

# Antifungals, Oral Review

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## Antifungals, Oral Review

### FDA-Approved Indications

Drug	Manufacturer	FDA-Approved Indication(s) for oral use
clotrimazole (Mycelex Troche®) <sup>1</sup>	generic	<ul style="list-style-type: none"> <li>Treatment of oropharyngeal candidiasis</li> <li>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</li> </ul>
fluconazole (Diflucan®) <sup>2</sup>	generic	<ul style="list-style-type: none"> <li>Treatment of oropharyngeal, esophageal, and vaginal candidiasis</li> <li>Treatment of urinary tract infections, peritonitis, systemic infections including candidemia, disseminated candidiasis, and pneumonia</li> <li>Cryptococcal meningitis in AIDS patients</li> <li>Prevention of candidiasis in patients undergoing bone marrow transplantation with cytotoxic chemotherapy and/or radiation</li> </ul>
flucytosine (Ancobon®) <sup>3</sup>	Valeant	<ul style="list-style-type: none"> <li>Serious infections caused by susceptible strains of <i>Candida</i> or <i>Cryptococcus</i> in combination with amphotericin B</li> </ul>
griseofulvin suspension <sup>4</sup>	generic	<ul style="list-style-type: none"> <li>Ringworm infections of the body, skin, hair, and nails, namely tinea corporis, tinea pedis, tinea cruris, tinea barbae, tinea capitis, and tinea unguium (onychomycosis)</li> </ul>
griseofulvin (Grifulvin® V) <sup>5</sup>	OMJPI	
griseofulvin (Gris-PEG®) <sup>6</sup>	Pedinol	
itraconazole (Sporanox®) <sup>7</sup>	generic, Janssen	<ul style="list-style-type: none"> <li>Blastomycosis, histoplasmosis, and aspergillosis in non-immunocompromised and immunocompromised patients</li> <li>Onychomycosis of the fingernail and/or toenail due to dermatophytes (tinea unguium) in non-immunocompromised patients</li> </ul>
ketoconazole (Nizoral®) <sup>8</sup>	generic	<ul style="list-style-type: none"> <li>Candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, paracoccidioidomycosis, and severe recalcitrant cutaneous dermatophyte infections not responding to topical therapy or oral griseofulvin</li> </ul>
miconazole (Oravig) <sup>9</sup>	Par Pharmaceuticals	<ul style="list-style-type: none"> <li>Local treatment of oropharyngeal candidiasis (OPC) in adults</li> </ul>
nystatin (Mycostatin®) <sup>10</sup>	generic	<ul style="list-style-type: none"> <li>Gastrointestinal and oral candidiasis</li> </ul>
posaconazole (Noxafil®) <sup>11</sup>	Schering	<ul style="list-style-type: none"> <li>Prophylaxis of invasive <i>Aspergillus</i> and <i>Candida</i> infections in patients 13 years and older who are at high risk of developing these infections due to being severely immunocompromised (e.g. hematopoietic stem cell transplant recipient with graft versus host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy)</li> <li>Treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole</li> </ul>
terbinafine (Lamisil®) <sup>12</sup>	generic	<ul style="list-style-type: none"> <li>Onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium)</li> </ul>
terbinafine (Lamisil® Granules) <sup>13</sup>	Novartis	<ul style="list-style-type: none"> <li>Treatment of tinea capitis in patients four years of age and older</li> </ul>
terbinafine (Terbinex™) <sup>14</sup>	JSJ Pharmaceuticals	<ul style="list-style-type: none"> <li>Treatment of onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium)</li> </ul>
voriconazole (Vfend®) <sup>15</sup>	generic, Pfizer	<ul style="list-style-type: none"> <li>Treatment of invasive aspergillosis</li> <li>Serious fungal infections caused by <i>Scedosporium apiospermum</i> and <i>Fusarium solani</i></li> <li>Treatment of esophageal candidiasis</li> <li>Treatment of candidemia in non-neutropenic patients and disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds</li> </ul>

## Overview

The antifungal agents have different spectrums of activity and are FDA-approved to treat a variety of infections. Few trials have been performed to compare safety and efficacy profiles of the drugs. In addition, many of the agents carry black box warnings related to adverse events and/or drug interactions.

The Infectious Diseases Society of America (IDSA) 2009 guidelines on the treatment of oropharyngeal candidiasis in adults include clotrimazole troches (Mycelex) or nystatin for mild disease; for moderate to severe disease, fluconazole (Diflucan) is recommended.<sup>16</sup> For fluconazole-refractory disease, itraconazole solution or posaconazole suspension (Noxafil) may be used. In other refractory cases, voriconazole (Vfend) or amphotericin B oral suspension may be administered. Chronic suppressive therapy for patients with human immunodeficiency virus (HIV) is not always necessary. If suppressive therapy is required, fluconazole is recommended.

Since highly active antiretroviral therapy (HAART) for the treatment of HIV for infants and children is widely available and utilized in the US, routine primary prophylaxis of candidiasis is not indicated.<sup>17</sup> Uncomplicated infections can be effectively treated with topical therapy such as clotrimazole troches or nystatin. Troches should not be used in infants. Systemic therapy with fluconazole, ketoconazole, or itraconazole may be considered for the initial treatment of oropharyngeal candidiasis. Fluconazole is more effective than nystatin for infants. Itraconazole has equivalent efficacy to fluconazole for oropharyngeal candidiasis, but it is less well tolerated. Ketoconazole absorption can be variable so it is recommended to use fluconazole or itraconazole solutions when available.

For esophageal candidiasis in adults, fluconazole, oral or IV, is considered first line.<sup>18</sup> Fluconazole or itraconazole are preferred for children for the management of esophageal candidiasis.<sup>19</sup> Posaconazole, itraconazole, or voriconazole may be used in patients with fluconazole-refractory infections.

Onychomycosis is a fungal infection of the nail bed (skin beneath the nail plate) with secondary involvement of the nail plate (visible part of the nail on fingers and toes). Dermatophytes, yeasts, and molds are the primary pathogens associated with onychomycosis. More common in toenails than fingernails, the disease often causes the end of the nail to separate from the nail bed. The most common clinical presentations are distal and lateral subungual onychomycosis (which usually affects the great or first toe) and white superficial onychomycosis (which generally involves the third or fourth toes).<sup>20</sup> Additionally, debris (white, green, yellow, or black) may build up under the nail plate and discolor the nail bed.<sup>21</sup> Onychomycosis is often chronic, difficult to eradicate, and has a tendency to recur and is found more frequently in the elderly.

Opportunistic fungal infections are particularly likely to occur in patients during corticosteroid, immunosuppressant, or antimetabolite therapy, or in patients with Acquired Immunodeficiency Syndrome (AIDS), azotemia, diabetes mellitus, bronchiectasis, emphysema, tuberculosis, lymphoma, leukemia, or burns. Histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis, paracoccidioidomycosis, and sporotrichosis are systemic mycoses which can cause disease in both healthy and immunocompromised individuals. In contrast, mycoses caused by opportunistic fungi such as *Candida albicans*, *Aspergillus spp*, *Trichosporon*, *Torulopsis (Candida) glabrata*, *Fusarium*, *Alternaria*, and *Mucor* are generally found only in an immunocompromised host.

**Pharmacology**

<b>Drug</b>	<b>Mechanism of Action</b>
clotrimazole (Mycelex Troche) <sup>22</sup>	Inhibits the action of fungal ergosterol synthesis; interacts with the cytochrome P450 enzyme 14-alpha demethylase; inhibits growth of pathogenic yeasts by altering cell membrane permeability
fluconazole (Diflucan) <sup>23</sup>	Highly selective inhibitor of fungal cytochrome P450 sterol C-14 alpha-demethylation, which results in fungistatic activity
flucytosine (Ancobon) <sup>24</sup>	Enters the fungal cell and is metabolized to 5-fluorouracil, which is extensively incorporated into fungal RNA and inhibits synthesis of both DNA and RNA; the result is unbalanced growth and death of the fungal organism
griseofulvin <sup>25</sup>	Fungistatic amounts are deposited in the keratin, which is gradually exfoliated and replaced by non-infected tissue
itraconazole (Sporanox) <sup>26</sup>	Inhibits the cytochrome P450-dependent synthesis of ergosterol, a vital component of fungal cell membranes
ketoconazole (Nizoral) <sup>27</sup>	Impairs the synthesis of ergosterol, a vital component of fungal cell membranes
miconazole (Oravig) <sup>28</sup>	Inhibits cytochrome P450-dependent 14- $\alpha$ demethylase in the biosynthetic pathway of ergosterol
nystatin (Mycostatin) <sup>29</sup>	Binds to sterols in the fungal cell membranes which leads to fungistatic activity
posaconazole (Noxafil) <sup>30</sup>	Inhibits cytochrome P450-dependent 14- $\alpha$ demethylase in the biosynthetic pathway of ergosterol
terbinafine (Lamisil, Lamisil Granules, Terbinex) <sup>31,32,33</sup>	Inhibits squalene epoxidase, a key enzyme in fungal sterol biosynthesis; fungicidal <i>in vitro</i> depending on organism and concentration
voriconazole (Vfend) <sup>34</sup>	Inhibits ergosterol synthesis by interacting with the 14-alpha-lanosterol demethylation step, a cytochrome P450 enzyme

In the Terbinex kit, topical hydroxypropyl chitosan or HPCH (Eco Formula) is a companion topical product designed to enhance nail growth and improve the appearance of dystrophic nails.

**Pharmacokinetics**

Drug	Bioavailability (%)	Half-life (hr)	Metabolism	Excretion (%)	CYP 450 Enzyme Inhibition
clotrimazole (Mycelex Troche) <sup>35</sup>	negligible absorption	--	--	--	--
fluconazole (Diflucan) <sup>36</sup>	>90	20-50	--	Renal: 91	2C9, 3A4
flucytosine (Ancobon) <sup>37</sup>	78-89	2.4-4.8	Small amount of flucytosine is deaminated (probably by gut bacteria) to 5-fluorouracil and reabsorbed	Renal: 90 Fecal: <10	--
griseofulvin <sup>38</sup>	varies with formulation absorption increases with a fat meal	9-24	No active metabolites	Renal, fecal and perspiration excretion	--
itraconazole (Sporanox) <sup>39</sup>	55	64	Several metabolites; hydroxyitraconazole is the major active metabolite	Renal: 40 Fecal: 3-18	3A4
ketoconazole (Nizoral) <sup>40</sup>	-- (requires acidic pH)	8	Several inactive metabolites	Renal: 13 Bile: 87	3A4
miconazole (Oravig) <sup>41</sup>	--	24	No active metabolites	Renal: <1	2C9, 3A4
nystatin (Mycostatin) <sup>42</sup>	poorly absorbed	--	--	Predominantly feces	--
posaconazole (Noxafil) <sup>43</sup>	-- (varies based on fed or fasting state)	20-66	No active metabolites	Renal: 13 Fecal: 71	3A4
terbinafine (Lamisil, Terbinex) <sup>44,45</sup>	40	200-400	No active metabolites	Renal: 70	2D6
terbinafine (Lamisil Granules) <sup>46</sup>	--	9.3-13.8	No active metabolites	Renal: 70	2D6
voriconazole (Vfend) <sup>47</sup>	96	dose dependent	N-oxide metabolite is inactive; several other inactive metabolites	Renal: 80-83	2C19, 2C9,3A4

## ***Contraindications/Warnings***

### clotrimazole (Mycelex)

Clotrimazole is not indicated for systemic mycoses including systemic candidiasis.<sup>48</sup>

### fluconazole (Diflucan)<sup>49</sup>

Fluconazole is contraindicated in patients with hypersensitivity to fluconazole or any of its excipients. There is no information regarding cross-hypersensitivity among fluconazole and other azole antifungal agents. Caution should be used in prescribing fluconazole to patients with hypersensitivity to other azoles.

Fluconazole is contraindicated with concurrent administration of terfenadine and cisapride; both agents are no longer available in the US.

Fluconazole has been associated with rare reports of anaphylaxis, serious hepatic toxicity, and exfoliative skin disorders during treatment.

Fluconazole has been associated with rare cases of serious hepatic toxicity, including fatalities, primarily in patients with serious underlying medical conditions. There has been no obvious relationship to total daily dose, duration of therapy, sex, or age of the patients in the known cases of fluconazole-associated hepatotoxicity. Fluconazole hepatotoxicity has usually, but not always, been reversible upon discontinuation. Patients with abnormal liver function tests during fluconazole therapy should be monitored for more severe hepatic injury. Discontinue fluconazole therapy if clinical signs and symptoms of liver disease develop during therapy.

### flucytosine (Ancobon)

There is a boxed warning associated with flucytosine which stresses monitoring of renal, hepatic, and hematologic status.<sup>50</sup> Use with extreme caution in patients with renal impairment or bone marrow depression.

### griseofulvin (Grifulvin V, Gris-PEG)<sup>51,52</sup>

Griseofulvin is contraindicated in patients with porphyria, hepatocellular failure and in patients with a history of hypersensitivity to griseofulvin.<sup>53</sup> Griseofulvin should not be prescribed to pregnant patients. If patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Since griseofulvin has demonstrated harmful effects *in vitro* on the genotype in bacteria, plants and fungi, males should wait at least six months after completing griseofulvin therapy before fathering a child.

Lupus erythematosus or lupus-like syndromes have been reported in patients receiving griseofulvin.

Photosensitivity skin reactions have been associated with griseofulvin therapy. Patients should be warned to avoid exposure to intense natural or artificial sunlight. Severe skin reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) and erythema multiforme have been reported with griseofulvin use. These reactions may be serious and may result in hospitalization or death. If severe skin reactions occur, griseofulvin should be discontinued.

Elevated liver function tests and jaundice have been reported with griseofulvin use. These reactions may be serious and may result in hospitalization or death. Patients should be monitored for hepatic adverse events and discontinuation of griseofulvin considered if warranted.

Griseofulvin is produced by a species of *Penicillium*; patients with penicillin hypersensitivity theoretically could exhibit a cross-sensitivity to griseofulvin. However, patients with penicillin hypersensitivity have been treated with griseofulvin without adverse effects. Similar warnings may apply to patients with cephalosporin hypersensitivity or carbapenem hypersensitivity because of the structural similarity of cephalosporins and carbapenems to penicillin.

Concomitant use of griseofulvin and oral contraceptives has been reported to reduce the efficacy of the oral contraceptive and cause breakthrough bleeding. Patients who experience breakthrough bleeding while receiving these drugs together should notify their prescribers. An alternate or additional form of contraception should be used during concomitant treatment and should be continued for one month after griseofulvin discontinuation. Additionally, patients taking non-oral combination contraceptives, estrogens, or progestins for hormone replacement therapy may also experience reduced clinical efficacy; dosage adjustments may be necessary.

#### itraconazole (Sporanox)<sup>54</sup>

Itraconazole should not be administered to women considering pregnancy or who are pregnant. Simvastatin and lovastatin, which are metabolized by CYP 3A4, are contraindicated with itraconazole. Itraconazole should not be administered with ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine, and methylergometrine (methylergonovine). Additionally, co-administration with pimozide, quinidine, oral midazolam, cisapride, triazolam, levacetylmethadol (levomethadyl) and dofetilide are contraindicated as concomitant use may result in elevated plasma concentrations of those drugs leading to potentially serious adverse events.

Itraconazole is contraindicated in patients with ventricular dysfunction as evidenced by congestive heart failure (CHF) or a history of CHF. A black box warning associated with itraconazole stresses that itraconazole should not be used for onychomycosis in patients with evidence of ventricular dysfunction or CHF due to the risk of pulmonary edema and/or CHF. Negative inotropic effects have been observed with intravenous itraconazole. Serious cardiovascular events, including QTc prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred when itraconazole is co-administered with inhibitors of CYP450 3A4 isoenzyme. Such patients should be monitored for signs and symptoms of CHF during treatment. If signs or symptoms of CHF appear during administration of itraconazole, discontinue administration.

Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole. In addition, itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be used when coadministering itraconazole and calcium channel blockers due to an increased risk of CHF. Concomitant administration of itraconazole and nisoldipine is contraindicated.

Transient or permanent hearing loss has been reported in patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated. The hearing loss usually resolves when treatment is stopped but can persist in some patients.

Itraconazole capsules and oral solution should not be used interchangeably as the drug exposure is greater with the oral solution than with the capsules when the same dose of drug is administered. Only the oral solution has demonstrated efficacy for oral and/or esophageal candidiasis.

Serious hepatotoxicity, including liver failure and death, has been associated with itraconazole. Some patients did not have an underlying medical condition or pre-existing liver disease. Hepatotoxicity may develop as early as the first week of treatment. If signs or symptoms develop that are consistent with liver disease, itraconazole therapy should be discontinued and liver function testing performed.

itraconazole (Sporanox) and terbinafine (Lamisil, Lamisil Granules)<sup>55,56</sup>

Both itraconazole and terbinafine prescribing information recommend, “Prior to initiating treatment, appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis of onychomycosis.” A warning for both terbinafine and itraconazole states that neither agent should be used in patients with pre-existing liver disease, and rare cases of liver failure have occurred during use of either product.

ketoconazole (Nizoral)<sup>57,58</sup>

Ketoconazole should not be administered with terfenadine, astemizole, cisapride, or triazolam.

A black box warning states that ketoconazole has been linked to hepatic toxicities and fatalities. Monitoring of hepatic function is recommended.

miconazole (Oravig)<sup>59</sup>

Miconazole is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis) to miconazole, milk protein concentrate, or any other component of the product.

Allergic reactions, including anaphylactic reactions and hypersensitivity, have been reported with the administration of miconazole products, including Oravig. Discontinue miconazole immediately at the first sign of hypersensitivity.

nystatin (Mycostatin)<sup>60</sup>

Nystatin suspension contains significant amounts of sucrose; it should be used cautiously in patients with diabetes mellitus.

posaconazole (Noxafil)<sup>61</sup>

Posaconazole is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis) to posaconazole, any other component of the product, or hypersensitivity to any other azole antifungal. Posaconazole is contraindicated in coadministration with sirolimus and ergot alkaloids. Posaconazole is also contraindicated in coadministration with the CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide, halofantrine, or quinidine, since this may result in increased plasma concentrations of these agents leading to QTc prolongation and rare occurrences of torsades de pointes. Posaconazole is contraindicated with simvastatin due to the accumulation of simvastatin and risk for rhabdomyolysis.

Infrequent cases of hepatic reactions such as mild to moderate elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, and/or clinical hepatitis have been reported with posaconazole. Liver enzyme elevations were generally reversible upon discontinuation or in some cases, normalized without drug interruption, and rarely required drug discontinuation. More serious hepatic reactions including cholestasis or hepatic failure including fatalities have been reported in patients with serious underlying medical conditions such as hematologic malignancy during treatment with posaconazole. Posaconazole 800 mg daily has been associated with the more severe hepatic reactions. Liver function tests should be evaluated at therapy initiation and during the course of posaconazole therapy. If abnormal liver function tests occur during posaconazole therapy, monitor for the development of more severe hepatic injury. Posaconazole should be discontinued if worsening of liver function tests continues.

Elevated cyclosporine levels resulting in rare serious adverse events including nephrotoxicity, leukoencephalopathy, and death were reported in clinical efficacy trials for posaconazole. Dose reduction and more frequent monitoring of cyclosporine and tacrolimus should be performed when posaconazole therapy is initiated.

Posaconazole should be administered with caution to patients with potentially proarrhythmic conditions and should not be administered with drugs that are known to prolong the QTc interval and are metabolized through CYP3A4. Rigorous attempts to correct potassium, magnesium, and calcium should be made before starting posaconazole.

terbinafine (Lamisil, Lamisil Granules, Terbinex)<sup>62,63,64</sup>

Terbinafine is contraindicated in patients with a history of allergic reaction to oral terbinafine because of the risk of anaphylaxis.

Severe hepatic injury, including liver failure, with some leading to death or liver transplantation has occurred with the use of oral terbinafine. Assessment of serum transaminases are advised before initiation of treatment with terbinafine. Terbinafine should be discontinued if biochemical or clinical evidence of liver injury occurs.

Severe neutropenia, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with terbinafine use. If a progressive skin rash occurs, treatment with terbinafine should be discontinued. **Depressive symptoms have been reported with terbinafine.**

**Taste disturbance including loss of taste disturbance, including taste loss, has been reported with the use of terbinafine. Taste disturbances can be severe enough to result in decreased food intake, weight loss, and depressive symptoms. Resolution of taste disturbance may resolve within several weeks after discontinuation of treatment, but may be prolonged (greater than one year). If symptoms of a taste disturbance occur, discontinue terbinafine.**

voriconazole (Vfend)<sup>65</sup>

Coadministration of voriconazole is contraindicated with CYP3A4 substrates including terfenadine, astemizole, cisapride, pimozide, or quinidine because increased plasma concentrations of these drugs can lead to QTc prolongation and rare occurrences of torsades de pointes. Voriconazole should not be given concurrently with sirolimus (increased sirolimus concentrations), rifampin, carbamazepine, and long-acting barbiturates (decreased voriconazole concentrations), high-dose ritonavir 400 mg every 12 hours (decreased voriconazole concentrations), and St. John's Wort. Use caution when administering efavirenz and

voriconazole (decreased voriconazole concentrations and increased efavirenz concentrations). Additionally, voriconazole should not be given with rifabutin as voriconazole concentrations are decreased, and rifabutin concentrations are increased. Ergot alkaloids should not be used with voriconazole.

Voriconazole prescribing information should be consulted for a detailed description of drug interactions and required dosage modifications prior to initiating therapy. Monitoring liver enzymes before and during therapy is recommended. Visual disturbances associated with therapy have not been studied beyond 28 days. Electrolyte disturbances including hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to initiation of therapy with voriconazole as electrolyte disturbances increase the risk of cardiac arrhythmias.

As with other azole antifungals, hypersensitivity to voriconazole or any of the excipients contraindicates its use. There is no information regarding cross-sensitivity among voriconazole and other azole antifungal agents.

Voriconazole is associated with rare cases of serious hepatic reactions including clinical hepatitis, cholestasis, and fulminant hepatic failure with fatalities. Severe hepatic reactions have occurred in patients with serious underlying medical conditions, predominantly hematological malignancy. Hepatic reactions such as hepatitis and jaundice have occurred in patients with no identifiable risk factors. Liver dysfunction was reversible after discontinuation of voriconazole in most cases. Liver function tests should be performed prior to voriconazole therapy and during therapy to monitor for hepatic injury.

Voriconazole tablets contain lactose and should not be given to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

### ***Drug Interactions***

Numerous drug interactions are associated with antifungal agents. See chart on next page.

Due to low systemic absorption, drug interactions with clotrimazole (Mycelex) and nystatin are limited.<sup>66,67</sup>

Clotrimazole is an inhibitor of hepatic cytochrome P450 (CYP) 3A4, and tacrolimus is metabolized by CYP3A4.<sup>68, 69</sup> Administration of clotrimazole troches to renal transplant patients receiving tacrolimus caused clinically significant increases in the relative oral bioavailability, Tmax, and trough concentrations of tacrolimus.<sup>70,71</sup> Tacrolimus blood concentrations should be monitored closely whenever clotrimazole therapy is initiated or discontinued. Close monitoring can minimize toxicity due to increased tacrolimus levels or prevent an acute rejection episode due to subtherapeutic tacrolimus levels.

Flucytosine can cause significant hematologic toxicity. It should be used cautiously with all antineoplastic agents, especially those that cause bone marrow depression. Cytarabine can competitively inhibit flucytosine, antagonizing its antifungal activity. Other bone marrow depressants include carbamazepine, clozapine, phenothiazines, zidovudine, and other blood dyscrasia-causing medications.

Posaconazole (Noxafil) is primarily metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux.<sup>72</sup> Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. The UDP inducers

include efavirenz, rifabutin, and phenytoin. The UDP inducers reduce C<sub>max</sub> and area under the curve (AUC) of posaconazole thus reducing bioavailability. Avoid concurrent use with efavirenz, rifabutin, or phenytoin unless the benefit outweighs the risk.

Patients should be monitored for breakthrough fungal infections while on posaconazole when concurrently taking esomeprazole or cimetidine (due to an increase in gastric pH) as well as metoclopramide (due to an increase in gastrointestinal motility). Esomeprazole and metoclopramide have each shown to reduce C<sub>max</sub> and AUC of posaconazole. Other PPIs have not been studied in combination with posaconazole.

No clinically relevant effect on posaconazole bioavailability and/or plasma concentrations was observed when administered with an antacid, glipizide, ritonavir, loperamide, or H<sub>2</sub>-receptor antagonists other than cimetidine; therefore, no posaconazole dose adjustments are required when used concomitantly with these products.

Concomitant administration of digoxin and itraconazole has led to increased plasma concentrations of digoxin.<sup>73</sup> Fentanyl plasma concentrations could be increased or prolonged by concomitant use of itraconazole and may cause potentially fatal respiratory depression.

Concomitant administration of miconazole (Oravig) and warfarin has resulted in enhancement of anticoagulant effect. Cases of bleeding and bruising following the concomitant use of warfarin and topical, intravaginal, or oral miconazole were reported. Closely monitor prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests if miconazole is administered concomitantly with warfarin. Also monitor for evidence of bleeding.<sup>74</sup>

Although the systemic absorption of miconazole following miconazole (Oravig) administration is minimal and plasma concentrations of miconazole are substantially lower than when given intravenously, the potential for interaction with drugs metabolized through CYP2C9 and CYP3A4 such as oral hypoglycemics, phenytoin, or ergot alkaloids cannot be ruled out.

Below is a list of common substrates for CYP 450 enzymes affected by oral antifungal agents.

- Selected substrates for the 2C9 system: diazepam, phenytoin, S-warfarin
- Selected substrates for the 2C19 system: phenytoin, thioridazine
- Selected substrates for the 2D6 system: carvedilol, clozapine, cyclobenzaprine, donepezil, flecainide, fluphenazine, fluoxetine, galantamine, haloperidol, hydrocodone, maprotiline, meperidine, methadone, methamphetamine, metoprolol, mexiletine, morphine, paroxetine, perphenazine, propafenone, propranolol, risperidone, thioridazine, timolol, tramadol, trazodone, and venlafaxine
- Selected substrates for the 3A4 system: triazolam, alprazolam, diazepam, atorvastatin, lovastatin, simvastatin, cyclosporine, tacrolimus, buspirone, terfenadine, astemizole, cisapride, and pimozide

## Drug Interactions Table

Consult package inserts for detailed information.

Drug	CYP 450 enzyme inhibition	Contraindications	Dose adjustments needed	Monitoring of other drug effects
fluconazole (Diflucan) <sup>75</sup>	2C9, 3A4	terfenadine cisapride astemizole pimozide	renal impairment rifampin celecoxib tacrolimus midazolam triazolam	cyclosporine warfarin phenytoin sulfonylureas theophylline
flucytosine (Ancobon) <sup>76</sup>	--	--	renal impairment; drugs which reduce GFR barbiturates	--
griseofulvin (Grifulvin V, Gris-PEG) <sup>77, 78</sup>	--	--		warfarin cyclosporine tretinoin, ATRA sunitinib nilotinib
itraconazole (Sporanox) <sup>79</sup>	3A4	cisapride oral midazolam pimozide quinidine dofetilide nisoldipine triazolam levomethadyl ergot alkaloids lovastatin simvastatin	Decreases elimination of drugs metabolized by CYP3A4; dosing modification is required.  See package insert for complete detailed drug list.	See package insert for full details
ketoconazole (Nizoral) <sup>80</sup>	3A4	astemizole terfenadine cisapride triazolam rifampin isoniazid	cyclosporine tacrolimus methylprednisolone midazolam	digoxin warfarin sulfonylureas phenytoin
miconazole (Oravig) <sup>81</sup>	2C9, 3A4	--	--	warfarin oral hypoglycemic phenytoin ergot alkaloids
posaconazole (Noxafil) <sup>82</sup>	3A4	terfenadine astemizole pimozide cisapride quinidine ergot alkaloids halofantrine sirolimus simvastatin	vinca alkaloids statins (3A4 inhibitors) calcium channel blockers (3A4 inhibitors) cyclosporine tacrolimus midazolam phenytoin	cimetidine cyclosporine tacrolimus rifabutin midazolam phenytoin ritonavir atazanavir efavirenz digoxin esomeprazole metoclopramide

Drug Interactions Table (continued)

Drug	CYP 450 enzyme inhibition	Contraindications	Dose adjustments needed	Monitoring of other drug effects
terbinafine (Lamisil, Lamisil Granules, Terbinex) <sup>83,84</sup>	2D6	thioridazine	TCAs, SSRIs, beta-blockers, monoamine oxidase inhibitors–type b rifampin	warfarin cyclosporine theophylline cimetidine
voriconazole (Vfend) <sup>85</sup>	2C19, 2C9,3A4	rifampin ritonavir (high dose) carbamazepine long-acting barbiturates rifabutin sirolimus terfenadine astemizole cisapride pimozide quinidine ergot alkaloids St. John's Wort	cyclosporine tacrolimus statins (3A4 inhibitors) benzodiazepines (midazolam, triazolam, alprazolam) calcium channel blockers phenytoin omeprazole vinca alkaloids methadone alfentanil efavirenz NSAIDS efavirenz	warfarin coumarin derivatives sulfonylureas protease inhibitors non-nucleoside reverse transcriptase inhibitors oral contraceptives with ethinyl estradiol and norethindrone ritonavir (low-dose) fentanyl oxycodone and other long acting narcotic analgesics

**Adverse Effects**

Drug	Nausea	Headache	Rash	Vomiting	Abd. Pain	Diarrhea	Pruritus	Elevated LFT
clotrimazole (Mycelex troche) <sup>86</sup>	reported	nr	nr	reported	nr	nr	reported	15
fluconazole (Diflucan) <sup>87</sup> n=4,048	3.7	1.9	1.8	1.7	1.7	1.5	nr	reported
flucytosine (Ancobon) <sup>88</sup>	reported	reported	reported	reported	reported	reported	reported	reported
griseofulvin (Grifulvin V, Gris-PEG) <sup>89,90</sup>	reported	reported	reported	reported	nr	reported	nr	reported
itraconazole (Sporanox) <sup>91</sup> n=112 200 mg daily X 12 wks	3	10	3-4	reported	4	4	reported	4
ketoconazole (Nizoral) <sup>92</sup>	3	<1	nr	3	1.2	< 1	1.5	reported
miconazole (Oravig) <sup>93</sup>	0.7-6.6	5-7.6	nr	0.7-3.8	1.4-2.5	6-9	nr	nr
nystatin (Mycostatin) <sup>94</sup>	reported	nr	nr	reported	reported	reported	nr	nr
posaconazole (Noxafil) <sup>95</sup>	9-29	8-20	3-15	7-28	5-18	10-29	nr	3-6
fluconazole (oral pharyngeal candidiasis)	11	9	4	7	6	13		5-10
terbinafine (Lamisil, Terbinex) <sup>96,97</sup> n=465	2.6	12.9	5.6	reported	2.4	5.6	2.8	3.3
terbinafine (Lamisil Granules) <sup>98</sup> n=1,042	2	7	2	5	2	3	1	nr
voriconazole (Vfend) <sup>99</sup> n=1,655	5.4	3	5.3-7	4.4	< 2	< 2	< 2	1.8-12.4

Incidence is reported as a percentage. Adverse events data are obtained from prescribing information and therefore should not be considered comparative or all inclusive. Incidences for placebo indicated in parentheses. nr = not reported

Voriconazole is reported to be associated with abnormal visual disturbances (21 percent IV and oral therapy) which resolve with discontinuation of therapy.<sup>100</sup>

In patients with normal gastrointestinal, renal, and hematologic function, flucytosine is generally associated with few adverse events, although rash, GI discomfort, diarrhea (five to 10 percent), and reversible elevations in hepatic enzymes are occasionally observed. In patients with renal dysfunction or in patients on concomitant amphotericin B, leukopenia, thrombocytopenia, and enterocolitis may occur. Flucytosine is associated with dose-dependent, potentially lethal bone marrow suppression.<sup>101</sup>

### **Special Populations**<sup>102,103,104,105,106,107,108,109,110,111,112</sup>

#### Pediatrics

Clotrimazole (Mycelex) troches have been used in children ages three years and older. Nystatin (Mycostatin) has been used in infants.<sup>113</sup> Safety and effectiveness of ketoconazole (Nizoral) have been established for children over two years of age. Terbinafine (Lamisil Granules) is approved for the treatment of tinea capitis for ages four years and older. The safety and efficacy of terbinafine tablets (Terbinex/Lamisil) have not been established in pediatric patients. Eco Formula (component of Terbinex kit) should be kept out of the reach of children.

Safety and effectiveness of griseofulvin (Gris-Peg, Grifulvin V) have been established for children over age two years. Fluconazole safety and effectiveness data exist for children older than six months. Intravenous fluconazole has been used in preterm infants; however, efficacy has not been established in infants less than six months of age.<sup>114</sup>

Safety and effectiveness of posaconazole (Noxafil) in pediatric patients less than 13 years of age have not been established. Safety and effectiveness of itraconazole have not been proven in pediatric patients. Voriconazole (Vfend) does not have safety and effectiveness data in children less than 12 years old. Pharmacokinetics and safety data were collected in a small trial with intravenous voriconazole in children ages two to 11 years.<sup>115</sup>

No studies of flucytosine (Ancobon) in pediatric patients exist; however, published reports of use of flucytosine with and without amphotericin B in doses of 25-200 mg/kg per day are available. No unexpected serious adverse effects were reported.

Safety and effectiveness of miconazole (Oravig) in pediatric patients less than the age of 16 years have not been established. The ability of pediatric patients to comply with the application instructions has not been evaluated. Use in younger children is not recommended due to potential risk of choking.

#### Pregnancy

Terbinafine is Pregnancy Category B. Clotrimazole, flucytosine, posaconazole, fluconazole, itraconazole, ketoconazole, nystatin, miconazole (Oravig), and griseofulvin are Pregnancy Category C. Voriconazole is Pregnancy Category D.

Two cases of conjoined twins have been reported with first trimester use of griseofulvin. Griseofulvin should not be used in pregnant patients. Griseofulvin therapy should be discontinued if the patient becomes pregnant during treatment, and potential hazards to the fetus should be explained.

#### Elderly

Transient or permanent hearing loss has been reported in elderly patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated.

**Hepatic Impairment**

For patients with mild to moderate cirrhosis (Child-Pugh Class A and B), use the standard loading dose regimens of voriconazole, however, reduce the maintenance dose of voriconazole by one-half.

**Dosages**

Drug	Oral Dosage Forms	Adult Dosage
clotrimazole (Mycelex Troche) <sup>116</sup>	10 mg troche	<ul style="list-style-type: none"> <li>• <b>Treatment:</b> One troche (10 mg) five times per day for 14 consecutive days</li> <li>• <b>Prophylaxis:</b> One troche (10 mg) three times per day</li> </ul>
fluconazole (Diflucan) <sup>117</sup>	50, 100, 150, 200 mg tablets 10 mg/mL, 40 mg/mL suspension	<ul style="list-style-type: none"> <li>• Oropharyngeal and esophageal candidiasis: 200 mg X 1, then 100 mg daily</li> <li>• Vaginal candidiasis: 150 mg orally X 1</li> <li>• Urinary tract infections and peritonitis: 50 to 200 mg daily</li> <li>• Cryptococcal meningitis: 400 mg X 1, then 200 mg daily</li> <li>• Undergoing bone marrow transplant: 400 mg daily until neutrophils &gt;1,000 cells/m<sup>3</sup> for seven days</li> </ul>
flucytosine (Ancobon) <sup>118</sup>	250, 500 mg capsules	<ul style="list-style-type: none"> <li>• 50 – 150 mg/kg/day in divided doses every six hours</li> </ul>
griseofulvin (Grifulvin V, Gris-PEG) <sup>119, 120</sup>	<p><u>Microsized:</u> Grifulvin V: 125 mg/5 mL suspension; 250, 500 mg tablets</p> <p><u>Ultramicrosized:</u> Gris-PEG: 125, 250 mg tablets</p>	<p><u>Microsized:</u></p> <ul style="list-style-type: none"> <li>• Onychomycosis: 1 g orally once a day for at least 4 months (fingernails) or at least 6 months (toenails)</li> <li>• Tinea barbae: 500 to 1,000 mg orally once a day until infection has cleared</li> <li>• Tinea capitis: 500 mg orally once a day for 4 to 6 weeks</li> <li>• Tinea corporis: 500 mg orally once a day for 2 to 4 weeks</li> <li>• Tinea cruris: 500 mg orally once a day until infection has cleared</li> <li>• Tinea pedis: 1 g orally once a day for 4 to 8 weeks</li> </ul> <p><u>Ultramicrosized:</u></p> <ul style="list-style-type: none"> <li>• Onychomycosis : 750 mg orally in divided doses for at least 4 months (fingernails) or at least 6 months (toenails)</li> <li>• Tinea barbae: 375 mg orally once a day or 375 to 750 mg in divided doses until infection has cleared</li> <li>• Tinea capitis: 375 mg orally once a day or in divided doses for 4 to 6 weeks</li> <li>• Tinea corporis: 375 mg orally once a day or in divided doses for 2 to 4 weeks</li> <li>• Tinea cruris: 375 mg orally once a day or in divided doses until infection has cleared</li> <li>• Tinea pedis: 750 mg orally in divided doses for 4 to 8 weeks</li> </ul>

**Dosages (continued)**

Drug	Oral Dosage Forms	Adult Dosage
itraconazole (Sporanox) <sup>121</sup>	100 mg capsule 10 mg/mL solution	<ul style="list-style-type: none"> <li>Onychomycosis (toenail): 200 mg daily for 12 weeks</li> <li>Onychomycosis (fingernail): two treatment pulses, which consist of 200 mg twice daily for one week. The pulses are separated by a three-week period without itraconazole.</li> <li>Treatment of Blastomycosis 200 mg orally 3 times daily for 3 days, then 1—2 times daily for 6—12 months</li> <li>Treatment of Histoplasmosis: 200—400 mg/day orally. For life-threatening cases, a loading dose of 200 mg orally three times daily for the first 3 days is recommended by the manufacturer and treatment should continue for at least 3 months until clinical parameters and laboratory tests indicated the active fungal infection has subsided.</li> <li>Treatment of Aspergillosis: 200 to 400 mg daily</li> </ul>
ketoconazole (Nizoral) <sup>122</sup>	200 mg tablet	<ul style="list-style-type: none"> <li>200 to 400 mg daily</li> </ul>
miconazole (Oravig) <sup>123</sup>	50 mg buccal tablets	<ul style="list-style-type: none"> <li>one 50 mg buccal tablet to the upper gum region (canine fossa) once daily for 14 consecutive days</li> </ul>
nystatin (Mycostatin) <sup>124, 125, 126</sup>	Variety of dosage forms and strengths  First Duke's mouthwash compounding kit consists of nystatin, diphenhydramine, and hydrocortisone.  First Mary's mouthwash compounding kit consists of nystatin, diphenhydramine, tetracycline, and hydrocortisone.	<ul style="list-style-type: none"> <li>Gastrointestinal candidiasis: 500,000 to 1,000,000 units three times daily</li> <li>Oral candidiasis : 400,000 to 600,000 units four times daily</li> </ul>
posaconazole (Noxafil) <sup>127</sup>	200 mg/5 mL oral suspension	<ul style="list-style-type: none"> <li>Prophylaxis of invasive fungal infections: 200 mg (5 mL) three times daily during or immediately following (within 20 minutes) a full meal or with a liquid nutritional supplement in patients who can not eat a full meal. Duration of therapy is based on recovery from neutropenia or immunosuppression.</li> <li>Oropharyngeal candidiasis: Loading dose of 100 mg twice daily on day 1 then 100 mg once daily for 13 days.</li> <li>Oropharyngeal candidiasis refractory to fluconazole and/or itraconazole: 400 mg twice daily. Duration to be determined by patient's severity of underlying disease and clinical response.</li> </ul>
terbinafine (Lamisil, Lamisil Granules) <sup>128, 129</sup>	250 mg tablet	<ul style="list-style-type: none"> <li>Onychomycosis (toenail): 250 mg daily for 12 weeks</li> <li>Onychomycosis (fingernail): 250 mg daily for six weeks</li> </ul>
terbinafine (Terbinex) <sup>130</sup>	250 mg tablet	<ul style="list-style-type: none"> <li>Onychomycosis (toenail): 250 mg daily for 12 weeks</li> <li>Onychomycosis (fingernail): 250 mg daily for six weeks</li> <li>A thin layer of EcoFormula should be applied daily to clean, dry nails preferably before bedtime.</li> </ul>

**Dosages (continued)**

Drug	Oral Dosage Forms	Adult Dosage
voriconazole (Vfend) <sup>131</sup>	50, 200 mg tablets 200 mg/5 mL suspension	<p><u>IV</u>: (IV load is required to initiate therapy for all infections except esophageal candidiasis)</p> <ul style="list-style-type: none"> <li>6 mg/kg every 12 hours X two doses then 3-4 mg/kg every 12 hours</li> <li><u>Oral</u>: &gt; 40 kg: 200 mg every 12 hours &lt; 40 kg: 100 mg every 12 hours</li> <li><u>Concurrent phenytoin therapy</u>:  <p><u>IV</u>: 5 mg/kg every 12 hours                      Oral: &gt; 40 kg: 400 mg every 12 hours                      &lt; 40 kg: 200 mg every 12 hours</p> </li> </ul> <p>Oral voriconazole should be taken one hour before or one hour after a meal.</p>

Dosage recommendations for pediatric patients are listed below.

Drug	Oral Dosage Forms	Ages	Pediatric Dosage								
clotrimazole (Mycelex Troche) <sup>132</sup>	10 mg troche	> three years	<ul style="list-style-type: none"> <li>Oropharyngeal candidiasis: One troche (10 mg) five times per day</li> </ul>								
fluconazole (Diflucan) <sup>133</sup>	50, 100, 150, 200 mg tablets 10 mg/mL, 40 mg/mL suspension	six months to 13 years	<ul style="list-style-type: none"> <li>Oropharyngeal candidiasis: 6mg/kg X 1; then 3 mg/kg daily for at least two weeks</li> <li>Esophageal candidiasis: 6 mg/kg X 1; then 3 mg/kg daily for at least three weeks</li> <li>Cryptococcal meningitis: 12 mg/kg X 1; then 6 to 12 mg/kg daily</li> <li>Systemic infections: 6 to 12 mg/kg daily</li> <li>Equivalent dosing</li> </ul> <table border="1"> <thead> <tr> <th>Pediatric dose</th> <th>Adult dose</th> </tr> </thead> <tbody> <tr> <td>3 mg/kg daily</td> <td>100 mg daily</td> </tr> <tr> <td>6 mg/kg daily</td> <td>200 mg daily</td> </tr> <tr> <td>12 mg/kg daily</td> <td>400 mg daily</td> </tr> </tbody> </table> <ul style="list-style-type: none"> <li>Pediatric dose should not exceed 600 mg daily.</li> </ul>	Pediatric dose	Adult dose	3 mg/kg daily	100 mg daily	6 mg/kg daily	200 mg daily	12 mg/kg daily	400 mg daily
Pediatric dose	Adult dose										
3 mg/kg daily	100 mg daily										
6 mg/kg daily	200 mg daily										
12 mg/kg daily	400 mg daily										
Griseofulvin (Grifulvin V, Gris-PEG) <sup>134, 135, 136</sup>	<p><u>Microsized</u>:                      Grifulvin V: 125 mg/5 mL suspension;                      250, 500 mg tablets</p> <p><u>Ultramicrosized</u>:                      Gris-PEG: 125, 250 mg tablets</p>	> two years	<p><u>Microsized</u>:</p> <ul style="list-style-type: none"> <li>Pediatrics: 10-20 mg/kg daily (max: 1 g) given in one to two divided doses</li> <li>Children weighing 30 to 50 pounds – 125 mg to 250 mg daily.</li> <li>Children weighing over 50 pounds – 250 mg to 500 mg daily.</li> </ul> <p><u>Ultramicrosized</u>:</p> <ul style="list-style-type: none"> <li>Pediatrics: 3.3-7.3 mg/kg/day</li> <li>Children weighing 35-60 pounds - 125 mg to 187.5 mg daily.</li> <li>Pediatric patients weighing over 60 pounds - 187.5 mg to 375 mg daily.</li> </ul>								

**Dosages (continued)**

Drug	Oral Dosage Forms	Ages	Pediatric Dosage						
ketoconazole (Nizoral) <sup>137</sup>	200 mg tablet	> two years	<ul style="list-style-type: none"> <li>3.3-6.6 mg/kg/day</li> </ul>						
nystatin (Mycostatin) <sup>138</sup>	various	neonates and older	<ul style="list-style-type: none"> <li><b>Oral candidiasis:</b> 100,000 to 600,000 units four times daily</li> </ul>						
terbinafine (Lamisil Granules) <sup>139</sup>	125 mg packet 187.5 mg packet	> four years	<ul style="list-style-type: none"> <li>Tinea capitis: Dose, based on body weight, given once daily for six weeks: <table border="1" data-bbox="841 512 1198 600"> <tbody> <tr> <td>&lt; 25 kg</td> <td>125 mg</td> </tr> <tr> <td>25-35 kg</td> <td>187.5 mg</td> </tr> <tr> <td>&gt; 35 kg</td> <td>250 mg</td> </tr> </tbody> </table> </li> <li>Sprinkle contents of pack on a spoonful of pudding or other soft non-acidic food such as mashed potatoes. Do not use apple sauce or fruit-based foods. Swallow entire spoonful without chewing. Take with food.</li> </ul>	< 25 kg	125 mg	25-35 kg	187.5 mg	> 35 kg	250 mg
< 25 kg	125 mg								
25-35 kg	187.5 mg								
> 35 kg	250 mg								

**Clinical Trials**Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials of oral agents used in the outpatient setting are considered the most relevant in this category. Many of the more recent studies have focused on inpatient use of the antifungal agents. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. No clinical trials evaluating the Terbinex kit met the inclusion criteria.

fluconazole (Diflucan) and voriconazole (Vfend) – esophageal candidiasis

In a double-blind, placebo-controlled trial, 256 immunocompromised patients, most of whom were HIV-positive with biopsy-proven esophageal candidiasis, were randomized to voriconazole (400 mg for one dose; then 200 mg twice daily), fluconazole (400 mg for one dose; then 200 mg daily), or placebo. The study evaluated efficacy, tolerability, and safety.<sup>140</sup> Patients were on therapy for at least seven days after clinical signs and symptoms resolved or for a maximum of six weeks. Patients underwent endoscopy at day 43 to determine efficacy. Endoscopy-documented success (98.3 percent versus 95.1 percent, respectively) as well as symptomatic success (88 percent versus 91.1 percent, respectively) was similar between voriconazole and fluconazole. Visual disturbances were reported in 18 percent of voriconazole patients compared to five percent with fluconazole. More patients discontinued voriconazole due to laboratory abnormalities or treatment-related adverse effects.

griseofulvin oral suspension and terbinafine granules (Lamisil Granules) – tinea capitis

Terbinafine oral granules and griseofulvin oral suspension were compared for efficacy and safety in the treatment of tinea capitis in children ages four to 12 years in two investigator-blinded studies.<sup>141</sup> Patients were randomized to terbinafine 5-8 mg/kg daily or griseofulvin 10-20 mg/kg for six weeks of treatment. The 1,549 patients were followed for an additional four weeks. End of study complete cure was defined as a negative fungal culture and microscopy with no symptoms. Mycologic cure was defined as negative fungal culture and microscopy. Clinical cure was the absence of symptoms. The pooled intent-to-treat population consisted of 1,286 patients. Rates of complete cure and mycologic cure were significantly higher for terbinafine than for griseofulvin (45.1 versus 39.2 percent and 61.5 versus 55.5 percent, respectively; each  $p < 0.05$ ). Most griseofulvin patients (86.7 percent) received 10 to 19.9 mg/kg per day; complete cure rate was not found to be higher among patients who received more than griseofulvin 20 mg/kg per day compared with those who received less than 20 mg/kg per day. Complete cure rate was statistically significantly greater for terbinafine compared to griseofulvin in trial 1 (46.23 versus 34.01 percent, respectively) but not in trial 2 (43.99 versus 43.46 percent, respectively). Clinical cure was similar between the two drugs based on the pooled data. Subgroup analyses revealed that terbinafine was significantly better than griseofulvin for all cure rates among patients with *Trichophyton tonsurans* but not *Microsporum canis* ( $p < 0.001$ ). For *M. canis*, mycologic and clinical cure rates were significantly better with griseofulvin than with terbinafine ( $p < 0.05$ ). Therapies were well tolerated.

miconazole (Oravig) versus clotrimazole troches

In a randomized, double-blind, double-dummy trial, miconazole buccal 50 mg tablets daily were compared to clotrimazole 10 mg troches five times daily for 14 days in 577 HIV-positive patients with oropharyngeal candidiasis.<sup>142,143</sup> Patients were required to have symptoms and microbiological documentation of candidiasis for study entry. Clinical cure was defined as a complete resolution of signs and symptoms of oropharyngeal candidiasis at the test-of-cure visit (days 17-22). Clinical cure was achieved in 61 percent of miconazole patients compared to 65 percent of clotrimazole patients ( $p = NS$ ) in the intent to treat population. Clinical relapse occurred in 27.3 and 27.8 percent of patients, respectively. Mycological cure (eradication of *Candida* on days 17-22) occurred in 27.2 and 24.7 percent of patients, respectively. Adverse events were similar between treatments.

terbinafine (Lamisil) versus itraconazole (Sporanox) - onychomycosis

In a prospective, randomized, double-blind, multicenter study, researchers compared the efficacy and tolerability of continuous terbinafine with intermittent itraconazole for treatment of toenail onychomycosis.<sup>144</sup> The study included 496 patients diagnosed with toenail onychomycosis caused by a dermatophyte. Patients were randomly assigned to four parallel groups: terbinafine 250 mg per day for 12 or 16 weeks or itraconazole 400 mg per day for one week in every four weeks for 12 or 16 weeks. The primary outcome measure was mycological cure, defined as negative microscopy and negative culture of samples from the target toenail. At week 72, mycological cure rates were 75.5 percent in the 12-week terbinafine group and 80.8 percent in the 16-week terbinafine group, compared with 38.3 percent in the itraconazole 12-week study group and 49.1 percent in the itraconazole 16-week group. All treatments were well tolerated, with no significant differences in the number or type of adverse events reported. Researchers concluded continuous terbinafine is more effective than intermittent itraconazole for the treatment of toenail onychomycosis.

In a five-year, blinded, prospective follow-up study to the aforementioned study, the long-term effectiveness of terbinafine was compared to itraconazole in 151 patients.<sup>145</sup> At the end of five years, mycologic cure achieved with one treatment course was found in 46 percent and 13 percent of the terbinafine-treated and itraconazole-treated patients, respectively ( $p < 0.001$ ). Mycologic and clinical relapse rates were significantly higher in the itraconazole-treated group, 53 percent and 48 percent, respectively, compared to the terbinafine-treated group, 23 percent and 21 percent, respectively.

posaconazole (Noxafil), fluconazole (Diflucan) and/or itraconazole (Sporanox)

Due to the lack of other comparative data with posaconazole, this study is included in the review. In a randomized, multicenter study, safety and efficacy of posaconazole ( $n=304$ ), fluconazole ( $n=240$ ), and itraconazole ( $n=58$ ) were compared for invasive fungal infection prophylaxis in patients with prolonged neutropenia.<sup>146</sup> Patients were undergoing treatment for acute myelogenous leukemia or myelodysplastic syndrome. In this investigator-blinded study, patients received prophylaxis with the assigned treatment with each cycle of chemotherapy until recovery from neutropenia and complete remission occurred or until the occurrence of an invasive fungal infection or for up to 12 weeks. Proven or probable invasive fungal infections were reported in two percent of the posaconazole group and eight percent in the fluconazole or itraconazole group (absolute reduction, 6 percent; 95% CI, -9.7 to -2.5;  $p < 0.001$ ). Invasive aspergillosis was significantly lower in the posaconazole group (one percent versus seven percent,  $p < 0.001$ ). Survival was significantly higher in the posaconazole group (16 percent mortality) than in the fluconazole/itraconazole group (22 percent mortality,  $p=0.04$ ). Serious adverse effects were significantly more common in the posaconazole group (six percent versus two percent;  $p=0.01$ ). The most common adverse effects related to the gastrointestinal tract.

In a multicenter, randomized, double-blind trial, oral posaconazole and fluconazole were compared for prophylaxis against invasive fungal infections in patients with graft-versus-host disease (GVHD) who were receiving immunosuppressive therapy.<sup>147</sup> Six hundred allogeneic hematopoietic stem-cell transplant patients were enrolled. At the end of the 112-day treatment period, posaconazole and fluconazole were similarly effective in preventing all invasive fungal infections (5.3 and 9 percent, respectively; odds ratio=0.56; 95% CI, 0.30 to 1.07,  $p=0.07$ ). Posaconazole was superior to fluconazole in preventing proven or probable invasive aspergillosis (2.3 and 7 percent, odds ratio=0.31, 95% CI, 0.13 to 0.75,  $p=0.006$ ). Overall mortality was similar in the two groups; however, the number of deaths from invasive fungal infections was lower in the posaconazole group (1 and 4 percent,  $p=0.046$ ). Treatment-related adverse effects were similar in both groups (36 percent for posaconazole and 38 percent for fluconazole).

Due to the lack of other comparative data with posaconazole, this study is included in the review. Posaconazole was compared to fluconazole in a multicenter, randomized, single-blinded trial evaluating efficacy and safety in the treatment of oropharyngeal candidiasis in patients with HIV/AIDS.<sup>148</sup> Patients ( $n=350$ ) were randomized to posaconazole or fluconazole 200 mg on day one then 100 mg daily for 13 days. Clinical success, defined as cure or improvement on day 14, was observed in 91.7 and 92.5 percent for posaconazole and fluconazole groups, respectively (95% CI, -6.61 to 5.04). Mycological success was 68 percent in both arms on day 14, but mycological success on day 42 was 40.6 and 26.4 percent for posaconazole and fluconazole, respectively ( $p=0.038$ ). Clinical relapse rates were 31.5 percent for posaconazole and 38.2 percent for fluconazole. Adverse effects were similar.

## Meta-Analysis

A meta-analysis determined mycological cure rate in randomized clinical trials is consistently 76 percent for terbinafine (Lamisil) and 63 percent for pulse dose itraconazole (Sporanox).<sup>149</sup> Thirty-six randomized, controlled trials evaluated the efficacy of terbinafine, itraconazole, fluconazole (Diflucan), and griseofulvin (Grifulvin V, Gris-PEG) in the treatment of dermatophyte toenail onychomycosis.<sup>150</sup> Studies were required to use a standard dosage regimen (pulse or continuous), treatment duration, and follow-up period. Mycological and clinical response rates were compared for the randomized controlled trials and open trials for each of the agents. Studies were pooled from earliest (1966) to most recent to determine the cumulative meta-analytical average. The overall cumulative meta-average for mycological cure rates were terbinafine  $76 \pm 3$  percent (18 studies), itraconazole pulse  $63 \pm 7$  percent (six studies), itraconazole continuous  $59 \pm 5$  percent (seven studies), fluconazole  $48 \pm 5$  percent (three studies), and griseofulvin  $60 \pm 6$  percent (three studies). When comparing randomized controlled trials and open-label trials, the cumulative meta-analytical average for mycological cure rates were significantly higher in the open-label trials for terbinafine, itraconazole pulse dose, and fluconazole.

Randomized controlled trials (21 studies) that evaluated systemic antifungal therapy for tinea capitis in immunocompetent children (n=1,812) were identified.<sup>151</sup> All studies required a tinea capitis diagnosis to be confirmed by microscopy or growth of dermatophytes in culture or both. For infections caused by *Trichophyton* species, terbinafine for four weeks and griseofulvin for eight weeks showed similar efficacy (RR 1.09; 95% CI, 0.95 to 1.26). Two studies found cure rates to be similar following treatment with itraconazole and griseofulvin for six weeks. There was no difference between itraconazole and terbinafine for treatment periods lasting two to three weeks in two studies involving 160 children (RR 0.93; 95% CI, 0.72 to 1.19). Two studies that included 140 children found similar cure rates between two to four weeks of fluconazole with six weeks of griseofulvin (RR 0.92; 95% CI, 0.8 to 1.05). For *Microsporum* infections, no significant difference in cure rates were observed between terbinafine and griseofulvin, based on one small study of 29 children (RR 0.64; 95% CI, 0.19 to 2.20). Shorter treatment durations may improve treatment adherence.

A meta-analysis compared griseofulvin (Grifulvin V, Gris-PEG) and terbinafine in the treatment of tinea capitis in children.<sup>152</sup> Randomized, clinical studies with treatment for at least six weeks were included. Identification of the dermatophyte was required for inclusion. A total of six trials were evaluated. Outcome parameters were compared at 12 to 16 weeks after enrollment. The common odds ratio was 0.86, which tells us that the studies included had similar outcomes. When *Trichophyton* species were isolated in studies looking at outcomes at 12 weeks, the results trended toward terbinafine. Outcomes after eight weeks for both treatments were similar. Authors concluded terbinafine for two to four weeks is at least as effective as griseofulvin for at least six weeks for *Trichophyton* infections of the scalp. With other pathogens, griseofulvin may be a superior agent.

Another meta-analysis evaluated seven trials with griseofulvin for the treatment of tinea capitis. Overall cure rate after four to six weeks post-treatment was 73.4 percent (seven studies; n=438 patients).<sup>153</sup> Higher efficacy rates were reported with the use of higher dosages of griseofulvin (>18 mg/kg/day). When broken down by species, the mean efficacy for *Trichophyton* and *Microsporum* were 67.6 percent (five studies, n=396) and 88.1 percent (two studies, n=42 patients), respectively.

A Cochrane review found very few comparative trials on which to evaluate efficacy of prophylaxis of oropharyngeal candidiasis in HIV-positive patients.<sup>154</sup> It appeared that ketoconazole, fluconazole, itraconazole, and clotrimazole improved treatment outcomes in the treatment of oropharyngeal candidiasis. An update was performed evaluating clinical trials performed between 2005 and 2009.<sup>155</sup> Five additional studies were identified. Only one study was performed in children; therefore, little evidence exists. For adults, very few comparative trials for each comparison exist. Due to insufficient evidence, no conclusion could be made about the effectiveness of clotrimazole, nystatin, amphotericin B, itraconazole or ketoconazole with regard to oropharyngeal candidiasis prophylaxis.

### Summary

Oral antifungal agents are useful in the treatment of a variety of infections in both the immunocompetent and immunocompromised patient. Oral antifungals used in the outpatient setting generally treat fungal infections such as oropharyngeal candidiasis, urinary tract infections, superficial skin infections, and onychomycosis. Due to its excellent penetration into many tissues, fluconazole (Diflucan) is effective *Candida* treatment for a variety of infections, lacking concerns about pH-dependent absorption such as that seen with ketoconazole (Nizoral). Effective therapy for oropharyngeal candidiasis includes fluconazole, itraconazole, ketoconazole, nystatin, and clotrimazole troches (Mycelex). Voriconazole (Vfend) has been shown to have similar efficacy to fluconazole in the treatment of esophageal candidiasis; however, more adverse effects are reported with voriconazole. Posaconazole (Noxafil) has an indication for treatment of oropharyngeal candidiasis when refractory to itraconazole and/or fluconazole. Nystatin is also used to treat intestinal candidiasis and may be used in infants and children.

In comparative trials, terbinafine (Lamisil) demonstrated higher treatment success rates of toenail onychomycosis in immunocompetent patients compared to itraconazole (Sporanox). Terbinafine also demonstrated higher clinical success rates in the treatment of tinea capitis than griseofulvin (Grifulvin V, Gris-PEG), however, griseofulvin had higher success rates in those infections caused by *Microsporum*.

Utility of griseofulvin for treatment of onychomycosis has decreased since the introduction of the azole antifungals and terbinafine. Duration of therapy is often longer than with other agents, which may result in increased adverse effects and require monitoring of liver, renal, and hematopoietic function. However, griseofulvin is still a useful agent in the treatment of many fungal skin infections that do not respond to topical therapies.

For serious fungal infections, posaconazole, flucytosine (Ancobon), voriconazole, itraconazole, and fluconazole have indications for the treatment and/or prophylaxis of various serious fungal infections.

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