

Noxafil[®]/Vfend[®] Prior Authorization Criteria

Vfend Injection will NOT be included in the Noxafil/Vfend Prior Authorization program for Blue Cross and Blue Shield of Illinois because these plans do not cover injectable Vfend under the pharmacy benefit.

Brand	Generic	Dosage Form
Noxafil [®]	posaconazole	oral suspension
Vfend [®]	voriconazole	oral tablets, oral suspension, injection

PROGRAM OBJECTIVES

The intent of the prior authorization (PA) criteria for Noxafil and Vfend is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines. The PA process allows for approval for labeled indications and may require trial and failure of another antifungal agent when Noxafil or Vfend are indicated in guidelines as an alternative agent for the diagnosis unless the patient has an allergy, contraindication, or intolerance to the recommended initial treatment choice. Noxafil or Vfend may also be approved for a nonlabeled indication if recommended in guidelines.

PROGRAM FUNCTIONALITY

Electronic Edits

The overall process for a prior authorization will not allow the targeted drugs to adjudicate through the claims system. When a patient requests a targeted drug listed in Table 1 below, the system will reject the claim with the message indicating that prior authorization is necessary. The Prior Authorization (PA) Criteria for Approval would then be applied to requests submitted by the patient's practitioner for evaluation.

Table 1: Targeted Agents for Noxafil and Vfend Prior Authorization

Agent	GPI (multisource code)
Noxafil (posaconazole)	
40 mg/mL suspension	11407060001820 (M, N, O, or Y)
Vfend (voriconazole)	
50 mg tablet	11407080000320 (M, N, O, or Y)
200 mg tablet	11407080000340 (M, N, O, or Y)
40 mg/mL suspension	11407080001920 (M, N, O, or Y)
200 mg injection	11407080002120 (M, N, O, or Y)

Prior Authorization (PA) Criteria for Approval

No claims for Noxafil or Vfend will be automatically paid at the point of sale. The Prior Authorization (PA) Criteria for Approval provide the manual review process for all claims for targeted agents in this PA program.

The PA criteria for voriconazole allow approval of the agent for diagnoses indicated in product labeling. Voriconazole may be approved as initial therapy for treatment of *Aspergillus*. Approval for other indications will require trial and failure of another antifungal agent (fluconazole, itraconazole, amphotericin B, caspofungin, micafungin, or anidulafungin) before approval of voriconazole unless the patient has an allergy, intolerance, or contraindication to one of the other antifungal alternatives. Treatment guidelines suggest a duration of therapy for the treatment oral candidiasis of one week to three weeks. Approval for this indication will be limited to one month. Treatment guidelines suggest duration of antifungal therapy post-HSCT transplant should be 75 to 100 days; approval for these patients will be for four months. Voriconazole for treatment of blastomycosis will be approved for 12 months. Other indications do not have a defined recommended length of therapy and approval will be for six months. Analysis of duration of therapy for posaconazole and voriconazole for claims paid through Prime Therapeutics indicates that >90% of patients are treated for six months or less.⁵ Renewal criteria are identical to initial criteria.

Noxafil (posaconazole)

Initial and Renewal Evaluation

1. Is posaconazole prescribed for the treatment of oropharyngeal candidiasis?
If yes, continue to 2. If no, continue to 3.
2. Has the patient tried and failed fluconazole for the treatment of this infection?
If yes, approve for one month. If no, continue to 7.
3. Is the patient at high risk of developing invasive *Aspergillus* or *Candida* due to being severely immunocompromised, such as an allogeneic hematopoietic stem cell transplant [HSCT] recipient; or a patient with a hematologic malignancy (leukemia, lymphoma, myelodysplastic syndrome) with prolonged neutropenia from chemotherapy; or a high-risk solid organ (lung, heart-lung, liver, pancreas, small bowel) transplant patient?
If yes, continue to 4. If no, continue to 5.
4. Is posaconazole prescribed for prophylaxis of invasive *Aspergillus* or *Candida*?
If yes, approve for 4 months. If no, continue to 8.
5. Is posaconazole prescribed for one of the following?
 - a. invasive *Aspergillus*
 - b. fungal infection caused by *Scedosporium apiospermum*
 - c. fungal infection caused by *Fusarium*
 - d. fungal infection caused by *Zygomycetes*
 - e. OtherIf a, b, c, or d continue to 6. If e, continue to 8.
6. Has the patient tried and failed another antifungal agent?
If yes, approve for 6 months. If no, continue to 7.
7. Does the patient have an allergy, contraindication, or intolerance to an alternative antifungal agent (fluconazole for oropharyngeal candidiasis)?
If yes, approve for 1 month for oropharyngeal candidiasis and approve for 6 months for other indications. If no, continue to 8.
8. Has the prescriber submitted and the pharmacist reviewed evidence supporting the use of posaconazole for the intended diagnosis for this patient?
If yes, pharmacist must review and may approve for up to 6 months. If no, deny.

Vfend (voriconazole)

Initial and Renewal Evaluation

1. Is voriconazole prescribed to treat the following:
 - a. invasive *Aspergillus*
 - b. fungal infection caused by *Scedosporium apiospermum*
 - c. fungal infection caused by *Fusarium* species
 - d. esophageal candidiasis
 - e. candidemia in nonneutropenic patient
 - f. blastomycosis
 - g. antifungal prophylaxis
 - h. OtherIf a, b, or c approve for 6 months. If d or e, continue to 2. If f, continue to 4. If g, continue to 6. If h, continue to 7.
2. Has the patient tried and failed fluconazole or another antifungal agent?
If yes, approve for one month for esophageal candidiasis and 6 months for other candidemia diagnoses. If no, continue to 3.
3. Does the patient have an allergy, contraindication, or intolerance to an alternative antifungal agent?
If yes, approve for one month for esophageal candidiasis and 6 months for other candidemia diagnoses. If no, continue to 7.
4. Has the patient tried and failed itraconazole?
If yes, approve for 6 months. If no, continue to 5.
5. Does the patient have an allergy, contraindication, or intolerance to itraconazole?
If yes, approve for 6 months. If no, continue to 7.
6. Is the patient at high risk of developing invasive *Aspergillus* or *Candida* due to being severely immunocompromised, such as an allogeneic hematopoietic stem cell transplant [HSCT] recipient; a patient with a hematologic malignancy (leukemia, lymphoma, myelodysplastic syndrome) with prolonged neutropenia from chemotherapy; or a high-risk solid organ (lung, heart-lung, liver, pancreas, small bowel) transplant patient?
If yes, approve for 4 months. If no, continue to 7.
7. Has the prescriber submitted and the pharmacist reviewed evidence supporting the use of voriconazole for the intended diagnosis for this patient?
If yes, pharmacist must review and may approve for up to 6 months. If no, deny.

CLINICAL RATIONALE

Product labeling for posaconazole includes Food and Drug Administration approved indications for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients who are at high risk of developing these infections due to being severely immunocompromised and posaconazole is also indicated for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole.¹ Treatment guidelines (see Table 2: Summary of Guidelines) recommend posaconazole as initial treatment for salvage therapy, (In the case of invasive fungal infection, salvage therapy generally refers to the treatment of infected individuals who are refractory or intolerant to initial therapy administered for at least seven days.), *Aspergillus* and for prophylaxis 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 [See Formulary Chapter 1.9A: Antifungal agents imidazole & triazole agents, guidelines from the Infectious Disease Society of America (IDSA)].^{3,4} Posaconazole is an alternative for the treatment of oropharyngeal candidiasis, invasive *aspergillosis*, scedosporiosis, and zygomycosis.³

The prior authorization criteria for posaconazole allows approval of the agent for diagnoses indicated in product labeling; candidiasis, and prophylaxis of invasive *Aspergillus* or *Candida* in patients who are severely immunocompromised. In treatment guidelines, posaconazole is not considered a first-line agent with the exception of prophylaxis of *Aspergillus* in immunocompromised individuals. The PA process will require trial and failure of another antifungal agent (fluconazole, itraconazole, amphotericin B, caspofungin, micafungin, or anidulafungin) before approval of posaconazole unless the patient has an allergy, intolerance, or contraindication to one of the other antifungal alternatives. The PA process will also allow approval of posaconazole as an alternative to first-line therapy for scedosporiosis and zygomycosis as suggested in guidelines.³ Treatment guidelines suggest duration of therapy for the treatment oral candidiasis of one week to three weeks; approval for this indication will be limited to one month. Treatment guidelines suggest duration of antifungal therapy post-HSCT transplant should be 75 to 100 days; approval for these patients will be for four months. Other indications do not have a defined recommended length of therapy and approval will be for six months. Analysis of duration of therapy for posaconazole and voriconazole for claims paid through Prime Therapeutics indicates that greater than ninety percent of patients are treated for six months or less.⁵ Renewal criteria are identical to initial approval criteria.

Product labeling for voriconazole includes Food and Drug Administration approved indications of candidemia, esophageal candidiasis, *Scedosporium apiospermum*, *Fusarium*, and invasive *Aspergillus*.¹ Infectious disease guidelines indicate voriconazole as a first-line agent for the treatment of invasive aspergillosis, fusariosis, scedosporiosis, and zygomycosis.^{3,4} Treatment guidelines indicate voriconazole as an alternative agent for the treatment of oral or esophageal candidiasis after fluconazole, as an alternative agent for the treatment of invasive candidemia,³ and as alternative agent after use of itraconazole for blastomycosis infections.⁹

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 organisms are *Candida* and *Aspergillus*.^{6,12-17} 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.¹²⁻¹⁷ 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.^{8,13-17} The 2004 guidelines from the American Society of Transplantation recommend amphotericin B, itraconazole and/or fluconazole, depending on the specific situation.¹³ 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.^{4,16,17}

Table 2: Summary of Antifungal Treatment Guidelines^{3,4}

INFECTION	GUIDELINE	INITIAL TREATMENT	ALTERNATIVES
<i>Aspergillus</i> , invasive, pulmonary	Walsh et al. (2008) ⁶	voriconazole	amphotericin B
<i>Aspergillus</i> (prophylaxis in HSCT recipients with GVHD at high risk, AML, or myelodysplastic syndrome at high risk)	Walsh et al. (2008) ⁶	posaconazole	itraconazole, micafungin
Aspergillosis	Treatment Guidelines from the Medical Letter (2008) ³	voriconazole ≥ 10 weeks or amphotericin B	posaconazole, itraconazole, or caspofungin
Blastomycosis	Chapman SW, et al. (2008) ⁹	amphotericin B itraconazole	fluconazole voriconazole
Candidiasis, esophageal		fluconazole,	voriconazole,

INFECTION	GUIDELINE	INITIAL TREATMENT	ALTERNATIVES
	Pappas PG et al. (2009) ⁸	echinocandin ^a amphotericin B	posaconazole itraconazole
Candidiasis, oropharyngeal or esophageal	Treatment Guidelines from the Medical Letter (2008) ³	fluconazole or caspofungin, anidulafungin micafungin or amphotericin B	voriconazole for 1-3 weeks posaconazole for 1-3 weeks itraconazole for 1-3 weeks
	NCCN (2009) ¹¹	fluconazole	voriconazole posaconazole echinocandin ^a
Candidiasis, oropharyngeal	Pappas PG et al. (2009) ⁸	clotrimazole troches nystatin fluconazole	itraconazole posaconazole voriconazole amphotericin B oral amphotericin B-d echinocandin ^a
Candidiasis, esophageal	Pappas PG et al. (2009) ⁸	fluconazole echinocandin ^a amphotericin B-d	itraconazole posaconazole voriconazole
Suspected candidiasis	Pappas PG et al. (2009) ⁸ nonneutropenic	fluconazole echinocandin ^a	amphotericin B
	Pappas PG et al. (2009) ⁸ neutropenic	amphotericin B caspofungin voriconazole	fluconazole
Candida endophthalmitis	Pappas PG et al. (2009) ⁸	fluconazole amphotericin B	amphotericin B voriconazole echinocandin ^a
Candidemia	Pappas PG et al. (2009) ⁸	Fluconazole (nonneutropenic) amphotericin B (neutropenic) echinocandin ^a (neutropenic and nonneutropenic)	amphotericin B (nonneutropenic) voriconazole (neutropenic) fluconazole (neutropenic)
	Treatment Guidelines from the Medical Letter (2008) ³	fluconazole or caspofungin, anidulafungin micafungin or amphotericin B	Voriconazole
	ASBMT (2009) ¹⁰	fluconazole	micafungin
Fusariosis	Treatment Guidelines from the Medical Letter (2008) ³	amphotericin B or voriconazole	
Scedosporiosis	Treatment Guidelines from the Medical Letter (2008) ³	voriconazole for 12 weeks	itraconazole or posaconazole
Zygomycosis	Treatment Guidelines from the Medical Letter: Antifungal Drugs (2008) ³	amphotericin B for 6-10 weeks	posaconazole

INFECTION	GUIDELINE	INITIAL TREATMENT	ALTERNATIVES
Cancer-related antifungal prophylaxis : intermediate risk (neutropenic)	NCCN (2009) ¹¹	fluconazole	
Cancer-related antifungal prophylaxis: intermediate to high risk -MDS (neutropenic) -AML (neutropenic -Autologous HSCT with mucositis -Allogeneic HSCT (neutropenic) -Significant GVHD	NCCN (2009) ¹¹	posaconazole or voriconazole or amphotericin B fluconazole or micafungin fluconazole or micafungin or itraconazole or voriconazole or posaconazole or amphotericin B posaconazole voriconazole echinocandin ^a amphotericin B	
Anti-yeast (Candida) prophylaxis pre-engraftment Post-engraftment prophylaxis against Candida if risk (eg GVHD) For anti-mold prophylaxis	ASBMT (2009) ¹⁰	fluconazole posaconazole or voriconazole posaconazole or voriconazole	micafungin

HSCT=hematopoietic stem cell transplant, GVHD=graft versus host disease, AML= acute myeloid leukemia, MDS = Myelodysplastic syndrome, NCCN = National Comprehensive Cancer Network, ASBMT = American Society for Blood and Marrow Transplantation
a: echinocandins = caspofungin, micafungin, anidulafungin

FDA APPROVED INDICATIONS^{1,2}

The following information is taken from individual drug prescribing information and is provided here as background information only. Not all FDA-approved indications may be considered medically necessary. All criteria are found in the section "Prior Authorization Criteria for Approval."

Noxafil

Noxafil (posaconazole) is indicated for prophylaxis of invasive *Aspergillus* and *Candida* infection in patients 13 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

Noxafil is indicated for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole.

Vfend

Vfend (voriconazole) is indicated for use in the treatment of the following fungal infections:

- Invasive aspergillosis: In clinical trials, the majority of isolates recovered were *Aspergillus fumigatus*. There were a small number of cases of culture-proven disease due to species of *Aspergillus* other than *A. fumigatus*.
- Candidemia in nonneutropenic patients and the following *Candida* infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds.
- Esophageal candidiasis.
- Serious fungal infections caused by *Scedosporium apiospermum* (sexual form of *Pseudallescheria boydii*) and *Fusarium* spp. including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy.

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

Table 3: FDA-Approved Indications^{1,2}

	Noxafil (posaconazole)	Vfend (voriconazole)
Candidemia		√ ^{a,b}
Esophageal candidiasis		√
Oropharyngeal candidiasis (thrush)	√ ^c	
Infections due to <i>Scedosporium apiospermum</i> and <i>Fusarium</i>		√ ^d
Aspergillosis		√ ^f
Prophylaxis of invasive <i>Aspergillus</i> infections	√ ^e	
Prophylaxis of invasive <i>Candida</i> infections	√ ^e	
Youngest indicated age	13 years and older	12 years and older
Youngest studied age	8 years	12 years

^a including other forms of *Candida* infections (disseminated infections in skin and infections in abdomen, bladder wall, kidney, and wounds)

^b for nonneutropenic patients

^c including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole

^d in patients intolerant of or refractory to other therapy

^e in patients who are severely immunocompromised, such as hematopoietic stem cell transplant recipients with graft versus host disease, or patients with hematologic malignancies with prolonged neutropenia from chemotherapy

^f invasive disease

REFERENCES

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Document History

Original Prime Standard approved by Prime National P&T Committee: UM Criteria Review 11/2008
Initial Client Review Prime Standard criteria approved by HCSC Corporate Clinical Committee 01/2009
Administrative addition, textbox to clarify Vfend injectable is not part of ST program, 07/2009
Annual Review Prime Standard criteria approved by P&T UM Committee 11/2009
Client Specific Annual Review Client Specific criteria approved by HCSC Corporate Clinical Committee 03/2010