BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

CRESEMBA® (isavuconazonium sulfate) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for CRESEMBA (isavuconazonium sulfate)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by an Infectious Disease Specialist, Transplant Physician, or Oncologist, or in consultation with one

Indication
- Invasive aspergillosis
- Invasive mucormycosis

- Invasive aspergillosis or invasive mucormycosis susceptible to Cresemba treatment initiated in an inpatient setting and continued in outpatient setting

Age Requirement

- 6 years of age or older and weighs at least 16 kilograms

Baseline Clinical Evaluation

- Fungal culture report confirms causative organism(s) are sensitive to isavuconazonium only
- Liver tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin

Alternative Therapies

- For invasive aspergillosis:
  - Failure (trial for at least three months duration), contraindication, intolerance to **ONE** of the following:
    1. Vfend (voriconazole)
    2. Posaconazole (Noxafil or generic) tablet
- For invasive mucormycosis:
  - Failure (trial for at least three months duration), contraindication, intolerance to **BOTH** of the following:
    1 Lipid formulation of amphotericin B (liposomal amphotericin B or amphotericin B lipid complex)
    2 Posaconazole (Noxafil or generic) tablet

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the U.S. Food and Drug Administration (FDA) (see Definitions section)

Safety

- No concomitant use with strong CYP3A4 inhibitors such as ketoconazole or high-dose ritonavir (400 mg every 12 hours)
- No concomitant use with strong CYP3A4 inducers such as rifampin, carbamazepine, St. John's wort, or long-acting barbiturates
- Does not have familial short QT syndrome

Documentation Requirements

- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (fungal culture sensitivity, liver function tests)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration:

- 3 months OR end of plan year

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Criteria for Continuation of Therapy (renewal therapy)

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification

- Continues to be seen by or in consultation with an Infectious Disease Specialist, Transplant Physician, or Oncologist

Clinical Response

- Positive clinical response defined as **TWO** of the following:
  - Clinical signs and symptoms of infection are resolving
  - Radiographic abnormalities are improving
  - No evidence of disease progression

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No new contraindications or significant adverse drug effects such as:
  - Liver toxicity (hepatitis, cholestasis, hepatic failure)
  - Severe cutaneous reactions (Stevens Johnson syndrome)

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use (liver function tests)

Continuation Therapy Criteria Approval Duration:

- 3 months OR end of plan year

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

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Generic Equivalent (if available)

Description:

Cresemba (isavuconazonium) capsule is an azole antifungal medication indicated for use in individuals 6 years of age or older who weigh 16 kilograms or more for the treatment of invasive aspergillosis and invasive mucormycosis. Isavuconazonium is a pro-drug that is converted to its active component, isavuconazole.

Aspergillus is a life-threatening infection seen in immunocompromised patients. Invasive aspergillosis is an important cause of mortality and morbidity in patients with prolonged neutropenia, hematologic malignancies, and allogenic hematopoietic stem cell transplantation (HSCT) recipients.

Mucormycosis is a very aggressive invasive fungal disease. Invasive mucormycosis is a rare, life-threatening mold infection, usually seen in immunocompromised patients, such as those with hematologic malignancies and in HSCT recipients.

Isavuconazole has activity against most strains of the following microorganisms, both *in vitro* and in clinical infections: *Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger,* and Mucorales such as *Rhizopus oryzae* and Mucormycetes species.

Studies suggest cross-resistance between isavuconazole and other azoles. The relevance of cross-resistance to clinical outcome has not been fully characterized. Individuals failing prior azole therapy may require alternative antifungal therapy.

Empiric therapy with an antifungal that has adequate coverage against the suspected causative organism is recommended until the diagnosis is confirmed. Definitive choice of systemic antifungal therapy is based on sensitivity data from fungal cultures, identification of causative organism, site of infection, immune status of the patient, and other patient characteristics. Once these results of the laboratory tests become available, antifungal therapy should be adjusted accordingly.

An Infectious Diseases Society of America (IDSA) summary guideline provides a comprehensive, evidence-based review of antifungal therapy for the management of aspergillosis and other fungal infections. The European Society of Clinical Microbiology and Infectious Disease (ESCMID) and the European Confederation of Medical Mycology (ECMM) joint guideline provides a comprehensive, evidence-based summary of antifungal therapy specifically for the treatment of mucormycosis. The 2016 IDSA guideline identifies voriconazole as the preferred primary therapy for most invasive syndromes of aspergillus. Other primary agents, depending on the syndrome: include liposomal amphotericin B, caspofungin, micafungin, and posaconazole. Alternative agents are also presented when primary agents cannot be used, depending on the syndrome present, include: liposomal amphotericin B, lipid complex amphotericin B, aerosolized amphotericin B, isavuconazole, caspofungin, micafungin, posaconazole, itraconazole, and voriconazole when it was not used as a primary agent. For mucormycosis the 2014 ESCMID/ECMM lists posaconazole or lipid formulations of amphotericin as first-line options for treatment of mucormycosis in certain types of individuals. The guideline lists posaconazole, lipid formulations of amphotericin B, and caspofungin for salvage treatment of mucormycosis in specific types of populations in adults. Posaconazole is recommended as prophylaxis for mucormycosis in neutropenia or graft-versus-host disease.

Isavuconazonium is a prodrug that is hydrolyzed in the blood by esterases, predominantly by butylcholinesterase, to the active component isavuconazole. Isavuconazole inhibits the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14-alpha-demethylase. This enzyme is responsible for the conversion of lanosterol to ergosterol. An accumulation of

methylated sterol precursors and a depletion of ergosterol within the fungal cell membrane weakens the membrane structure and function. Mammalian cell demethylation is less sensitive to isavuconazole inhibition.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Resources:

Cresemba (isavuconazonium sulfate) oral product information, revised by Astellas Pharma US, Inc. 12-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Palmer SM, Zaas A, Messin JA. Fungal infections following lung transplantation. In: UpToDate, Blumberg EA, Hachem RR, White N (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through January 2025. Topic last updated July 23, 2023. Accessed February 24, 2025.

Wingard JR. Prophylaxis of invasive fungal infections in adults hematopoietic cell transplant recipients. In: UpToDate, Bow E, White N (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through January 2025. Topic last updated October 25, 2023. Accessed February 24, 2025.

Wingard JR. Prophylaxis of invasive fungal infections in adults with hematologic malignancies. In: UpToDate, Bow E, White N (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through January 2025. Topic last updated December 04, 2024. Accessed February 24, 2025.

Patterson TF. Treatment and prevention of invasive aspergillosis. In: UpToDate, Kauffman CA, Hall KK. (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through January 2025. Topic last update May 11, 2023. Accessed February 24, 2025.

Kosmidis C. Chronic pulmonary aspergillosis: Treatment. In: UpToDate, Kauffman CA, White N (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through January 2025. Topic last updated January 31, 2024. Accessed February 24, 2025.

Cox GM. Mucormycosis (zygomycosis). In: UpToDate, Kauffman CA, White N (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through January 2025. Topic last update August 25, 2023. Accessed February 24, 2025.