This program applies to Medicaid.

**FDA APPROVED INDICATIONS AND DOSAGE\textsuperscript{1,2,14}**

<table>
<thead>
<tr>
<th>Agent</th>
<th>FDA Indication</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cresemba\textsuperscript{®}</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>
</tbody>
</table>
| **Noxafil\textsuperscript{®}** (posaconazole) oral suspension, delayed-release tablet, injection | Prophylaxis against invasive \textit{Aspergillus} and \textit{Candida} 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 | **Prophylaxis of invasive \textit{Aspergillosis} or \textit{Candida}**  
Suspension - 200 mg 3 times daily  
Tablets, Injection - 300 mg twice daily first day, then 300 mg once a day.  
**Oropharyngeal candidiasis, non refractory**  
Suspension - 100 mg twice on day one then 100 mg daily for 13 days  
**Refractory oropharyngeal candidiasis**  
Suspension - 400 mg twice daily. |
| **Vfend\textsuperscript{®}** (voriconazole) tablets\textsuperscript{a}, oral suspension\textsuperscript{a}, injection\textsuperscript{a} | Treatment of invasive aspergillosis  
Treatment of candidemia and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds  
Treatment of esophageal candidiasis  
Treatment of serious fungal infections caused by \textit{Scedosporium apiospermum} and \textit{Fusarium} species, including \textit{Fusarium solani}, in patients intolerant of, or refractory to, other therapy | **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  
**Candidemia**  
Loading dose- 6 mg/kg IV every 12 hours for the first 24 hours  
Maintenance dose- 3-4 mg/kg IV every 12 hours or 200 mg orally every 12 hours  
**Esophageal Candidiasis**  
200 mg orally every 12 hours |

\textsuperscript{a} – available as generic
CLINICAL RATIONALE

Esophageal candidiasis and candidemia\textsuperscript{3,7}
Infectious Diseases Society of America (IDSA) guidelines recommend fluconazole as the first line oral therapy for candidemia in nonneutropenic patients and for esophageal candidiasis.\textsuperscript{3} Fluconazole is also recommended for prophylaxis against esophageal candidiasis in at-risk patients.\textsuperscript{3} For patients with fluconazole-refractory disease, guidelines recommend itraconazole or voriconazole.\textsuperscript{7} Up to 80% of patients with fluconazole refractory esophageal candidiasis will respond to itraconazole. Voriconazole has demonstrated effectiveness for both mucosal and invasive candidiasis. Its clinical use has been primarily for step-down oral therapy in patients with infection due to \textit{C. krusei} and fluconazole-resistant, voriconazole-susceptible \textit{C. glabrata}.\textsuperscript{3}

Oropharyngeal candidiasis\textsuperscript{3}
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.\textsuperscript{3}

Aspergillus and rare fungal infections\textsuperscript{4,7,11-13}
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 is 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, CNS aspergillosis, and aspergillosis endocarditis, pericarditis, and myocarditis in most patients, with posaconazole, isavuconazomium, and amphotericin B 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.

IDSA has not published guidelines for treatment of the rare fungal infections scedosporiosis or mucormycosis. Voriconazole demonstrated superiority compared to amphotericin B in the treatment of invasive aspergillosis. Infectious diseases guidelines indicate voriconazole as a first line agent for the treatment of invasive aspergillosis, fusariosis, and scedosporiosis, but currently do not list it as an alternative for zygomycosis. Posaconazole is an alternative for the treatment of invasive aspergillosis, scedosporiosis, and zygomycosis. Many of these fungal infections are life-threatening with high mortality rates.

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.\textsuperscript{19} The only antifungal drug approved for this indication is amphotericin B, which is associated with several adverse events and also has limitations with regard to use in patients with renal impairment.\textsuperscript{19} For adults and children, surgical debridement in addition to immediate first-line antifungal treatment with liposomal or lipid-complex amphotericin B is recommended. Posaconazole or isuvaconazole can be used as step-down therapy for patients who have responded to amphotericin B or as salvage therapy for treatment of mucormycosis.\textsuperscript{21} For salvage treatment, ESCMID and ECMM strongly recommends posaconazole. Reversal of predisposing condition is also strongly recommended. Treatment is recommended until a complete response is demonstrated on imaging and permanent reversal of predisposing factors.\textsuperscript{15} Epidemiological reports have found a high mortality rate in patients with mucormycosis who did not receive treatment.\textsuperscript{16-18}
**Blastomycosis and histoplasmosis**

Itraconazole is the recommended therapy for the treatment of chronic cavity pulmonary histoplasmosis. Other forms of histoplasmosis are generally treated with amphotericin B. IDSA guidelines recommend itraconazole as the first line oral agent for the treatment of mild to moderate blastomycosis. Itraconazole is also recommended in patients as a step down from amphotericin B for more severe cases of blastomycosis. Fluconazole and voriconazole are considered alternatives for the treatment of blastomycosis.

**Solid Organ Transplant Patients**

Solid organ transplant patients, especially those with liver, pancreas, lung, or heart-lung transplants, may be at risk for fungal infections. The most common infecting fungal organism is *Candida*. Since prophylactic drug therapy may be associated with toxicity and resistance, guidelines recommend that it be targeted to patients at highest risk of morbidity and mortality. Factors that may place a patient at high risk of a fungal infection include: primary allograft dysfunction, nonfunction, or retransplantation; prolonged operative duration; high intra-operative blood product requirement and bleeding complications; pretransplant immunosuppression; pre-operative CMV infection; prolonged ICU requirement or mechanical ventilation; prolonged use of broad-spectrum antibacterial therapy; renal failure; fungal colonization, unrecognized recipient fungal infection, or donor fungemia or positive fungal cultures; gastrointestinal translocation or transplantation of a colonic segment. 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. Due to development of increased resistance to itraconazole and fluconazole, posaconazole and voriconazole have been studied as prophylactic therapy in solid organ transplant patients and may be recommended by some clinicians. The 2016 IDSA Aspergillus treatment guidelines suggest use of voriconazole or itraconazole for aspergillus prophylaxis after lung transplant.

**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 includes 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, published in 2008, 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**

19. Center for Drug Evaluation and Research. Application number: 207500Orig1s000/207501Orig1s000. FDA Medical review. Accessed in July 2018 at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207500Orig1207501Orig1s000MedR.pdf
Cresemba® (isavuconazonium), Noxafil® (posaconazole), and Vfend® (voriconazole) Prior Authorization

OBJECTIVE
The intent of the Cresemba (isavuconazonium), Noxafil (posaconazole), and Vfend (voriconazole) Prior Authorization (PA) program is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or clinical practice guidelines. The PA process allows for approval for labeled indications and may require trial and failure of another antifungal agent when Cresemba, Noxafil, and Vfend are indicated in clinical practice guidelines as an alternative agent for the diagnosis, unless the patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to the recommended initial treatment choice. Cresemba, Noxafil, or Vfend may also be evaluated for a nonlabeled indication if recommended in clinical practice guidelines or if the prescriber submits documentation in support of the requested therapeutic use.

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

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Cresemba (isavuconazonium) will be approved when BOTH of the following are met:
  1. The patient does NOT have any FDA labeled contraindication(s) to the requested agent AND
  2. ONE of the following:
     a. The patient has a diagnosis of invasive aspergillosis
     OR
     b. The patient has a diagnosis of invasive mucormycosis
     OR
     c. The prescriber has submitted documentation supporting use of the requested agent for the intended diagnosis for this patient which has been reviewed and approved by the Clinical Review pharmacist

Length of approval: 6 months

Noxafil (posaconazole) will be approved when BOTH of the following are met:
  1. The patient does NOT have any FDA labeled contraindication(s) to the requested agent AND
  2. ONE of the following:
     a. The patient has a diagnosis of oropharyngeal candidiasis AND patient has tried and had an inadequate response to fluconazole or an alternative antifungal agent or patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to fluconazole or an alternative antifungal agent
     OR
     b. The requested agent is prescribed for prophylaxis of invasive Aspergillus or Candida AND the patient is severely immunocompromised, such as a hematopoietic stem cell transplant (HSCT) recipient; or hematologic malignancy with prolonged neutropenia from chemotherapy; or is a high-risk solid organ (lung, heart-lung, liver, pancreas, small bowel) transplant patient
     OR
     c. The patient has an infection caused by Scedosporium or Zygomycetes
     OR
d. The patient has a diagnosis of invasive *Aspergillus* AND patient has tried and had an inadequate response to an alternative antifungal agent or patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to an alternative antifungal agent
   OR

e. The prescriber has submitted documentation supporting use of the requested agent for the intended diagnosis, which has been reviewed and approved by a Clinical Review pharmacist

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

**Vfend (voriconazole)** will be approved when BOTH of the following are met:

1. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
   AND
2. ONE of the following:
   a. The patient has a diagnosis of invasive *Aspergillus*
   OR
   b. The patient has an infection caused by *Scedosporium apiospermum* or *Fusarium*
   OR
   c. The patient has a diagnosis of esophageal candidiasis or candidemia in nonneutropenic patient AND patient has tried and had an inadequate response to fluconazole or an alternative antifungal agent or patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to an alternative antifungal agent
   OR
   d. The patient has a diagnosis of blastomycosis AND patient has tried and had an inadequate response to itraconazole OR patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to itraconazole
   OR
   e. The requested agent is being prescribed for prophylaxis of invasive *Aspergillus* or *Candida* AND the patient is severely immunocompromised, such as a hematopoietic stem cell transplant (HSCT) recipient; or hematologic malignancy with prolonged neutropenia from chemotherapy; or is a high-risk solid organ (lung, heart-lung, liver, pancreas, small bowel) transplant patient
   OR
   f. The prescriber has submitted documentation supporting use of the requested agent for the intended diagnosis, which has been reviewed and approved by a Clinical Review pharmacist

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

**Renewal Evaluation**

**Cresemba (isavuconazonium)** will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the Prime Therapeutics Prior Authorization process
   AND
2. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
   AND
3. ONE of the following:
   a. The patient has a diagnosis of invasive aspergillosis and the patient has continued indicators of active disease (e.g. continued radiologic findings, positive cultures, positive serum galactomannan assay)
   OR
b. The patient has a diagnosis of invasive mucormycosis and 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 documentation supporting continued use of the requested agent for the intended diagnosis, which has been reviewed and approved by a Clinical Review pharmacist

**Length of approval:** 6 months

**Noxafil (posaconazole)** will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the Prime Therapeutics Prior Authorization process

AND

2. The patient does NOT have any FDA labeled contraindication(s) to the requested agent

AND

3. ONE of the following:

   a. The requested agent is being prescribed for prophylaxis of invasive *Aspergillus* or *Candida* and the patient continues to be severely immunocompromised as indicated by: neutropenia, ongoing graft versus host disease, and/or long term use of high dose corticosteroids (> 1 mg/kg/day of prednisone or equivalent)

   OR

   b. The patient has a diagnosis of invasive *Aspergillus* or has an infection caused by *Scedosporium*, or *Zygomycetes* and the patient has continued indicators of active disease (e.g. continued radiologic findings, positive cultures, positive serum galactomannan assay for *Aspergillus*)

   OR

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

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

**Length of approval:** 6 months

**Vfend (voriconazole)** will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the Prime Therapeutics Prior Authorization process

AND

2. The patient does NOT have any FDA labeled contraindication(s) to the requested agent

AND

3. ONE of the following:

   a. The patient has a diagnosis of invasive *Aspergillus*, infection caused by *Scedosporium apiospermum* or *Fusarium*, esophageal candidiasis, candidemia in nonneutropenic patient or blastomycosis and the patient has continued indicators of active disease (e.g. continued radiologic findings, positive cultures, positive serum galactomannan assay for *Aspergillus*)

   OR

   b. The requested agent is being prescribed for prophylaxis of invasive *Aspergillus* or *Candida* and the patient continues to be severely immunocompromised as indicated by: neutropenia, ongoing graft versus host disease, and/or long term use of high dose corticosteroids (> 1 mg/kg/day of prednisone or equivalent)

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

**Length of approval:**
- one month for esophageal candidiasis
- 6 months for all other indications