Clinical Policy: Isavuconazonium (Cresemba)

Reference Number: CP.PMN.154
Effective Date: 11.16.16
Last Review Date: 05.23
Line of Business: Commercial, HIM, Medicaid

Revision Log

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
- Invasive mucormycosis

Cresemba for injection is indicated in adults and pediatric patients 1 year of age and older. Cresemba capsules are indicated in adults and pediatric patients 6 years of age and older who weigh 16 kg and greater.

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. One of the following (a or b):
   a. Request for injection for intravenous administration: Age ≥ 1 year;
   b. Request for capsules or injection for nasogastric tube administration, both of the following (i and ii):
      i. Age ≥ 6 years;
      ii. Body weight ≥ 16 kg;
3. Prescribed by or in consultation with an infectious disease specialist, oncologist, or transplant specialist;
4. If age ≥ 2 years, failure of voriconazole at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed one of the following (a or b):
   a. Adults (age ≥ 18 years) (i and ii):
      i. Loading dose: 372 mg every 8 hours for 48 hours (total 6 doses);
      ii. Maintenance dose: 372 mg per day;

b. Pediatrics (age < 18 years): age- and weight-based loading and maintenance dose in section V, up to a maximum of 372 mg per day.

Approval duration: 3 months

B. Mucormycosis (must meet all)**:**

1. Diagnosis of invasive mucormycosis;
2. One of the following (a or b):
   a. Request for injection for intravenous administration: Age ≥ 1 year;
   b. Request for capsules or injection for nasogastric tube administration, both of the following (i and ii):
      i. Age ≥ 6 years;
      ii. Body weight ≥ 16 kg;
3. Prescribed by or in consultation with an infectious disease specialist;
4. Dose does not exceed one of the following (a or b):
   a. Adults (age ≥ 18 years) (i and ii):
      i. Loading dose: 372 mg every 8 hours for 48 hours (total 6 doses);
      ii. Maintenance dose: 372 mg per day;
   b. Pediatrics (age < 18 years): age- and weight-based loading and maintenance dose in section V, up to a maximum of 372 mg per day.

Approval duration: 3 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;

b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*

2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. Adults (age ≥ 18 years): 372 mg per day;
   b. Pediatrics (age < 18 years): age- and weight-based maintenance dose in section V, up to a maximum of 372 mg per day.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, 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, HIM.PA.154 for health insurance marketplace, 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.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
voriconazole (Vfend®)	**Aspergillosis** IV: • *Adults, pediatric patients 12 to 14 years of age weighing ≥ 50 kg, and pediatric patients ≥ 15 years:* 6 mg/kg IV every 12 hours for the first 24 hours, followed by 4 mg/kg IV every 12 hours • *Pediatric patients 2 to < 12 years of age and 12 to 14 years of age weighing < 50 kg:* 9 mg/kg IV every 12 hours for the first 24 hours, followed by 8 mg/kg IV every 12 hours PO: • *Adults, pediatric patients 12 to 14 years of age weighing ≥ 50 kg, and pediatric patients ≥ 15 years:* 200 mg PO every 12 hours beginning after at least 7 days of IV voriconazole therapy • *Pediatric patients 2 to < 12 years of age and 12 to 14 years of age weighing < 50 kg:* 9 mg/kg PO every 12 hours (maximum dose of 350 mg every 12 hours) beginning after at least 7 days of IV voriconazole therapy Clinical practice guidelines suggest voriconazole as primary therapy. Treat for at least 6 to 12 weeks with duration dependent on extent and length of immunosuppression, infection site, and disease improvement.	See regimen

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

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), 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 because strong CYP3A4 inducers can significantly decrease the plasma concentration of isavuconazole
  - Familial short QT syndrome. Cresemba shortened the QTc interval in a concentration-related manner
- Boxed warning(s): none reported

V. Dosage and Administration

<table>
<tr><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>Invasive aspergillosis, invasive mucormycosis</td><td>
Adults
Loading dose: 372 mg (one vial IV, two 186 mg capsules PO, or five 74.5 mg capsules PO) every 8 hours for a total of 6 doses in 48 hours

Maintenance dose (starting 12 to 24 hours after the last loading dose): 372 mg (1 vial IV, two 186 mg capsules PO, or five 74.5 mg capsules PO) QD

Pediatric patients
• Loading dose is administered every 8 hours for a total of 6 doses in 48 hours
• Maintenance dose is administered QD starting 12 to 24 hours after the last loading dose
<table>
<tr><th>Age</th><th>Body weight</th><th>Dose</th></tr>
<tr><td colspan="3">Cresemba for injection (372 mg vial): IV</td></tr>
<tr><td>1 to < 3 years</td><td>< 18 kg</td><td>15 mg/kg</td></tr>
<tr><td rowspan="2">3 to < 18 years</td><td>< 37 kg</td><td>10 mg/kg</td></tr>
<tr><td>≥ 37 kg</td><td>372 mg (1 vial)</td></tr>
<tr><td colspan="3">Cresemba capsules (74.5 mg capsule): PO</td></tr>
<tr><td rowspan="4">6 to < 18 years</td><td>16 to < 18 kg</td><td>149 mg (2 capsules)</td></tr>
<tr><td>18 to < 25 kg</td><td>223.5 mg (3 capsules)</td></tr>
<tr><td>25 to < 32 kg</td><td>298 mg (4 capsules)</td></tr>
<tr><td>≥ 32 kg</td><td>372 mg (5 capsules)</td></tr>
</table>
Cresemba for injection may also be administered via nasogastric tube administration in patients who are 6 years of age and older and weighing 16 kg and greater.
</td><td>
Adults: Loading dose: 1,116 mg/day

Maintenance dose: 372 mg/day

Pediatric patients: 372 mg/day
</td></tr>
</table>

VI. Product Availability

- Capsule: 186 mg of isavuconazonium sulfate (equivalent to 100 mg of isavuconazole), 74.5 mg of isavuconazonium sulfate (equivalent to 40 mg of isavuconazole)
- Single-dose vial for injection: 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole)

VII. References

1. Cresemba Prescribing Information. Northbrook, IL: Astellas, Inc.; December 2023. Available at: www.cresemba.com. Accessed December 14, 2023.
2. Patterson TF, Thompson GR, 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 Aug 15;63(4):e1-e60. doi: 10.1093/cid/ciw326.

3. Tissot F, Agrawal S, Pagano L, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica. Mar 2017. 102(3) 433-444.
4. Centers for Disease Control and Prevention. Fungal diseases: treatment of mucormycosis. Last updated January 14, 2021. Available at: https://www.cdc.gov/fungal/diseases/mucormycosis/treatment.html. Accessed January 31, 2023.
5. Clinical Pharmacology [database online]. Elsevier, Inc.; 2023. Available at: https://www.clinicalkey.com/pharmacology.
6. Cornely OA, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infectious Diseases. 2019; 19(12): E405-E421.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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.	05.21.19	08.19
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.	02.24.20	05.20
2Q 2021 annual review: added oncologist and transplant specialist as prescriber options per specialist feedback; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	01.12.21	05.21
2Q 2022 annual review: no significant changes; revised max quantity from 2 vials to 1 vial per FDA labeling; references reviewed and updated.	01.25.22	05.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.04.22	
2Q 2023 annual review: no significant changes; references reviewed and updated.	01.31.23	05.23
RT4: added 74.5 mg capsule due to recent market launch.	09.25.23	
RT4: revised to reflect pediatric expansion for both indications; for invasive aspergillosis, clarified that required trial of voriconazole only applies to age ≥ 2 years and updated Appendix B dosing regimens per voriconazole's package insert.	12.14.23	

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.