BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 5/19/16**
SECTION: DRUGS	**LAST REVIEW DATE: 5/16/19**
	LAST CRITERIA REVISION DATE: 5/16/19
	ARCHIVE DATE:

CRESEMBA® (isavuconazonium sulfate) oral capsule

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

CRESEMBA® (isavuconazonium sulfate) oral capsule (cont.)

Criteria:

- **Criteria for initial therapy:** Cresemba (isavuconazonium sulfate) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in infectious diseases or is in consultation with Infectious Disease

  2. Individual is 18 years of age or older

  3. **For a diagnosis of invasive aspergillosis,** individual has failure, contraindication or intolerance to:
     - Vfend (voriconazole) **OR**
     - Lipid formulation of amphotericin B (either liposomal amphotericin B or amphotericin B lipid complex)

  4. **For a diagnosis of invasive mucormycosis,** individual has failure, contraindication or intolerance to:
     - Noxafil (posaconazole) **OR**
     - Lipid formulation of amphotericin B (either liposomal amphotericin B or amphotericin B lipid complex)

  5. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     - Liver enzymes
     - Fungal culture report shows causative organism(s) are sensitive to isavuconazonium only

  6. There are **NO** contraindications:
     - Contraindications include:
       - Hypersensitivity to Cresemba
       - Use with strong CYP3A4 inhibitors, such as ketoconazole or high-dose ritonavir (400 mg every 12 hours)
       - Use with strong CYP3A4 inducers, such as rifampin, carbamazepine, St. John's wort, or long acting barbiturates
       - Use in patients with familial short QT syndrome

  Initial approval duration: 3 months

- **Criteria for continuation of coverage (renewal request):** Cresemba (isavuconazonium sulfate) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in infectious diseases or is in consultation with Infectious Disease

  2. Individual's condition responded and has not worsened while on therapy
     - Response is defined as **TWO** of the following:
       - Clinical signs and symptoms of infection are resolving
       - Radiographic abnormalities are improving
       - There is no evidence of disease progression

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- Worsening is defined as any of the following:
  - Signs and symptoms of the infection have not resolved
  - Individual has persistent immune defects
  - Radiographic abnormalities continue to progress

3. The indication for use is one that requires a longer duration than the usual duration

4. Individual has been adherent with the medication

5. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
   - Contraindications or adverse effect:
   - Significant adverse effect such as:
     - Liver toxicity
     - Exfoliative cutaneous reactions or Stevens Johnson syndrome

6. There are no significant interacting drugs

Renewal duration: 3 months

- Cresemba (isavuconazonium sulfate) for all other indications not previously listed or if above criteria not met is considered ***experimental or investigational*** based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing or frequency outside the FDA-approved dosing and frequency

Description:

Cresemba (isavuconazonium) is an azole antifungal medication indicated for use in individuals 18 years of age or older 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.

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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.

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Resources:

Cresemba (isavuconazonium sulfate) product information accessed 04-26-18 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8f7f73b8-586a-4df0-935f-fecd4696c16c

Cresemba. Package Insert. Revised by manufacturer 6/2015. Accessed 04-21-2016, 04-28-2017, 03-14-2018.

Cornley OA, Arikan-Akdagli S, Dannaoui E, et al.: ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clin Microbiol Infect 2014 Apr; 20 (Suppl. 3):5-26.

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. CID 2016 Aug 15; 63 (4):e1-e60.

UpToDate: Treatment and prevention of invasive aspergillosis. Current through Mar, 2019. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-and-prevention-of-invasive-aspergillosis?search=invasive%20aspergillosis&source=search_result&selectedTitle=1~96&usage_type=default&display_rank=1#H19380268

UpToDate: Mucormycosis (zygomycosis). Current through Mar, 2019. https://www-uptodate-com.mwu.idm.oclc.org/contents/mucormycosis-zygomycosis?search=invasive%20mucormycosis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

UpToDate: Fungal infections following lung transplantation. Current through Mar, 2019. https://www-uptodate-com.mwu.idm.oclc.org/contents/fungal-infections-following-lung-transplantation?search=invasive%20mucormycosis&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3

UpToDate: Prophylaxis of invasive fungal infections in adults with hematologic malignancies. Current through Mar, 2019. https://www-uptodate-com.mwu.idm.oclc.org/contents/prophylaxis-of-invasive-fungal-infections-in-adults-with-hematologic-malignancies?search=invasive%20mucormycosis&source=search_result&selectedTitle=4~150&usage_type=default&display_rank=4

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.