This program applies to Medicaid.

The BCBS MN Step Therapy Supplement also applies to this program for Medicaid.

Program specific denial language for prerequisite step therapy component does not apply. Instead, supplemental program denial language will apply.

### FDA APPROVED INDICATIONS AND DOSAGE\(^1,2,14\)

<table>
<thead>
<tr>
<th>Agent</th>
<th>FDA Indication</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cresemba®</strong> (isavuconazonium) capsules, injection</td>
<td>Treatment of invasive aspergillosis and invasive mucormycosis</td>
<td>Loading Dose - 372 mg every 8 hours for 6 doses. Maintenance Dose - 372 mg once daily starting 12-24 hours after the last loading dose.</td>
</tr>
<tr>
<td><strong>Noxafil®</strong> (posaconazole) oral suspension, delayed-release tablet^a, injection</td>
<td>Prophylaxis against invasive <em>Aspergillus</em> and <em>Candida</em> in patients who are at high risk of developing these infections due to being severely immunocompromised. Treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole or fluconazole (oral suspension only) Noxafil injection is indicated in patients 18 years of age and older. Noxafil tablets and suspension are indicated in patients 13 years of age and older</td>
<td>Prophylaxis of invasive <em>Aspergillosis or Candida</em> Suspension - 200 mg 3 times daily Tablets, Injection - 300 mg twice daily first day, then 300 mg once a day. <strong>Oropharyngeal candidiasis, non refractory</strong> Suspension - 100 mg twice on day one then 100 mg daily for 13 days <strong>Refractory oropharyngeal candidiasis</strong> Suspension - 400 mg twice daily.</td>
</tr>
</tbody>
</table>
| **Vfend®** (voriconazole)^a tablets, oral suspension, injection | Treatment of adults and pediatric patients 2 years of age and older with:  
  • Invasive aspergillosis  
  • Candidemia in non-neutropenics and other deep tissue *Candida* infections  
  • Esophageal candidiasis  
  • Serious fungal infection caused by *Scedosporium* | **Adults:**  
  **Invasive Aspergillosis, Scedosporiosis and Fusariosis**  
  IV -Loading dose- 6 mg/kg IV every 12 hours for the first 24 hours  
  Maintenance dose- 4 mg/kg IV every 12 hours  
  Oral - 200 mg orally every 12 hours |
**CLINICAL RATIONALE**

**Esophageal candidiasis and candidemia**

Infectious Diseases Society of America (IDSA) guidelines recommend fluconazole as the first line oral therapy for esophageal candidiasis and candidemia in nonneutropenic patients. Fluconazole is also recommended for prophylaxis against esophageal candidiasis in at risk patients. For patients with fluconazole-refractory disease, guidelines recommend itraconazole or voriconazole. Voriconazole has demonstrated effectiveness for both mucosal and invasive candidiasis, but offers little advantage over fluconazole as initial therapy. Its clinical use has been primarily for step-down oral therapy in patients with infection due to *C. krusei* and fluconazole-resistant, voriconazole-susceptible *C. glabrata*.4

**Oropharyngeal candidiasis**
First line therapy for oropharyngeal candidiasis includes clotrimazole troches or nystatin suspension for mild or moderate disease or fluconazole for severe disease. Guidelines recommend posaconazole or itraconazole for fluconazole-refractory disease.\(^4\)

**Aspergillus**

IDSA guidelines recommend posaconazole for prophylaxis against aspergillus in hematopoietic stem cell transplant (HSCT) recipients with graft versus host disease (GVHD) at high risk, acute myeloid leukemia (AML), or myelodysplastic syndrome at high risk. Voriconazole or posaconazole are recommended for prophylaxis against invasive aspergillosis in patients with prolonged neutropenia at high risk for infection. IDSA guidelines recommend voriconazole for treatment of invasive pulmonary aspergillosis. Liposomal amphotericin B and isavuconazole are possible alternative therapies. An individualized approach should be used for refractory or progressive aspergillosis, but can include amphotericin B, micafungin, caspofungin, posaconazole, or itraconazole.\(^5\)

**Rare fungal infections**

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and European Confederation of Medical Mycology (ECMM) joint clinical guidelines for the diagnosis and management of mucormycosis recommend diagnosis of mucormycosis using direct microscopy, histopathology, and culture. Invasive mucormycosis is a serious and rare disease in which active controlled clinical trials are not feasible. At the time the guideline was written, the only antifungal drug approved for this indication was amphotericin B, which is associated with several adverse events and also has limitations with regard to use in patients with renal impairment.\(^6\) Isavuconazonium has shown activity against Mucorales such as *Rhizopus oryzae* and Mucormycetes species.\(^1\)

IDSA has not published guidelines for treatment of the rare fungal infection scedosporiosis. However, there are joint guidelines from the European Society for Clinical Microbiology and Infectious Diseases and European Confederation of Medical Mycology. Voriconazole is the only compound with good activity *in vitro* against *S. aurantiacum* and demonstrated the strongest activity against *S. prolificans* among drugs tested. *Acremonium* infection treatment is limited to case reports, with voriconazole, amphotericin B and posaconazole as the suggested antifungals. *Fusarium* infections in immunocompromised patients have reported varying results with voriconazole, and amphotericin B.\(^7\)

**Blastomycosis**

IDSA guidelines recommend itraconazole as the first line oral agent for the treatment of mild to moderate pulmonary or disseminated extrapulmonary blastomycosis. Itraconazole is also recommended in patients as a step down from amphotericin B for more severe cases of these infections. Fluconazole and voriconazole are considered alternatives for the treatment of blastomycosis.\(^8\)

**Solid Organ Transplant Patients**

In solid organ transplant patients, invasive fungal infections are aggressive and associated with high mortality rates. *Candida* is the most common cause of opportunistic fungal infections.\(^10\) Antifungal strategies are based on individual risk factors, incidence of fungal infections at a particular center, clinical experience, and specific post-transplant complications.\(^11\) The 2013 guidelines from the American Society of Transplantation recommend amphotericin B, itraconazole, fluconazole, voriconazole, posaconazole, and/or an echinocandin, depending on the specific situation.\(^12,13\) The 2016 IDSA Aspergillus treatment guidelines suggest use of voriconazole or itraconazole for aspergillus prophylaxis after lung transplant.\(^5\)

**Hematopoietic Stem Cell Transplant (HSCT) Recipients**
Patients undergoing hematopoietic stem cell transplants are at an increased risk of infection with infection being the primary cause of death in 8% of autologous HSCT patients and 17%-20% of allogeneic HCT recipients. Risk factors for fungal infection in this population include mucositis, neutropenia, and GVHD. Additionally, allogeneic transplant recipients are at a significantly higher risk for fungal infection than those receiving autologous marrow stem cells. Guidelines recommend fluconazole as the drug of choice for the prophylaxis of invasive candidiasis though there is increasing resistance to fluconazole. The IDSA guidelines for treatment of Aspergillosis, recommend posaconazole for antifungal prophylaxis in HSCT recipients with GVHD at high risk of infection. Itraconazole may be an alternative but its utility is limited by tolerability issues. Voriconazole has demonstrated efficacy in secondary prophylaxis of invasive aspergillosis.

For additional clinical information see the Prime Therapeutics Formulary Chapter 1.9A: Antifungal Agents, Imidazole and Triazole Agents.

REFERENCES
8. Deleted.
Cresemba (isavuconazonium), Noxafil (posaconazole), and Vfend (voriconazole) Prior Authorization

TARGET AGENTS
Cresemba® (isavuconazonium)
Noxafil® (posaconazole)\textsuperscript{a}
Vfend® (voriconazole)\textsuperscript{a}
\textsuperscript{a} available as generic; included as target in PA program

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Cresemba will be approved when BOTH of the following are met:

1. ONE of the following:
   a. The patient has a diagnosis of invasive aspergillosis \textbf{OR}
   b. The patient has a diagnosis of invasive mucormycosis \textbf{OR}
   c. The prescriber has submitted information supporting use of the requested agent for the requested indication \textbf{AND}

2. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of approval: 6 months

Noxafil will be approved when BOTH of the following are met:

1. ONE of the following:
   a. The patient has a diagnosis of oropharyngeal candidiasis AND ONE of the following:
      i. The patient has tried and had an inadequate response to itraconazole or fluconazole \textbf{OR}
      ii. The patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to BOTH fluconazole AND itraconazole \textbf{OR}
   b. BOTH of the following
      i. The requested agent is prescribed for prophylaxis of invasive \textit{Aspergillus} or \textit{Candida} \textbf{AND}
      ii. The patient is severely immunocompromised (e.g., hematopoietic stem cell transplant (HSCT) recipients, a hematologic malignancy with prolonged neutropenia from chemotherapy), or is a high-risk solid organ (lung, heart-lung, heart, pancreas, liver, kidney, small bowel) transplant patient. \textbf{OR}
   c. The patient has an infection caused by \textit{Scedosporium} or \textit{Zygomycetes} \textbf{OR}
   d. BOTH of the following:
      i. The patient has a diagnosis of invasive \textit{Aspergillus} AND ONE of the following:
         A. The patient has tried and had an inadequate response to voriconazole, amphotericin B, or isavuconazole \textbf{OR}
         B. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to voriconazole, amphotericin B, and isavuconazole
OR
  e. The prescriber has submitted information supporting use of the requested agent for the requested indication

AND
  2. The patient does NOT have any FDA labeled contraindications to the requested agent

**Length of approval:** 1 month for oropharyngeal, 6 months for all other indications

**Vfend** will be approved when BOTH of the following are met:
  1. ONE of the following:
     a. The patient has a diagnosis of invasive *Aspergillus*
     OR
     b. BOTH of the following:
        i. The requested agent is being prescribed for prophylaxis of invasive *Aspergillus* or *Candida*
        AND
        ii. The patient is severely immunocompromised (e.g., hematopoietic stem cell transplant (HSCT) recipients, a hematologic malignancy with prolonged neutropenia from chemotherapy), or is a high-risk solid organ (lung, heart-lung, heart, pancreas, liver, kidney, small bowel) transplant patient
     OR
     c. The patient has a diagnosis of esophageal candidiasis, candidemia, or other deep tissue *Candida* infection AND ONE of the following:
        i. The patient has tried and had an inadequate response to fluconazole
        OR
        ii. The patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to fluconazole
     OR
     d. The patient has an infection caused by *Scedosporium* or *Fusarium*
     OR
     e. The patient has a diagnosis of blastomycosis AND ONE of the following:
        i. The patient has tried and had an inadequate response to itraconazole
        OR
        ii. The patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to itraconazole
     OR
     f. The prescriber has submitted information supporting use of the requested agent for the requested indication

AND
  2. The patient does NOT have any FDA labeled contraindications to the requested agent

**Length of approval:** 1 month for esophageal candidiasis, 6 months for all other indications

**Renewal Evaluation**

**Cresemba** will be approved when ALL of the following are met:
  1. The patient has been previously approved for the requested agent through the plan’s prior authorization review process
  AND
  2. ONE of the following:
     a. BOTH of the following:
        i. The patient has a diagnosis of invasive aspergillosis
        AND
ii. The patient has continued indicators of active disease (e.g. continued radiologic findings, positive cultures, positive serum galactomannan assay)

OR

b. BOTH of the following:
   i. The patient has a diagnosis of invasive mucormycosis AND
   ii. the patient has continued indicators of active disease (e.g. continued radiologic findings, direct microscopy findings, histopathology findings, positive cultures, positive serum galactomannan assay)

OR
c. The prescriber has submitted information supporting continued use of the requested agent for the requested indication

AND

3. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of approval: 6 months

Noxafil will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan’s prior authorization review process

AND

2. ONE of the following:
   a. BOTH of the following:
      i. The requested agent is being prescribed for prophylaxis of invasive Aspergillus or Candida AND
      ii. The patient continues to be severely immunocompromised (e.g., hematopoietic stem cell transplant (HSCT) recipients, a hematologic malignancy with prolonged neutropenia from chemotherapy), or is a high-risk solid organ (lung, heart-lung, heart, pancreas, liver, kidney, small bowel) transplant patient.

   OR

   b. BOTH of the following:
      i. The patient has an infection caused by Scedosporium or Zygomycetes AND
      ii. The patient has continued indicators of active disease (e.g. continued radiologic findings, positive cultures, positive serum galactomannan assay for Aspergillus)

   OR

   c. BOTH of the following:
      i. The patient has a diagnosis of invasive Aspergillus AND
      ii. The patient has continued indicators of active disease (e.g. continued radiologic findings, positive cultures, positive serum galactomannan assay for Aspergillus)

   OR

   d. The prescriber has submitted information supporting continued use of the requested agent for the requested indication

AND

3. The patient does NOT have any FDA labeled contraindications to the requested agent

-For patients with a diagnosis of oropharyngeal candidiasis see Initial Evaluation criteria

Length of approval: 6 months
Vfend will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan’s prior authorization review process  
   AND

2. ONE of the following:
   a. BOTH of the following:
      i. The patient has a diagnosis of invasive Aspergillus  
         AND
      ii. The patient has continued indicators of active disease (e.g. continued radiologic findings, positive cultures, positive serum galactomannan assay for Aspergillus)
   
   OR

   b. BOTH of the following:
      i. The patient has a diagnosis of invasive Aspergillus or Candida  
         AND
      ii. The patient is severely immunocompromised (e.g., hematopoietic stem cell transplant (HSCT) recipients, a hematologic malignancy with prolonged neutropenia from chemotherapy), or is a high-risk solid organ (lung, heart-lung, heart, pancreas, liver, kidney, small bowel) transplant patient

   OR

   c. BOTH of the following:
      i. The patient has a diagnosis of esophageal candidiasis, candidemia, or other deep tissue Candida infection  
         AND
      ii. The patient has continued indicators of active disease (e.g. continued radiologic findings, positive cultures, positive serum galactomannan assay for Aspergillus)

   OR

   d. BOTH of the following:
      i. The patient has an infection caused by Scedosporium or Fusarium  
         AND
      ii. The patient has continued indicators of active disease (e.g. continued radiologic findings, positive cultures, positive serum galactomannan assay for Aspergillus)

   OR

   e. BOTH of the following:
      i. The patient has a diagnosis of blastomycosis  
         AND
      ii. The patient has continued indicators of active disease (e.g. continued radiologic findings, positive cultures, positive serum galactomannan assay for Aspergillus)

   OR

   f. The prescriber has submitted information supporting continued use of the requested agent for the intended diagnosis, which has been reviewed and approved by the Clinical Review pharmacist  
      AND

3. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of approval:  
1 month for esophageal candidiasis  
6 months for all other indications
This program applies to Medicaid.

Please note, this does not include or apply to quantity limit questions.

**STEP THERAPY SUPPLEMENT OBJECTIVE**
The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

**CONDITIONS FOR APPROVAL**
The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
   **AND**
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   **AND**
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

   **OR**

2. BOTH of the following
   a. The patient’s medication history includes the required prerequisite/preferred agent(s) or a drug in the same pharmacological class with the same mechanism of action as indicated by ONE of the following:
      i. Evidence of a paid claim(s) within the past 999 days
      **OR**
      ii. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days
   **AND**
   b. ONE of the following:
      i. The required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event
      **OR**
      ii. The prescriber has submitted an evidence-based and peer-reviewed clinical practice guideline supporting the use of the requested agent over the prerequisite/preferred agent(s)

   **OR**

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

**Length of Approval:** As per program specific criteria