Clinical Policy: Isavuconazonium (Cresemba)
Reference Number: CP.PMN.154
Effective Date: 11.16.16
Last Review Date: 05.20
Line of Business: Commercial, HIM, Medicaid

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Isavuconazonium (Cresemba®) is an azole antifungal.

FDA Approved Indication(s)
Cresemba is indicated for the treatment of:
- Invasive aspergillosis in patients 18 years of age and older.
- Invasive mucormycosis in patients 18 years of age and older.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Cresemba is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Aspergillosis (must meet all):
      1. Diagnosis of invasive aspergillosis;
      2. Age ≥ 18 years;
      3. Prescribed by or in consultation with an infectious disease specialist;
      4. Failure of voriconazole at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
      5. Dose does not exceed the following:
         a. Loading dose: 372 mg (2 capsules or 2 vials) every 8 hours for 48 hours (total 6 doses: 12 capsules or 6 vials);
         b. Maintenance dose: 372 mg (2 capsules or 2 vials) per day.
   Approval duration: 3 months

   B. Mucormycosis (must meet all):
      1. Diagnosis of invasive mucormycosis;
      2. Age ≥ 18 years;
      3. Prescribed by or in consultation with an infectious disease specialist;
      4. Dose does not exceed the following:
         a. Loading dose: 372 mg (2 capsules or 2 vials) every 8 hours for 48 hours (total 6 doses: 12 capsules or 6 vials);
         b. Maintenance dose: 372 mg (2 capsules or 2 vials) per day.
   Approval duration: 3 months
C. Other diagnoses/indications
   1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and CP.PMN.53 for Medicaid.

II. Continued Therapy
   A. All Indications in Section I (must meet all):
      1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
      2. Member is responding positively to therapy;
      3. If request is for a dose increase, new dose does not exceed 372 mg (2 capsules or 2 vials) per day.
      Approval duration: 6 months

   B. Other diagnoses/indications (must meet 1 or 2):
      1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
      Approval duration: Duration of request or 12 months (whichever is less); or
      2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:
   A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information
   Appendix A: Abbreviation/Acronym Key
   FDA: Food and Drug Administration

   Appendix B: Therapeutic Alternatives
   This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>voriconazole (Vfend®)</td>
<td>Aspergillosis IV: 6 mg/kg/dose IV every 12 hours on day 1, followed by 4 mg/kg/dose IV every 12 hours. If patient is unable to tolerate maintenance therapy, reduce dose to 3 mg/kg/dose IV every 12 hours.</td>
<td>Weight ≥ 40 kg: 12 mg/kg/day IV; 800 mg/day PO  Weight &lt; 40 kg:12 mg/kg/day IV; 400 mg/day PO</td>
</tr>
</tbody>
</table>
**Appendix C: Contraindications/Boxed Warnings**

- **Contraindication(s):**
  - Hypersensitivity to Cresemba.
  - 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 is contraindicated in patients with familial short QT syndrome. Cresemba shortened the QTc interval in a concentration-related manner.

- **Boxed warning(s):** none reported

### V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive aspergillosis or invasive mucormycosis</td>
<td>Loading dose: 372 mg (IV or 2 capsules PO) every 8 hours for a total of 6 doses in 48 hours</td>
<td>Loading dose: 1,116 mg/day</td>
</tr>
</tbody>
</table>
### Indication | Dosing Regimen | Maximum Dose
--- | --- | ---
 | Maintenance dose (starting 12 to 24 hours after the last loading dose): 372 mg (IV or 2 capsules PO) QD | Maintenance dose: 372 mg/day

### VI. Product Availability
- Capsule: 186 mg of isavuconazonium sulfate (equivalent to 100 mg of isavuconazole)
- Single-dose vial for injection: 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole)

### VII. References

### Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Description</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Converted to new template; minor changes to verbiage and grammar. References updated.</td>
<td>1.5.17</td>
<td>8.17</td>
</tr>
<tr>
<td>3Q 2018 annual review: new policy for Medicaid line of business; added age and prescriber requirements; re-auth: added positive response to therapy, modified max dose requirement to reflect dosage regimen for maintenance dose; references reviewed and updated.</td>
<td>04.30.18</td>
<td>08.18</td>
</tr>
<tr>
<td>3Q 2019 annual review: no significant changes; revised approval duration for commercial to 3/6 months for initial/continuation to align with Medicaid; clarified max dose requirements to add vial formulation; references reviewed and updated.</td>
<td>05.21.19</td>
<td>08.19</td>
</tr>
<tr>
<td>2Q 2020 annual review: added HIM line of business; retired HIM.PA.108; removed redirection to amphotericin B for HIM line of business for invasive mucormycosis indication; added t/f of voriconazole to criteria for invasive aspergillosis; separated invasive mucormycosis from invasive aspergillosis; references reviewed and updated.</td>
<td>02.24.20</td>
<td>05.20</td>
</tr>
</tbody>
</table>
Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members
and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

©2018 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.