

## Therapeutic Class Overview

### Antifungals, Oral

#### INTRODUCTION

- The oral class of antifungals includes multiple agents used to treat many different fungal infections, including aspergillosis, blastomycosis, histoplasmosis, candidiasis, onychomycosis, and ringworm infections (*Micromedex 2018*).
- The agents are often used in persons with human immunodeficiency virus (HIV) and neutropenia due to hematopoietic stem cell transplants, or after aggressive chemotherapy and radiation (*Centers for Disease Control and Prevention, National Institutes of Health, HIV Medicine Association of the Infectious Diseases Society of America [CDC/NIH/IDSA] 2018*).
- The most current treatment guidelines and therapy recommendations should be used when prescribing these agents, as resistant organisms have been reported.
- Clotrimazole, nystatin, and Oravig (miconazole) are not absorbed systemically. They are not used for systemic infections, but only for the treatment of oropharyngeal candidiasis (*Prescribing information: clotrimazole 2016, nystatin suspension 2017, Oravig 2016*).
- Cresemba (isavuconazonium sulfate), Diflucan (fluconazole), Vfend (voriconazole), and Noxafil (posaconazole) are available as oral and intravenous formulations. Ketoconazole and Lamisil (terbinafine) are available as oral and topical preparations. Sporanox (itraconazole) is only available as an oral formulation. Clotrimazole and nystatin are available as oral, topical, and vaginal formulations. Only the oral formulations will be discussed in this review.
- In May 2016, the Food and Drug Administration (FDA) recommended limiting the use of ketoconazole for the treatment of skin and nail fungal infections due to the risk of severe liver injuries and adrenal gland problems, and advised that it can lead to harmful drug interactions with other medications. Ketoconazole should be used for the treatment of certain fungal infections, known as endemic mycoses, only when alternative antifungal therapies are not available or tolerated (*FDA Drug Safety Communication 2016*).
- Medispan class: Antifungals, Imidazole-Related Antifungals

**Table 1. Medications Included Within Class Review**

Drug	Generic Availability
Ancobon (flucytosine)	✓
clotrimazole	✓
Cresemba (isavuconazonium sulfate)	--
Diflucan (fluconazole)	✓
griseofulvin microsize	✓
Gris-PEG (griseofulvin ultramicrosize)	✓
ketoconazole	✓
Lamisil (terbinafine)	✓
Noxafil (posaconazole)	--
Nystatin	✓
Onmel (itraconazole) <sup>a</sup>	--
Oravig (miconazole)	--
Sporanox (itraconazole)	✓ <sup>b</sup>
Vfend (voriconazole)	✓

<sup>a</sup> As of November 2018 Onmel is temporarily unavailable due to manufacturing delays.

<sup>b</sup> Oral capsule only. A generic oral solution is listed in the Orange Book but is not currently marketed by the generic manufacturer. (*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

**INDICATIONS**

**Table 2. Food and Drug Administration Approved Indications**

Indication	clotrimazole	fluconazole	flucytosine	griseofulvin	isavuconazonium sulfate	itraconazole	ketoconazole	nystatin	terbinafine	voriconazole	Noxafil (posaconazole)	Onmel (itraconazole)	Oravig (miconazole)
Oropharyngeal candidiasis	✓							✓			✓ <sup>a</sup>		✓
Oropharyngeal and esophageal candidiasis		✓				✓ <sup>b</sup>							
Esophageal candidiasis										✓ <sup>g</sup>			
Non-esophageal mucous membrane gastrointestinal candidiasis								✓ <sup>c</sup>					
Prophylactically to reduce the incidence of oropharyngeal candidiasis in patients immunocompromised by conditions that include chemotherapy, radiotherapy, or steroid therapy utilized in the treatment of leukemia, solid tumors, or renal transplantation	✓												
Serious infections caused by susceptible strains of <i>Candida</i> and/or <i>Cryptococcus</i>			✓ <sup>e</sup>										
Vaginal candidiasis		✓											
Cryptococcal meningitis		✓											
Prophylactically to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy		✓											
Treatment of the following ringworm infections: tinea corporis (ringworm of the body), tinea pedis (athlete's foot), tinea cruris (ringworm of the groin and thigh), tinea barbae (barber's itch), tinea capitis (ringworm of the scalp), and tinea unguium (onychomycosis, ringworm of the nails), caused by one or more of the following genera of fungi: <i>Trichophyton rubrum</i> , <i>T. tonsurans</i> , <i>T. mentagrophytes</i> , <i>T. interdigitalis</i> , <i>T. verrucosum</i> , <i>T. megnini</i> , <i>T. gallinae</i> , <i>T. crateriform</i> , <i>T. sulphureum</i> , <i>T. schoenleini</i> , <i>Microsporum audouini</i> , <i>M. canis</i> , <i>M. gypseum</i> and <i>Epidermophyton floccosum</i>				✓									
Onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium)						✓ <sup>f</sup>			✓ <sup>c</sup>				
Onychomycosis of toenail caused by <i>Trichophyton rubrum</i> or <i>T. mentagrophytes</i> in non-immunocompromised patients												✓	
Treatment of the following systemic infections in patients who have failed or are intolerant to							✓						

Indication	clotrimazole	fluconazole	flucytosine	griseofulvin	isavuconazonium sulfate	itraconazole	ketoconazole	nystatin	terbinafine	voriconazole	Noxafil (posaconazole)	Onmel (itraconazole)	Oravig (miconazole)
other therapies: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis													
Prophylaxis of invasive <i>Aspergillus</i> and <i>Candida</i> infections 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											✓		
Blastomycosis, pulmonary and extrapulmonary in immunocompromised and non-immunocompromised patients						✓ <sup>d</sup>							
Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, nonmeningeal histoplasmosis in immunocompromised and non-immunocompromised patients						✓ <sup>d</sup>							
Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy in immunocompromised and non-immunocompromised patients						✓ <sup>d</sup>							
Invasive aspergillosis					✓					✓ <sup>g</sup>			
Invasive mucormycosis					✓								
Candidemia in non-neutropenic patients and the following <i>Candida</i> infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds										✓ <sup>g</sup>			
Serious fungal infections caused by <i>Scedosporium apiospermum</i> (asexual form of <i>Pseudallescheria boydii</i> ) and <i>Fusarium</i> species including <i>Fusarium solani</i> , in patients intolerant of, or refractory to, other therapy										✓ <sup>g</sup>			

<sup>a</sup> Including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole. Tablets should not be used for this indication.

<sup>b</sup> Oral solution only.

<sup>c</sup> Oral tablets only.

<sup>d</sup> Oral capsules only.

<sup>e</sup> Should be used in combination with amphotericin B for the treatment of systemic candidiasis and cryptococcosis because of the emergence of resistance to flucytosine.

<sup>f</sup> In non-immunocompromised patients.

<sup>g</sup> For use in patients 12 years of age or older.

(Prescribing information: Ancobon 2018, clotrimazole 2016, Cresemba 2018, Diflucan 2018, griseofulvin 2016, Gris-PEG 2017, ketoconazole 2018, Lamisil 2017, Noxafil 2017, nystatin suspension 2017, nystatin tablets 2016, Onmel 2012, Oravig 2016, Sporanox 2018, Vfend 2017)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

## CLINICAL EFFICACY SUMMARY

- The oral antifungal agents are FDA-approved for a variety of indications. Head-to-head clinical trials have been conducted to evaluate the efficacy of the oral antifungal agents for the treatment of various indications. However, head-to-head trials for all agents approved for each indication are not available.
- For the treatment of aspergillosis, open-label trials have demonstrated the effectiveness of itraconazole for the treatment of pulmonary aspergillosis in patients who are immunocompromised and/or refractory to amphotericin B (Caillot 2003, Caillot et al 2001). Another study demonstrated the superiority of itraconazole over standard supportive measures in chronic cavitary pulmonary aspergillosis (CCPA) (Agarwal et al 2013). Posaconazole has been shown to be effective in the treatment of invasive aspergillosis in patients who are refractory to at least 7 days of antifungal therapy or intolerant to conventional therapy (Walsh et al 2007). In the treatment of invasive mucormycosis, isavuconazonium sulfate was studied in a single-arm, open-label trial and was associated with an all-cause mortality rate of 38% through day 42 and an end-of-treatment success rate of 31%. Isavuconazonium sulfate was shown to be noninferior to voriconazole as treatment for invasive aspergillosis for all-cause mortality at day 42 (McCormack 2015). Another trial found isavuconazonium sulfate noninferior to voriconazole in all-cause mortality at day 42 in patients receiving primary treatment for invasive mold disease primarily caused by *Aspergillus* species (Maertens 2016).
- Open-label studies evaluating the use of itraconazole in the treatment of blastomycosis and histoplasmosis have demonstrated clinical response and/or success rates of 81 to 90% (Dismukes et al 1992, Wheat et al 1995). In a multicenter, prospective trial, a relapse-free rate of 95.3% was demonstrated at 1 year in patients treated with itraconazole for a first episode of mild to moderate disseminated histoplasmosis who had successfully completed 12 weeks of induction therapy with itraconazole (Hecht et al 1997).
- In a double-blind, randomized, controlled trial, fluconazole and itraconazole were compared in pediatric patients with signs of sepsis and positive blood cultures for *Candida* species. Statistically similar cure rates were observed between groups (Mondal et al 2004). In another randomized, controlled trial, voriconazole and amphotericin B were compared in patients with candidemia and demonstrated no significant difference between groups in rates of successful response. However, significantly more patients infected with *C. tropicalis* had a successful response to voriconazole compared to amphotericin B (Kulberg et al 2005).
- Fluconazole with or without flucytosine has also been compared to therapy with amphotericin B with or without flucytosine for the treatment of *Cryptococcus* species infection with somewhat conflicting results. In a multicenter, randomized, controlled trial, no significant difference in successful treatment in HIV-infected patients with cryptococcal meningitis was demonstrated with oral fluconazole vs amphotericin B, with or without flucytosine (Saag et al 1992). Conversely, in a prospective, randomized controlled trial, significantly fewer treatment failures were demonstrated in patients with or without acquired immunodeficiency syndrome (AIDS) treated with amphotericin B plus flucytosine compared to oral fluconazole (Larsen et al 1990). A recent Cochrane review concluded that the most effective regimen for cryptococcal meningitis in patients with HIV is combination therapy with flucytosine and amphotericin B (Tenforde et al 2018).
- In the treatment of various dermatophyte infections, studies comparing ketoconazole and griseofulvin have shown conflicting results. Some studies demonstrate significantly better response to ketoconazole compared to griseofulvin (Jolly et al 1983, Legendre and Steltz 1980) while other studies failed to replicate this finding (Gan et al 1987, Stratigos et al 1983, Tanz et al 1985, Tanz et al 1988). Comparison of griseofulvin and terbinafine for the treatment of tinea corporis and tinea cruris showed significantly higher clinical and mycological cure rates for terbinafine at week 6 compared to griseofulvin and significantly higher rates of relapse with griseofulvin (Voravutinon 1993). A recent meta-analysis found that griseofulvin was more effective than terbinafine in treatment of children with tinea capitis caused by *Microsporum* species, and that terbinafine, itraconazole, and fluconazole are at least similar to griseofulvin in treatment of children with tinea capitis caused by *Trichophyton* species. The findings also suggested that terbinafine was more effective than griseofulvin in *T. tonsurans* infection (Chen et al 2016).

- A Cochrane review meta-analysis found limited results comparing antifungals for the treatment and prevention of oropharyngeal candidiasis in HIV positive children and adults, but did find fluconazole and ketoconazole were superior to nystatin in clinical cure. Itraconazole and fluconazole were superior to clotrimazole in clinical cure. They also found that fluconazole was effective for prevention (*Pienaar et al 2010*).
- Studies evaluating the oral antifungal agents as prophylaxis against fungal infections in immunocompromised patients have compared various agents head-to-head. A multicenter, prospective, randomized trial compared fluconazole, itraconazole solution, and posaconazole in patients after remission-induction chemotherapy. Significantly fewer invasive fungal infections occurred with posaconazole compared to fluconazole and itraconazole. Also of note, significantly fewer cases of invasive aspergillosis were observed and significantly fewer patients experienced treatment failure with posaconazole (*Cornely et al 2007*). Similarly, a study comparing fluconazole and posaconazole in patients with graft-versus-host-disease after hematopoietic stem cell transplantation demonstrated a significantly lower incidence of aspergillosis in the posaconazole group compared to the fluconazole group. Breakthrough fungal infections occurred in more patients in the fluconazole group (*Ullmann et al 2007*). A comparison between fluconazole and voriconazole in patients undergoing hematopoietic stem cell transplantation showed no significant difference between the groups' fungal-free survival rates and the incidence of invasive fungal infections (*Wingard et al 2010*). A network meta-analysis of 54 randomized trials concluded that posaconazole is the most effective antifungal for primary prophylaxis in patients with hematological malignancy, but mortality was similar among all of the agents included in the analysis (*Lee et al 2018*).
- Studies comparing the oral antifungal agents for the treatment of onychomycosis have shown varying results. Comparisons of itraconazole (continuous or pulse dose regimens) and terbinafine have demonstrated conflicting results. Some studies showed no difference between treatments (*Bahadir et al 2000, Degreef et al 1999, Honeyman et al 1997*) while others show significantly better results with terbinafine (*Brautigam 1998, Brautigam et al 1995, De Backer et al 1996, De Backer et al 1998, Evans et al 1999, Sigurgeirsson et al 1999, Sigurgeirsson et al 2002*). A study comparing griseofulvin microsize and terbinafine demonstrated significantly higher rates of negative cultures at 72 weeks with terbinafine compared to griseofulvin (*Hofmann et al 1995*). Similarly, 2 studies demonstrated significantly higher complete and mycological cure rates at 1 year for terbinafine compared to griseofulvin microsize (*Faergemann et al 1995, Haneke et al 1995*).
- A 2017 Cochrane review of oral antifungal agents for the treatment of onychomycosis concluded that terbinafine likely results in higher cure rates than azoles with similar tolerability. Terbinafine has better and tolerability than griseofulvin, and griseofulvin has similar cure rates compared to azoles but has worse tolerability (*Kreijkamp-Kaspers et al 2017*).
- In the treatment of vaginal candidiasis, oral fluconazole was found to be similar to topical antifungal agents in clinical response. These results were similar when comparing single-dose oral treatment with fluconazole and topical regimens of clotrimazole or miconazole for 1 dose (*van Heusden et al 1990, van Heusden et al 1994*).

## CLINICAL GUIDELINES

- A variety of treatment guidelines address the role of the oral antifungals in the treatment of infectious diseases. Due to changing resistance patterns, guidelines should be frequently referenced.
  - Treatment guidelines are available for HIV and neutropenic patients to guide selection of an appropriate antifungal to use in specific situations (*Freifeld et al 2011, CDC/NIH/IDSA 2018, NIH/CDC/IDSA/Pediatric Infectious Diseases Society/American Academy of Pediatrics 2018*).
  - Guidelines for community acquired pneumonia (CAP), skin and soft-tissue infections (SSTI), and catheter-related infections also address the treatment of fungal causes of infection, although they are less common than bacterial infections in most patients (*Mandell et al 2007, Mermel et al 2009, Stevens et al 2014*).
  - Guidelines also address the role of oral fluconazole (as well as vaginal/local antimicrobials) in the treatment of fungal vaginosis (*American College of Gynecology [ACOG] 2006 (reaffirmed in 2017), CDC 2015, Pappas et al 2016*).
  - Finally, multiple guidelines address the role of these agents in the treatment of specific fungal infections as one agent may be preferred due to volume of literature support, coverage/susceptibility patterns, and safety. Species with specific guidelines include *Aspergillus* species (*Patterson et al 2016*), *Blastomyces* species (*Chapman et al 2008*), *Candida* species (*CDC/NIH/IDSA 2018, Pappas et al 2016*), *Coccidioidomycosis* (*CDC/NIH/IDSA 2018, Galgiani et al 2016*), *Cryptococcus* species (*CDC/NIH/IDSA 2018, Perfect et al 2010*), *Histoplasmosis* (*CDC/NIH/IDSA 2018, Wheat et al 2007*), and *Sporotrichosis* (*Kauffman et al 2007*).

**SAFETY SUMMARY****• Contraindications:**

- Isavuconazonium sulfate: familial short QT syndrome
- Griseofulvin: porphyria, hepatocellular failure, and women who are or may become pregnant
- Ketoconazole: acute or chronic liver disease
- Miconazole: hypersensitivity to milk protein concentrate
- Itraconazole: treatment of onychomycosis in patients with evidence of ventricular dysfunction, or in women who intend to become pregnant
- Terbinafine: chronic or active hepatic disease

**• Boxed Warnings:**

- Flucytosine: use with extreme caution in patients with impaired renal function; close monitoring of hematologic, renal, and hepatic status of all patients is essential.
- Ketoconazole should only be used to treat serious systemic fungal infections when other effective antifungal therapy is not available or tolerated, and the potential benefits are considered to outweigh the potential risks; serious hepatotoxicity including death or need for liver transplantation have occurred; coadministration of the following drugs is contraindicated: dofetilide, quinidine, pimoziide, cisapride, methadone, disopyramide, dronedarone, and ranolazine due to potential QT prolongation and life-threatening ventricular dysrhythmias.
- Itraconazole should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF; coadministration of methadone, disopyramide, dofetilide, dronedarone, quinidine, isavuconazole, ergot alkaloids (such as dihydroergotamine, ergometrine [ergonovine], ergotamine, methylergometrine [methylergonovine]), irinotecan, lurasidone, oral midazolam, pimoziide, triazolam, felodipine, nisoldipine, ivabradine, ranolazine, eplerenone, cisapride, naloxegol, lomitapide, lovastatin, simvastatin, avanafil, ticagrelor and, in subjects with renal or hepatic impairment, colchicine, fesoterodine, and solifenacin is contraindicated. Coadministration with eliglustat is contraindicated in patients who are poor or intermediate metabolizers of CYP2D6 and in those taking strong or moderate CYP2D6 inhibitors. Coadministration of the former agents with itraconazole can cause elevated plasma concentrations of these drugs and may increase or prolong both the pharmacologic effects and/or adverse reactions to these drugs. Increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsades de pointes, a potentially fatal arrhythmia.

**• Warnings/Precautions:**

- Monitor for hepatotoxicity with all agents in the class.
- Flucytosine: monitor hematologic status and bone marrow suppression. Dose adjustments may be necessary in patients with renal impairment.
- Fluconazole, griseofulvin, terbinafine, and voriconazole: rare, sometimes fatal exfoliative skin disorders have occurred. Monitor for skin rashes and discontinue treatment if rash occurs.
- Fluconazole: administer with caution to patients with potentially proarrhythmic conditions or those with renal dysfunction. Women of childbearing potential who receive doses of 400 to 800 mg daily should use effective contraception during treatment and for 1 week after the last dose due to the potential for spontaneous abortion and congenital abnormalities with fluconazole exposure during the first trimester. Additionally, caution is advised when driving or operating heavy machinery as fluconazole may cause occasional dizziness or seizures.
- Griseofulvin: a possibility of cross-sensitivity with penicillin exists. Additionally, lupus-like syndromes or exacerbations of existing lupus have been reported. Patients should avoid exposure to intense or prolonged natural or artificial sunlight.
- Itraconazole: if neuropathy occurs and can be attributed to itraconazole, treatment should be discontinued. If a cystic fibrosis patient does not respond to treatment with itraconazole capsules, alternative therapy should be considered. **Some immunocompromised patients may have decreased bioavailability and require higher doses.** Finally, transient and permanent hearing loss have been reported.
- Ketoconazole: decrease in adrenal corticosteroid secretion can occur at doses of 400 mg and higher.
- Miconazole: monitor for hypersensitivity reactions and discontinue at the first sign of such reaction.
- Posaconazole: administer with caution to patients with potentially proarrhythmic conditions
- Terbinafine: taste and smell disturbances have been reported. Severe neutropenia has been reported. Discontinue treatment if neutrophil count is  $\leq 1000$  cells/mm<sup>3</sup>. Cases of thrombotic microangiopathy (TMA), including thrombotic

thrombocytopenic purpura and hemolytic uremic syndrome, have been reported. Discontinue treatment if clinical symptoms and laboratory measurements are consistent with TMA.

- Voriconazole: visual disturbances have been reported; galactose intolerance and skeletal disturbances may occur. Voriconazole may increase risk for QT prolongation, hepatic toxicity, and dermatologic reactions.
- Fetal toxicity may occur with some agents, including fluconazole (use in pregnancy should be avoided unless the benefits outweigh fetal risk), griseofulvin microsize, isavuconazonium sulfate, and voriconazole.
- In May 2016, the FDA issued a medication safety alert warning health care professionals to avoid prescribing ketoconazole oral tablets to treat skin and nail fungal infections. According to the FDA, the risk of serious liver damage and drug interactions with this agent outweigh the benefits when treating these conditions (*FDA Drug Safety Communication 2016*).

● **Adverse Effects:**

- A variety of adverse effects from mild to severe may occur with agents in this class. Consult individual package inserts for details.

● **Drug Interactions:**

- Many drug interactions occur with all of the agents in the class.
- Drugs metabolized through the cytochrome P450 system increase QT prolongation and may cause torsades de pointes.
- Consult individual package inserts for details about specific drug interactions and contraindications for concomitant use of certain medications. Agents that have contraindications related to drug interactions include isavuconazole, fluconazole, itraconazole (boxed warning), ketoconazole (boxed warning), posaconazole, and voriconazole.

**DOSING AND ADMINISTRATION**

**Table 3. Dosing and Administration**

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ancobon (flucytosine)	Capsules	Oral	Every 6 hours	In patients with renal or hepatic dysfunction, use with extreme caution; closely monitor hematologic, renal, and hepatic status.
clotrimazole	Lozenges	Oral	Three to 5 times daily	
Cresemba (isavuconazonium sulfate)	Capsules	Oral	Every 8 hours x 6 doses, then once daily	
Diflucan (fluconazole)	Tablets Suspension	Oral	Once daily	Pediatric weight-based dose equivalency is available. Dosing adjustments based on renal function are necessary. (see prescribing information)
griseofulvin microsize	Tablets Suspension	Oral	Once daily, or in divided doses	Should be taken after a meal with high fat content. Pediatric weight-based dosing is available. (see prescribing information) Contraindicated in women who are or may become pregnant.
Gris-PEG (griseofulvin ultramicronized)	Tablets	Oral	Once daily, or in divided doses	Pediatric weight-based dosing is available. (see prescribing information) Contraindicated in women who are or may become pregnant.
ketoconazole	Tablets	Oral	Once daily	Pediatric weight-based dosing is available. (see prescribing information)
Lamisil (terbinafine)	Tablets	Oral	Once daily	Pediatric (≥ 4 years) weight-based dosing is available. (see prescribing information)

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Use in patients with renal impairment (CrCL ≤ 50 mL/min) has not been studied. Contraindicated in patients with chronic or active liver disease.
Noxafil (posaconazole)	Suspension Tablets, delayed-release	Oral	Once to 3 times daily	The delayed-release tablet and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation. The suspension must be given with a full meal. The delayed-release tablets should be taken with food.
nystatin	Suspension Tablets	Oral	Three to 4 times daily	Suspension may be used in infants, children, and adults for the treatment of oral candidiasis.
Onmel (itraconazole)	Tablets	Oral	Once daily	Should be given with a full meal.
Oravig (miconazole)	Tablets	Buccal	Once daily	The tablet should be placed against the upper gum just above the incisor tooth. The tablet should not be chewed, crushed, or swallowed.
Sporanox (itraconazole)	Capsules Solution	Oral	Once or twice daily	Capsules should be taken with a full meal. Solution should be taken without food. Only the oral solution should be used for oropharyngeal and esophageal candidiasis; oral solution and capsules should not be used interchangeably. Dose may need to be adjusted to clinical response due to lower bioavailability in some immunocompromised patients.
Vfend (voriconazole)	Tablets Suspension	Oral	Every 12 hours	For Aspergillosis, Scedosporiosis, Fusariosis, and Candidemia, therapy should be initiated with IV voriconazole, then switched to the oral formulation for maintenance therapy.

See the current prescribing information for full details

## CONCLUSION

- The oral class of antifungals includes a variety of different agents used to treat many different fungal infections, including aspergillosis, blastomycosis, histoplasmosis, candidiasis, mucormycosis, onychomycosis, ringworm infections, and others.
- Resistant organisms have been reported; thus, it is important to verify susceptibility when resistant organisms are suspected. Current resistance patterns should be monitored for the antifungal agents in order to select the most appropriate therapy. Appropriate guidelines should be referenced often.
- Some patients may require intravenous therapy that is not specifically discussed in this review. Isavuconazonium, fluconazole, voriconazole, and posaconazole are available as oral and intravenous formulations. Some of these antifungal medications are also available in topical formulations.
- Clotrimazole, nystatin, and Oravig (miconazole) are not absorbed systemically. They are not used for systemic infections, but only for the treatment of oropharyngeal candidiasis.
- Onychomycosis can be treated with Onmel (itraconazole), Sporanox (itraconazole), or Lamisil (terbinafine). Griseofulvin is no longer used for this indication.
- The majority of the class is available generically. Cresemba (isavuconazonium sulfate), Noxafil (posaconazole), Onmel (itraconazole), and Oravig (miconazole) are available as brand only.



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