organ class were similar overall. However, isavuconazole-treated patients had a lower frequency of hepatobiliary disorders (n = 23 [9%] vs n = 42 [16%]; p = 0.016), eye disorders (n = 39 [15%] vs n = 69 [27%]; p = 0.002), and skin or subcutaneous tissue disorders (n = 86 [33%] vs n = 110 [42%]; p = 0.037). Drug-related adverse events were reported in 109 (42%) patients receiving isavuconazole and 155 (60%) receiving voriconazole (p < 0.001).

The authors concluded that isavuconazole was non-inferior to voriconazole for the primary treatment of suspected invasive fungal disease and was well tolerated compared with voriconazole, with fewer study-

drug-related adverse events.[3] The authors stated that the results support the use of isavuconazole for the primary treatment of patients with invasive fungal disease.

In a single-arm open-label trial (VITAL study), adult patients (age ≥ 18 years) with invasive fungal disease caused by rare fungi, including mucormycosis, were recruited from 34 centers worldwide.[4] Patients were given isavuconazole 200 mg (intravenous or oral). The primary endpoint was independent data review committee-determined overall response: complete or partial response (treatment success) or stable or progressive disease (treatment failure) according to pre-specified criteria. Mucormycosis cases treated with isavuconazole as primary treatment were matched with controls from the FungiScope Registry, recruited from 17 centers worldwide, who received primary amphotericin B-based treatment, and were analyzed for day-42 all-cause mortality.

There were 37 patients with mucormycosis that received isavuconazole for a median of 84 days (range 2 to 882).[4] By day 42, 4 (11%) patients had a partial response, 16 (43%) patients had stable invasive fungal disease, one (3%) patient had invasive fungal disease progression, three (8%) patients had missing assessments, and 13 (35%) patients had died. Of these, 35 patients (95%) had adverse events (n = 28 [76%] of reported adverse events were serious). Day-42 crude all-cause mortality in seven (33%) of 21 primary-treatment isavuconazole cases was similar to 13 (39%) of 33 amphotericin B-treated matched controls (weighted all-cause mortality: 33% *vs* 41%; p = 0.595).

The authors concluded that isavuconazole showed activity against mucormycosis with efficacy similar to amphotericin B and can be used for treatment of mucormycosis and is well tolerated.[4]

The 2016 Infectious Diseases Society of America (IDSA) guidelines for the diagnosis and management of aspergillosis recommend isavuconazole as an alternative therapy treatment regimen for invasive aspergillosis (strong recommendation; moderate-quality evidence).[5]

The above data support efficacy and safety of isavuconazole as an alternate treatment to current therapies described in the NCCN guidelines for cancer-related invasive mucormycosis. Thank you for your consideration of its inclusion.

The following articles are submitted in support of this proposed change.

Reference List:

1. FDA Briefing Document. Anti-infective drugs advisory committee meeting. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiInfectiveDrugsAdvisoryCommittee/UCM430747.pdf. Accessed 08-31-3016.
2. CRESEMBA [package insert]. Northbrook, IL: Astellas, Inc.
3. Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet 2016;387(10020):760-769.
4. Marty FM, Ostrosky-Zeichner L, Cornely OA, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis 2016;16(7):828-837.
5. Patterson TF, Thompson GR, 3rd, Denning DW, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;63(4):e1-e60.

Sincerely,

Kimberly Pulmano