Antifungals, Oral
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indication(s) for oral use
clotrimazole lozenge (troche)[1]	generic	▪ Treatment of oropharyngeal candidiasis ▪ To prophylactically 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
fluconazole (Diflucan®)[2]	generic, Pfizer	▪ Treatment of oropharyngeal, esophageal, and vaginal candidiasis ▪ Treatment of *Candida* urinary tract infections, peritonitis, candida systemic infections including candidemia, disseminated candidiasis, and pneumonia ▪ Cryptococcal meningitis ▪ Prevention of candidiasis in patients undergoing bone marrow transplantation receiving cytotoxic chemotherapy and/or radiation
flucytosine (Ancobon®)[3]	generic, Valeant/Bausch	▪ Used in combination with amphotericin B for the treatment of serious infections caused by susceptible strains of *Candida* or *Cryptococcus*
griseofulvin, microsize[4]	generic	▪ Ringworm infections of the body, skin, hair, and nails, namely tinea corporis, tinea pedis, tinea cruris, tinea barbae, tinea capitis, and tinea unguium (onychomycosis)
griseofulvin, ultramicrosize[5]	generic	
ibrexafungerp (Brexafemme®)[6]	Scynexis	▪ Treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis
isavuconazonium (Cresemba®)[7]	Astellas	▪ Treatment of invasive aspergillosis, and invasive mucormycosis in patients 18 years and older
itraconazole (Sporanox®)[8]	generic, Janssen	▪ Onychomycosis of the fingernail and/or toenail due to dermatophytes (tinea unguium) in non-immunocompromised patients ▪ Treatment in immunocompromised and non-immunocompromised patients with pulmonary and extrapulmonary blastomycosis, histoplasmosis; or patients with aspergillosis intolerant of amphotericin B; or aspergillosis refractory to amphotericin B
itraconazole* (Tolsura®)[9]	Mayne	▪ Treatment in immunocompromised and non-immunocompromised patients with pulmonary and extrapulmonary blastomycosis; histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis; or aspergillosis, if the patient is intolerant of or refractory to amphotericin B
ketoconazole[10]	generic	▪ Blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, paracoccidioidomycosis, only in patients who are intolerant to, or who have failed, other agents†
miconazole (Oravig®)[11]	Midatech	▪ Local treatment of oropharyngeal candidiasis in adults
oteseconazole (Vivjoa™)[12]	Mycovia	▪ Reduce the incidence of recurrent vulvovaginal candidiasis (RVVC) in females with a history of RVVC who are NOT of reproductive potential.

* Tolsura (itraconazole) is not indicated for the treatment of onychomycosis and is not interchangeable or substitutable with other itraconazole products.

† Ketoconazole is no longer to be used as first-line therapy for any fungal infection and should be reserved for only those cases where alternative therapies are unavailable or not tolerated. Please revisit the indications section of the package insert for details. Previously, ketoconazole was indicated for candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, and severe recalcitrant cutaneous dermatophyte infections not responding to topical or oral griseofulvin therapy. These indications were removed due to the risk of hepatic toxicity.[13]

FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-Approved Indication(s) for oral use
nystatin[14]	generic	▪ Gastrointestinal and oral candidiasis caused by *Candida albicans*
posaconazole (Noxafil®)[15]	generic, Merck	▪ Delayed-release tablet and oral suspension: Prophylaxis of invasive *Aspergillus* and *Candida* infections in patients 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) – Oral suspension is indicated in patients ≥ 13 years of age – Delayed-release oral tablets are indicated in patients ≥ 2 years of age who weigh > 40 kg ▪ Delayed-release tablets *only*: Treatment of invasive aspergillosis in patients ≥ 13 years of age ▪ Oral suspension *only*: Treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole in patients ≥ 13 years of age
terbinafine[16]	generic	▪ Onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium)
voriconazole (Vfend®)[17]	generic, Pfizer	Treatment of the following infections in those 2 years of age and older: ▪ Invasive aspergillosis ▪ Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani,* in patients intolerant of, or refractory to, other therapy ▪ Esophageal candidiasis ▪ Candidemia in non-neutropenics and other deep tissue *Candida* infections

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 boxed warnings related to adverse events and/or drug interactions.

According to the Infectious Diseases Society of America (IDSA) 2016 candidiasis guidelines, treatment of mild oropharyngeal candidiasis in adults include clotrimazole troches, miconazole mucoadhesive buccal tablet (Oravig), or nystatin for 7 to 14 days; for moderate to severe disease, fluconazole (Diflucan) is recommended daily for 7 to 14 days.[18] For fluconazole-refractory disease, itraconazole solution or posaconazole suspension (Noxafil) may be used for up to 28 days; oral alternatives include voriconazole (Vfend) or amphotericin B oral suspension. In HIV patients for whom chronic suppressive therapy is warranted, fluconazole 3 times per week is recommended.

Since highly active antiretroviral therapy (HAART) for the treatment of HIV for infants and children is widely available and utilized in the United States (US), primary prophylaxis of oropharyngeal candidiasis (OPC) is not routinely indicated.[19] Uncomplicated infections can be effectively treated with topical therapy such as clotrimazole troches or nystatin suspension for 7 to 14 days; however, troches should not be used in infants. Oral fluconazole for 7 to 14 days is recommended for moderate or severe OPC; except during pregnancy. If chronic suppressive therapy is necessary, fluconazole taken 3 times a week is recommended. Itraconazole and posaconazole oral liquids are as effective as fluconazole, but less tolerated and/or carry potential for more drug-drug interactions.[20]

IDSA states that systemic therapy is always required for esophageal candidiasis. In adults, fluconazole for 14 to 21 days is considered first-line oral therapy.[21] Itraconazole or voriconazole given intravenously

(IV) or orally may be used in patients with fluconazole-refractory infections; alternatives include an echinocandin, amphotericin B, or posaconazole. Fluconazole is recommended to suppress recurrent esophagitis. Oral fluconazole for 14 to 21 days is preferred for children for the management of esophageal candidiasis, but IV agents (e.g., fluconazole, amphotericin B, or an echinocandin) may be used in those unable to tolerate oral therapy. [22,23] Itraconazole or voriconazole may be used in fluconazole-refractory children. Fluconazole 3 times a week is recommended to suppress recurrent infection.

For the treatment of candidemia, IDSA recommends an echinocandin as initial therapy in neutropenic and nonneutropenic patients.[24] Fluconazole (IV or oral) is an alternative initial therapy in select patients. Amphotericin lipid formulation is reasonable if intolerance, limited availability, or resistance to other agents is present. Voriconazole offers little benefit over fluconazole but is recommended as step-down therapy from fluconazole in select patients. The minimum duration of therapy for candidemia is 2 weeks post resolution of symptoms and documented clearance of *Candida* from the bloodstream.

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).[25,26] 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).[27] Additionally, debris (white, green, yellow, or black) may build up under the nail plate and discolor the nail bed. Onychomycosis is often chronic, difficult to eradicate, tends to recur, and is found more frequently in the elderly. Treatment of onychomycosis depends on the clinical type of the onychomycosis, the number of affected nails, and the severity of nail involvement. While white superficial and distal lateral onychomycosis may be treated with topical antifungal agents, proximal subungual and distal lateral subungual cases require systemic treatment, including griseofulvin, itraconazole, and terbinafine. 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.[28] 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* species*, Trichosporon, Torulopsis (Candida) glabrata, Fusarium, Alternaria*, and *Mucor* are generally found only in an immunocompromised host.

The 2016 IDSA guidelines for the management of aspergillosis also recommends voriconazole as the initial treatment option for invasive and extrapulmonary aspergillosis infections.[29] Other azole antifungals approved for aspergillosis may be considered as alternatives in salvage therapy. Posaconazole or voriconazole are options for prophylaxis of invasive aspergillosis.

Vulvovaginal candidiasis (VVC) is caused by an overgrowth of *Candida* in the vagina and results in symptoms of vaginal itching and soreness, abnormal vaginal discharge, painful intercourse, and dysuria.[30] After bacterial vaginal infections, VVC is the second most common type of vaginal infection in the US causing an estimated 1.4 million outpatient visits. It is estimated that treatment with azole antifungals provides relief of symptoms and negative cultures in 80% to 90% of patients with uncomplicated VVC.[31] According to the IDSA 2016 clinical practice guideline for the management of candidiasis, in patients with uncomplicated VVC, current guidelines recommend a short-course (1 to 3

days) of a topical azole antifungal agent or a single dose 150 mg oral fluconazole (strong recommendation).[32] For severe acute *Candida* vulvovaginitis, fluconazole 150 mg every 72 hours for a total of 2 or 3 doses is recommended (strong recommendation). For recurring vulvovaginal candidiasis, 10 to 14 days of induction therapy with a topical antifungal agent or oral fluconazole, followed by oral fluconazole 150 mg weekly for 6 months, is recommended (strong recommendation). In women with HIV infection, the IDSA advises that uncomplicated VVC responds to a short-course of treatment with oral fluconazole, topical azoles, or oral itraconazole.[33] Severe or recurrent episodes of VVC in HIV-infected patients should be treated with oral fluconazole or topical antifungal therapy for at least 7 days. Ibrexafungerp (Brexafemme) was not available at the time these guidelines were developed.

Recurrent vulvovaginal candidiasis (RVVC) is a condition that exists when at least four discrete episodes occur in one year or at least three episodes not related to antibiotic use occur in one year.[34] The distinguishing hallmark of recurrent versus persistent infection is the presence of symptom-free intervals. Per the Centers for Disease Control and Prevention (CDC) the condition occurs in < 5% of females but does carry with it a substantial financial impact.[35] Oteseconazole (Vivjoa) was not available at the time these guidelines were developed.

PHARMACOLOGY[36,37,38,39,40,41,42,43,44,45,46,47,48,49]

Drug	Mechanism of Action
clotrimazole	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)	Highly selective inhibitor of fungal cytochrome P450 sterol C-14 alpha-demethylase, which results in fungistatic activity Fungal isolates with reduced susceptibility to other azoles may also show reduced susceptibility to fluconazole; the frequency of occurrence is unknown.
flucytosine (Ancobon)	Enters the fungal cell and is metabolized to 5-fluorouracil, which is extensively incorporated into fungal RNA and inhibits synthesis of both DNA, RNA, and protein synthesis; the result is unbalanced growth and death of the fungal organism
griseofulvin	Fungistatic amounts are deposited in the keratin precursor cell; the new keratin becomes resistant to fungal invasion
ibrexafungerp (Brexafemme)	Inhibits glucan synthase, an enzyme involved in the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall
isavuconazonium (Cresemba)	Isavuconazonium sulfate is a prodrug of isavuconazole, which inhibits the synthesis of ergosterol within the fungal cell membrane via inhibition of the enzyme lanosterol 14-alpha-demethylase, which in turn is responsible for the conversion of lanosterol to ergosterol; this results in a weakening of the cell membrane function and structure
itraconazole (Sporanox, Tolsura)	Inhibits the cytochrome P450-dependent synthesis of ergosterol, a vital component of the fungal cell membrane, resulting in increased cellular permeability and therefore leakage of cellular contents
ketoconazole	Impairs the synthesis of ergosterol, a vital component of fungal cell membranes
miconazole (Oravig)	Inhibits cytochrome P450-dependent 14-α demethylase in the biosynthetic pathway of ergosterol, an essential component of the fungal cell membrane
nystatin	Binds to sterols in the fungal cell membranes which leads to fungistatic activity
oteseconazole (Vivjoa)	Targets the fungal sterol 14α demethylase, an enzyme that catalyzes an early step in cell membrane formation and integrity

Pharmacology (continued)

Drug	Mechanism of Action
terbinafine	Inhibits squalene epoxidase, a key enzyme in fungal sterol biosynthesis; resulting in cell death due to increased cell membrane permeability; fungicidal *in vitro* depending on organism and concentration
posaconazole (Noxafil)	Inhibits cytochrome P450-dependent 14-α demethylase in the biosynthetic pathway of ergosterol which weakens the structure and function of the fungal cell membrane
voriconazole (Vfend)	Inhibits ergosterol synthesis by interacting with the 14-alpha-lanosterol demethylation step, a cytochrome P450 enzyme

PHARMACOKINETICS[50,51,52,53,54,55,56,57,58,59,60,61,62,63]

Drug	Bioavailability (%)	Half-life (hr)	Metabolism	Excretion (%)	CYP 450 Enzyme Inhibition
clotrimazole	negligible absorption	--	Small amount is absorbed and metabolized by the liver	Bile	--
fluconazole (Diflucan)	> 90	20-50	--	Renal: 91	2C9, 3A4
flucytosine (Ancobon)	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	varies with formulation; absorption increases with a high-fat meal	9-24	No active metabolites	Renal , fecal and perspiration excretion	--
ibrexafungerp (Brexafemme)	high-fat meal increases absorption	20	No active metabolites	Renal: 1 Fecal: 90	CYP2C8, CYP3A4
isavuconazonium (Cresemba)	98	130	Rapidly hydrolyzed into active drug	Renal: 45.6 Fecal: 46.1	3A4, 3A5
itraconazole (Sporanox)	55	64	Several metabolites; hydroxy-itraconazole is the major active one	Renal: 35 Fecal: 54	3A4
itraconazole (Tolsura)	nr	34 to 42 (fed conditions)			
ketoconazole	-- (requires acidic pH)	8	Several inactive metabolites	Renal: 13 Bile: 87 (Fecal: 57)	3A4
miconazole (Oravig)	--	24	No active metabolites	Renal: < 1	2C9, 3A4
nystatin	poorly absorbed	--	--	Predominantly feces	--
oteseconazole (Vivjoa)	--	138 days	No active metabolites	Fecal: 56 Urine: 26	BCRP
posaconazole (Noxafil)	-- (suspension: varies based on fed or fasting state) 54 (tablet)	20-66 (suspension) 26-31 (tablet)	No active metabolites	Renal: 13 Fecal: 71	3A4

Pharmacokinetics (continued)

terbinafine	40	200-400	No active metabolites	Renal: 70	2D6
voriconazole (Vfend)	96	dose dependent	N-oxide metabolite is inactive; several other inactive metabolites	Renal: 80-83	2C19, 2C9,3A4

CONTRAINDICATIONS/WARNINGS[64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81]

clotrimazole

Clotrimazole is not indicated for systemic mycoses including systemic candidiasis.

fluconazole (Diflucan)

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 associated with QT prolongation and is a moderate CYP3A4 inhibitor. Therefore, fluconazole is contraindicated with concurrent administration of drugs that prolong the QT interval and are metabolized via CYP3A4. Avoid concomitant administration of fluconazole with quinidine, pimozide, or erythromycin. In addition, concomitant use of fluconazole and voriconazole, a substrate for both CYP2C9 and CYP3A4, should be avoided due the risk of increased exposure of voriconazole. Fluconazole is known to be a strong inhibitor of CYP2C19 as well. Adverse drug events have been reported with concomitant use of agents utilizing this pathway. Additional postmarketing experience has led to reports of adrenal insufficiency, drug reaction with eosinophilia and systemic symptoms syndrome (DRESS), and fixed drug eruptions occurring with fluconazole use. Caution should be used when coadministering fluconazole with HMG-CoA reductase inhibitors (increased risk for rhabdomyolysis and myopathy) or ivacaftor (reduce dose of ivacaftor) or lurasidone (reduce dose of lurasidone).

Fluconazole has been associated with rare reports of anaphylaxis, serious hepatic toxicity, and exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis. Discontinuation of the drug is recommended if skin reactions occur.

Rare cases of serious hepatic toxicity, including fatalities, have occurred, primarily in patients with serious underlying medical conditions. There has been no obvious relationship to total daily dose, duration of therapy, or sex and 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)

Flucytosine is excreted primarily by the kidneys, and renal impairment leads to accumulation of drug. There is a boxed warning associated with flucytosine to use extreme caution in patients with impaired renal function. Monitoring of renal, hepatic, and hematologic status is stressed to prevent progressive accumulation of active drug. In addition, extreme caution in patients with bone marrow depression

should be exercised. Frequent monitoring of hepatic function and of the hematopoietic system is indicated during therapy.

Flucytosine use is contraindicated in patients with complete dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. There is a severe risk of drug toxicity if used in patients with DPD.

griseofulvin

Griseofulvin is contraindicated in patients with porphyria, hepatocellular failure, and in patients with a history of hypersensitivity to griseofulvin.

Griseofulvin should not be prescribed to pregnant patients. If a 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 6 months after completing griseofulvin therapy before fathering a child. 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 1 month after griseofulvin discontinuation. Additionally, patients using non-oral hormonal contraceptives, estrogens, or progestins for hormone replacement therapy may also experience reduced clinical efficacy; dosage adjustments may be necessary.

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.

Lupus erythematosus or lupus-like syndromes have been reported in patients receiving griseofulvin, as well as exacerbating the condition of those with systemic lupus erythematosus (SLE) or lupus-like syndrome.

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.

ibrexafungerp (Brexafemme)

Ibrexafungerp is contraindicated in pregnancy and with history of hypersensitivity to the active ingredient. Due to the risk of fetal toxicity, confirm negative pregnancy status prior to initiation of therapy. Females of reproductive potential should use effective contraception during treatment and for 4 days after the last dose.

isavuconazonium (Cresemba)

Isavuconazonium is contraindicated in patients with hypersensitivity to isavuconazole. Anaphylactic reactions have occurred, some with fatal outcomes. Discontinue use at the first sign of anaphylaxis. Do not use in the presence of strong CYP3A4 inhibitors or strong CYP3A4 inducers. Either can significantly increase or decrease plasma concentrations of isavuconazole.

Isavuconazole is known to shorten the QTc interval, therefore it is contraindicated in those adults with familial short QT syndrome.

Warnings for hepatic adverse drug reactions include increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) that are generally reversible and do not require discontinuation. More severe hepatic reactions such as hepatitis, cholestasis, or liver failure, including death, have been reported in patients with underlying medical conditions. Evaluate hepatic laboratory tests at baseline and during therapy. Discontinue drug if liver disease develops.

Fetal harm may occur when isavuconazonium is administered to pregnant females. Use in pregnancy should be considered only when the potential benefit outweighs risk to the fetus.

itraconazole (Sporanox, Tolsura)

Itraconazole is contraindicated in patients with history of hypersensitivity to the drug, pregnant women, and women considering pregnancy. Concomitant use of drugs metabolized by CYP 3A4 (e.g., simvastatin, lovastatin) is contraindicated with itraconazole. In general, coadministration of drugs that either affect the metabolism of itraconazole or whose metabolism is affected by itraconazole is contraindicated. 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, lev-acetylmethadol (levomethadyl), and dofetilide are contraindicated as concomitant use may result in elevated plasma concentrations of those drugs leading to potentially serious adverse events. See Drug Interaction section for additional drug-drug contraindications.

Itraconazole is contraindicated in patients with ventricular dysfunction as evidenced by congestive heart failure (CHF) or a history of CHF. A boxed 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 IV 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.

A boxed warning regarding drug interactions is now included in the label. There is a list of drugs contraindicated in the presence of itraconazole (see Drug Interactions section). Coadministration of any of these drugs with itraconazole can cause elevations of plasma concentrations thereby increasing or prolonging both the pharmacologic effects and/or the adverse reactions to the drugs. Do not use itraconazole in the presence of CYP3A4 substrates. For example, 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, as is coadministration of itraconazole with ivabradine.

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. Itraconazole 65 mg capsule (Tolsura) is not interchangeable or substitutable with other itraconazole products.

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.

Due to large pharmacokinetic variability in cystic fibrosis patients, consider switching to alternative antifungal therapy when the patient does not respond to itraconazole. Peripheral neuropathy has been reported with long-term therapy. Monitor and evaluate for neurological symptoms.

The itraconazole prescribing information recommends laboratory testing to confirm onychomycosis diagnosis.

ketoconazole

A boxed warning states that ketoconazole has been linked to hepatic toxicities and fatalities. Use in patients with hepatic disease is contraindicated. The presence of viral hepatitis and liver function tests should be assessed prior to therapy, and monitoring of hepatic function is recommended weekly during therapy.[82]

Ketoconazole should not be administered with terfenadine, astemizole, cisapride, or triazolam as concurrent administration has resulted in cardiovascular adverse events.

Ketoconazole tablets should only be used when other effective antifungal therapy is not available or not tolerated. QT prolongation can occur if certain drugs are coadministered with ketoconazole (see interactions chart). QT prolongation has resulted in life-threatening ventricular dysrhythmias such as torsades de pointes.

Adrenal insufficiency has also been reported due to the inhibition of production of adrenal corticosteroids at doses exceeding 400 mg daily. Monitor adrenal function in patients with existing adrenal concerns while they are utilizing oral ketoconazole therapy.

A medication guide outlining the risks associated with oral ketoconazole use has been approved for distribution by the FDA.

miconazole (Oravig)

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. Discontinue miconazole immediately at the first sign of hypersensitivity.

nystatin

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

oteseconazole (Vivjoa)

Use of oteseconazole in those with known hypersensitivity to the drug is contraindicated.

Oteseconazole has the potential to cause fetal harm and is therefore contraindicated in females who are of reproductive potential or who are pregnant or lactating.

posaconazole (Noxafil)

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 (sirolimus toxicity) and ergot alkaloids (ergotism). Posaconazole is also contraindicated in coadministration with the CYP3A4 substrates, 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 HMG-CoA reductase inhibitors primarily metabolized through CYP3A4 due to risk of rhabdomyolysis.

Electrolyte disturbances are known to occur with use of posaconazole; monitor and correct levels of magnesium, potassium, and calcium before and during therapy. Pseudoaldosteronism and pancreatitis also have been reported.

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 require 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 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 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 significantly increases the maximum concentration (Cmax) and area under the curve (AUC) of tacrolimus. Reduce tacrolimus dose by approximately one-third of the original dose upon initiation of

posaconazole treatment. Frequent monitoring of tacrolimus trough concentrations should be performed during and upon discontinuation of posaconazole treatment.

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.

Posaconazole has been known to prolong the sedative/hypnotic effects of midazolam; serum concentration of midazolam may be increased 5-fold. Monitor patients taking concomitant midazolam. In the event signs or symptoms of prolonged hypnosis/sedation signs are noted, have benzodiazepine receptor antagonists available for administration.

Use of posaconazole with vincristine has been associated with not only neurotoxicity, but other serious adverse reactions such as seizures, syndrome of inappropriate antidiuretic hormone secretion, peripheral neuropathy, and paralytic ileus. In patients being treated with a vinca alkaloid, it is advised that use of azole antifungals, including posaconazole, be reserved for those who have no alternative antifungal treatment option.

Use of posaconazole with venetoclax is contraindicated during initiation and during the titration phase in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) due to increased risk of adverse reactions.

terbinafine

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 has been reported. If neutrophil count is $\leq$ 1,000 cells/mm^3, discontinue the drug. Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with terbinafine use as has erythema multiforme, exfoliative dermatitis, and bullous dermatitis. If a progressive skin rash occurs, treatment with terbinafine should be discontinued. DRESS also has been reported.

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 1 year), or permanent. If symptoms of a taste disturbance occur, discontinue terbinafine.

In addition, smell disturbance and loss of smell has been reported. The changes may resolve after discontinuation of treatment but may be prolonged and possibly permanent. If symptoms of a smell disturbance occur, discontinue use.

Depression has been reported with terbinafine use, clinicians should be aware and monitoring for signs and symptoms of depression.

There is also a risk of thrombotic microangiopathy (TMA) associated with use of terbinafine. Some cases have been fatal. Discontinue terbinafine if symptoms consistent with TMA occur. Unexplained thrombocytopenia and anemia should lead to consideration of a TMA diagnosis.

The prescribing information recommends laboratory testing to confirm onychomycosis diagnosis. Terbinafine should not be used in patients with pre-existing liver disease, and rare cases of liver failure have occurred during use.

voriconazole (Vfend)

Due to the risk of arrhythmias and QT prolongation, correct potassium, calcium, and magnesium levels prior to use. Use of voriconazole in those with known hypersensitivity to the active drug or excipients is contraindicated.

Coadministration of voriconazole is contraindicated with CYP3A4 substrates including terfenadine, astemizole, pimozide, quinidine, ivabradine, rifabutin, sirolimus, or ergot alkaloids because increased plasma concentrations of these drugs can lead to QTc prolongation and rare occurrences of torsades de pointes. Voriconazole use with efavirenz 400 mg every 24 hours or higher is contraindicated. Voriconazole should not be given concurrently with sirolimus (increased sirolimus concentrations and decreased voriconazole concentration), rifampin, carbamazepine, and long-acting barbiturates (decreased voriconazole concentrations), high-dose ritonavir 400 mg every 12 hours (decreased voriconazole concentrations), ergotamines, and St. John's wort. Additionally, voriconazole should not be given with rifabutin due to the potential for decreased voriconazole concentration and increased rifabutin concentration. Ergot alkaloids should not be used with voriconazole. Coadministration with naloxegol is contraindicated due to risk of opioid withdrawal symptoms. Use of voriconazole with tolvaptan is contraindicated due to risk of adverse reactions. Coadministration of voriconazole with venetoclax during the therapy initiation and ramp-up phase is contraindicated in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma due to an increased risk of tumor lysis syndrome.

Concurrent administration of oral voriconazole and oral fluconazole has shown to result in an increase in Cmax and AUC of voriconazole by an average of 57% and 79%, respectively. Reduced dosing and/or frequency of voriconazole and fluconazole did not eliminate or decrease this effect. Concomitant administration of voriconazole and fluconazole at any dose is not recommended. Close monitoring for adverse events related to voriconazole is recommended if voriconazole is used sequentially after fluconazole, especially within 24 hours of the last dose of fluconazole.

Voriconazole prescribing information should be consulted for a detailed description of drug interactions and required dosage modifications prior to initiating therapy.

Visual disturbances (including optic neuritis and papilledema) associated with therapy have been reported. Monitor visual function if therapy continues beyond 28 days.

Electrolyte disturbances including hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to initiation of therapy with voriconazole to mitigate 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.

As with other azoles, voriconazole is associated with adrenal dysfunction, especially if corticosteroids of any type or route of administration are used concomitantly. Monitor during and after therapy for signs and symptoms of Cushing's syndrome or adrenal insufficiency and seek medical care immediately if signs or symptoms appear.

Pancreatitis has been reported with voriconazole use. Patients with risk factors for acute pancreatitis (e.g., recent chemotherapy, hematopoietic stem cell transplantation [HSCT]) should be monitored appropriately for development of pancreatitis.

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.

Embryo-fetal toxicity can occur; do not administer to pregnant patients unless the benefit to the mother outweighs the risk to the fetus. Advise those of reproductive potential to use effective contraception during treatment.

Discontinue voriconazole in the event of exfoliative cutaneous reactions. Avoid sunlight due to risk of photosensitivity and use protective measures if sun exposure is unavoidable, such as high sun protection factor sunscreen and protective clothing. The frequency of phototoxicity reactions is higher in pediatric patients. Stringent photoprotection measures are warranted in children and dermatologic follow-up is recommended even after discontinuation of voriconazole therapy.

Skeletal events such as fluorosis and periostitis have occurred with long-term voriconazole therapy. Discontinue use if these events occur.

DRUG INTERACTIONS[83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98]

Numerous drug interactions are associated with antifungal agents. See the Drug Interactions Table.

Due to low systemic absorption, drug interactions with clotrimazole and nystatin are limited.

Clotrimazole is an inhibitor of hepatic cytochrome P450 (CYP) 3A4, and tacrolimus is metabolized by CYP3A4.[99,100] Administration of clotrimazole troches to renal transplant patients receiving tacrolimus caused clinically significant increases in the relative oral bioavailability, time to maximum concentration (Tmax), and trough concentrations of tacrolimus.[101,102] 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.

Fluconazole (Diflucan) is a strong inhibitor of 2C19 and a moderate inhibitor of 3A4 and 2C9. The enzyme inhibiting effect persists up to 5 days after discontinuation of fluconazole. Clinically significant drug interactions have occurred with patients on combinations of drugs that utilize these enzyme systems; monitor patients on combinations of agents which use these pathways.

Ibrexafungerp (Brexafemme) is a substrate of CYP3A4. Drugs that inhibit or induce CYP3A may alter the plasma concentrations of ibrexafungerp and affect the safety and efficacy.

Isavuconazonium follows other azole antifungals in that use with strong CYP3A4 inhibitors or inducers is contraindicated as concomitant use can significantly increase/decrease isavuconazole concentrations.

Flucytosine (Ancobon) 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. 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 Cmax and area under the curve (AUC) of posaconazole thus reducing bioavailability. Avoid concurrent use with efavirenz, phenytoin, rifabutin, or cimetidine unless the benefit outweighs the risks. Frequent monitoring of adverse effects and toxicity of ritonavir and atazanavir should be performed during coadministration with posaconazole.

In patients taking both posaconazole and digoxin, increased plasma concentrations of digoxin have been noted. Monitor digoxin plasma concentrations of patients taking both agents concomitantly.

While some medications that are metabolized through the CYP3A4 system have specific contra-indications, any medication that is metabolized through this pathway and is taken concurrently with posaconazole should be monitored for adverse effects and toxicity. Dose adjustment may need to be considered.

Venetoclax is contraindicated in patients taking posaconazole. If they are to be used together, the venetoclax dose should be cut by 75%.

Patients should be monitored for breakthrough fungal infections while on posaconazole when concurrently taking the proton pump inhibitors (PPIs) 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 Cmax and AUC of posaconazole. Avoid concurrent administration of posaconazole oral suspension with esomeprazole unless the benefit outweighs the risks. Other PPIs have not been studied in combination with posaconazole. The drug interactions with esomeprazole and metoclopramide do not apply to posaconazole delayed-release tablets. There are no drug interactions or dosage adjustments needed when posaconazole delayed-release tablets are concomitantly used with antacids, H2-receptor antagonists, and proton pump inhibitors. Sporanox is known to interact with contraceptives as well; monitor for adverse effects in patients concomitantly using contraceptives.

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

Itraconazole, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred in patients using cisapride, pimozide, methadone, lev-acetylmethadol (levomethadyl), or quinidine, concomitantly with itraconazole and/or other CYP3A4 inhibitors. Coadministration of cisapride, oral midazolam, nisoldipine, felodipine, pimozide, quinidine, dofetilide, triazolam, lev-

acetylmethadol (levomethadyl), lovastatin, simvastatin, ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine), or methadone with itraconazole capsules or oral solution is contraindicated. See package insert for the full listing of drug interactions. Ketoconazole is a strong inhibitor of the CYP3A4 system. Due to this, use of this agent is contraindicated with certain other drugs that are metabolized by CYP3A4.

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.

Although the systemic absorption of miconazole following miconazole (Oravig) buccal 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.

Voriconazole requires dose adjustment in the presence of CYP3A4, CYP2C9, and CYP2C19 inhibitors and inducers. Monitor for adverse reactions or lack of response. Increase the dose when concurrent use of phenytoin or efavirenz occurs.

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 and pimozide

Drug Interactions Table

Consult package inserts for additional details.

Drug	CYP 450 enzyme inhibition	Contraindications	Dose adjustments needed	Monitoring of other drug effects
fluconazole (Diflucan)	2C9, 2C19, 3A4	erythromycin pimozide quinidine verapamil voriconazole - Avoid concurrent use	renal impairment rifampin celecoxib ibrutinib tacrolimus midazolam tolvaptan triazolam	cyclosporine fluconazole ibrutinib warfarin phenytoin sulfonylureas theophylline tolvaptan
flucytosine (Ancobon)	--	--	renal impairment drugs which reduce GFR	anti-neoplastic agents bone marrow suppressants

Drug Interactions Table (continued)

griseofulvin	--	--	barbiturates	warfarin cyclosporine tretinoin, ATRA sunitinib nilotinib
ibrexafungerp (Brexafemme)	3A4, 2C8	Strong and moderate CYP3A4 inducers	Strong CYP3A4 inhibitors	--
isavuconazonium (Cresemba)	3A4	Strong CYP3A4 inducers and inhibitors	Concurrent use is contraindicated	See package insert for details
itraconazole (Sporanox, Tolsura)	3A4	avanafil cisapride disopyramide dofetilide dronedarone eplerenone ergot alkaloids felodipine irinotecan isavuconazole ivabradine levomethadyl lomitapide lovastatin lurasidone methadone midazolam (oral) naloxegol nisoldipine pimozide quinidine ranolazine simvastatin telithromycin ticagrelor triazolam For patients with renal or hepatic impairment: colchicine fesoterodine solifenacin For poor or intermediate CYP2D6 metabolizers or patients who are taking strong or moderate CYP2D6 inhibitors: eliglustat	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

Drug Interactions Table (continued)

Drug	CYP 450 enzyme inhibition	Contraindications	Dose adjustments needed	Monitoring of other drug effects
ketoconazole	3A4	alprazolam cisapride dofetilide eplerenone ergot alkaloids statins isoniazid midazolam nisoldipine pimozide quinidine rifampin triazolam	cyclosporine methylprednisolone tacrolimus See package insert for detailed drug list	digoxin phenytoin sulfonylureas warfarin See package insert for full details
miconazole (Oravig)	2C9, 3A4	--	--	ergot alkaloids oral hypoglycemic phenytoin warfarin
posaconazole (Noxafil)	3A4	cimetidine* efavirenz* ergot alkaloids esomeprazole (suspension)* halofantrine statins phenytoin* pimozide quinidine rifabutin* sirolimus venetoclax	vinca alkaloids calcium channel blockers (3A4 inhibitors) cyclosporine tacrolimus midazolam phenytoin	atazanavir cyclosporine digoxin metoclopramide midazolam ritonavir tacrolimus
terbinafine	2D6	thioridazine	TCAs SSRIs beta-blockers monoamine oxidase inhibitors–type b rifampin	caffeine cimetidine cyclosporine fluconazole theophylline warfarin

*Avoid concomitant use unless benefits outweigh the risks

Drug Interactions Table (continued)

Drug	CYP 450 enzyme inhibition	Contraindications	Dose adjustments needed	Monitoring of other drug effects
voriconazole (Vfend)	2C19, 2C9, 3A4	carbamazepine efavirenz ergot alkaloids everolimus fluconazole ivabradine lemborexant (avoid use) long-acting barbiturates lurasidone naloxegol pimozide quinidine rifabutin rifampin ritonavir (high dose) sirolimus St. John's wort tolvaptan tyrosine kinase inhibitors (avoid use) venetoclax	alfentanil benzodiazepines (midazolam, triazolam, alprazolam) calcium channel blockers corticosteroids cyclosporine ivacaftor letermovir methadone NSAIDS omeprazole phenytoin statins (3A4 inhibitors) tacrolimus vinca alkaloids	coumarin derivatives fluconazole fentanyl glasdegib long-acting narcotics non-nucleoside reverse transcriptase inhibitors oral contraceptives with ethinyl estradiol and norethindrone oxycodone protease inhibitors ritonavir (low-dose) sulfonylureas warfarin

ADVERSE EFFECTS[103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118]

Drug	Nausea	Headache	Rash	Vomiting	Abd. Pain	Diarrhea	Pruritus	Elevated LFT
clotrimazole	reported	nr	nr	reported	nr	nr	reported	15
fluconazole (Diflucan) n=4,048	3.7	1.9	1.8	1.7	1.7	1.5	nr	reported
flucytosine (Ancobon)	reported	reported	reported	reported	reported	reported	reported	reported
griseofulvin	reported	reported	reported	reported	nr	reported	nr	reported
ibrexafungerp (Brexafemme)	11.9	nr	<2	2	11.4	16.7	nr	<2
isavuconazonium (Cresemba)	27.6	16.7	8.6	24.9	16.7	23.7	8.2	17.1
itraconazole (Sporanox) n=112 200 mg daily for 12 weeks	3	10	3-4	reported	4	4	reported	4
itraconazole (Tolsura)	11	4	9	5	2	3	3	3
ketoconazole	3	< 1	nr	3	1.2	< 1	1.5	reported
miconazole (Oravig)	0.7-6.6	5-7.6	nr	0.7-3.8	1.4-2.5	6-9	nr	nr
nystatin	reported	nr	nr	reported	reported	reported	nr	nr
oteseconazole (Vivjoa)	3.6%	7.4%	nr	nr	nr	nr	nr	nr
posaconazole suspension (Noxafil) fluconazole (oral pharyngeal candidiasis)	9-29 11	8-20 9	3-15 4	7-28 7	5-18 6	10-29 13	nr	3-6 5-10
posaconazole delayed-release tablet (Noxafil) (antifungal prophylaxis)	56	30	34	28	23	61	nr	reported
terbinafine n=465	2.6	12.9	5.6	reported	2.4	5.6	2.8	3.3
voriconazole (Vfend) 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

In patients with normal gastrointestinal, renal, and hematologic function, flucytosine is generally associated with few adverse events, although rash, gastrointestinal discomfort, diarrhea (5% to 10%), 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.

Fluconazole (Diflucan) clinical adverse effects were reported more often in patients infected with HIV but followed the same pattern as those patients without HIV. Postmarketing reports of adverse effects with fluconazole include, but are not limited to, fever, asthenia, fatigue, taste perversion, and insomnia (see package insert for full listing).

In the clinical trial, dizziness was also reported in 3.3% of patients treated with ibrexafungerp (Brexafemme) compared to 2.5% treated with placebo.

Incidence of rash with itraconazole was reported more often in immunocompromised patients receiving immunosuppressive medications.

Incidents of pancreatitis have been reported with posaconazole (Noxafil) use. Pyrexia at a rate of 59% has been reported with posaconazole delayed-release tablets.

Terbinafine tablets have been reported to be associated with liver enzyme abnormalities, taste disturbance and flatulence along with those adverse reactions listed in the table.

Voriconazole is reported to be associated with abnormal visual disturbances (21% IV and oral therapy) which resolve with discontinuation of therapy. Fever, chills, tachycardia, and hallucinations are also noted as common adverse reactions. Endocrine disorders to include Cushing's syndrome and adrenal dysfunction have been reported with post-marketing experience. Reported adverse reactions in pediatric patients include pyrexia, epistaxis, hypertension, hypokalemia, cough, thrombocytopenia, peripheral edema, hyperglycemia, tachycardia, dyspnea, hypocalcemia, hypophosphatemia, mucosal inflammation, hallucinations, hemoptysis, hypoalbuminemia, hypomagnesemia, renal impairment, abdominal distention, upper respiratory tract infection, and pancreatitis.

SPECIAL POPULATIONS[119,120,121,122,123,124,125,126,127,128,129,130,131,132]

Pediatrics

Clotrimazole troches have been used in children ages 3 years and older. Nystatin has been used in infants.[133] The safety and efficacy of terbinafine tablets have not been established in pediatric patients.

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 to 200 mg/kg per day are available. No unexpected serious adverse effects were reported.

Safety and effectiveness of griseofulvin have been established for children over age 2 years. Fluconazole safety and effectiveness data exist for children older than 6 months.

Safety and effectiveness of ibrexafungerp (Brexafemme) for treatment of vulvovaginal candidiasis (VVC) and oteseconazole (Vivjoa), for treatment of RVVC, have been established in post-menarchal pediatric females but have not been established in pre-menarchal pediatric females.

Safety and efficacy of isavuconazonium (Cresemba) have not been studied in persons under age 18 years.

Safety and effectiveness of itraconazole have not been proven in pediatric patients; however, patients aged 6 months to 16 years have been treated with itraconazole with no serious unexpected adverse events.

Ketoconazole tablets have been used in children down to age 2 years. A single daily dose of 3.3mg/kg up to 6.6mg/kg has been used for this population. There have been no studies in those under age 2 years.

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.

Safety and effectiveness of posaconazole (Noxafil) oral suspension and delayed-release tablets in pediatric patients less than 2 years of age have not been established. The delayed-release tablets and oral suspension are indicated to prevent invasive aspergillosis and *Candida* infections in patients 13 years and older who are at high risk for these infections. The delayed-release tablets are approved for the treatment of aspergillosis in patients 13 years and older. In addition, the oral suspension is approved for patients at least 13 years of age with oropharyngeal candidiasis.

Voriconazole (Vfend) is indicated for children ages ≥ 2 years. Dosing is weight- and indication-based for this population. There is a higher incidence of photosensitivity and elevated liver enzymes in this age group compared to adults, and a handful of commonly reported adverse reactions. Safety and efficacy in patients younger than 2 years have not been established.

Pregnancy

Clotrimazole and nystatin are Pregnancy Category C. Posaconazole (Noxafil), itraconazole (Sporanox, Tolsura), and miconazole (Oravig) may cause fetal harm as has been shown in animal data.

Previously, ketoconazole, posaconazole, itraconazole were assigned a pregnancy category of C. The category assignments have been replaced with content aligned with the Pregnancy and Lactation Labeling Rule (PLLR). Due to the risk of fetal harm, these drugs should not be used in pregnancy only when the benefit outweighs the risk.

Griseofulvin is Pregnancy Category X and contraindicated in pregnancy. Two cases of conjoined twins have been reported with first trimester use of griseofulvin. Griseofulvin therapy should be discontinued if the patient becomes pregnant during treatment, and potential hazards to the fetus should be explained.

Voriconazole was previously Pregnancy Category D but this was replaced with descriptive text in compliance with the PLLR. Voriconazole can cause fetal harm when administered during pregnancy.

Previously, terbinafine was assigned Pregnancy Category B, but this was replaced with descriptive text in compliance with the PLLR. Available data on use of terbinafine in pregnant women are insufficient to inform of a drug-associated risk of major birth defects, miscarriage, or adverse effects on the mother or fetus.

Retrospective epidemiological studies suggest a potential risk of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with fluconazole during the first trimester. Use during pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus.

Oteseconazole is contraindicated in females of reproductive potential and in pregnant women. Based on animal studies, it may cause fetal harm when administered to pregnant women. In addition, the drug exposure window of approximately 690 days (based on 5 times the half-life of oteseconazole) precludes adequate mitigation of the embryo-fetal toxicity risks.

There are no adequate and well-controlled studies of flucytosine (Ancobon) use in pregnant women. It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Based on animal studies, ibrexafungerp is contraindicated in pregnancy and pregnancy status should be confirmed prior to initiation of therapy.

Previously, isavuconazonium (Cresemba) was a pregnancy category C drug, but its labeling was updated to comply with the PLLR. Sound clinical studies have not been conducted in pregnant women; however, based on animal studies, isavuconazonium may cause fetal harm when administered during pregnancy. Women of reproductive potential should be advised to the potential risk to the fetus and should use an effective method of contraception during treatment and for 28 days after stopping isavuconazonium.

Data with itraconazole (Tolsura) use in pregnant women for the treatment of blastomycosis, histoplasmosis, or aspergillosis are insufficient to provide insight into potential risks in pregnant women. Itraconazole (Sporanox) has received reports of congenital abnormalities in post-marketing experience. Only use during pregnancy if the potential benefit outweighs fetal risk.

Geriatric

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

No dose adjustment is needed for isavuconazonium (Cresemba) in the elderly population. Pharmacokinetics remained unchanged between the younger adults (18 to 64 years) and elderly (≥ 65 years) population.

While the clinical study with ibrexafungerp (Brexafemme) did not include sufficient numbers of patients 65 years and older to establish whether they respond differently from younger individuals, no clinically meaningful differences in the pharmacokinetics of ibrexafungerp were observed between the age groups.

In clinical trials, no overall differences in safety or pharmacokinetics of posaconazole (Noxafil) were detected in patients elderly patients compared to younger adult patients.

Clinical studies of oral terbinafine did not include sufficient numbers of patients aged 65 years and older to determine response compared to younger individuals.

Clinical trials did not include an adequate number of patients > 65 years to inform of differences between oteseconazole compared to younger patients.

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. A dosage adjustment for pediatric patients with hepatic impairment has not been established.

There is limited data available with itraconazole (Sporanox, Tolsura) tablets in patients with hepatic impairment, therefore use with caution. Further, use of itraconazole is strongly discouraged in patients

with elevated liver enzymes or active liver disease or who have experienced liver toxicity with other medications. Liver failure and death have been reported with itraconazole use. Discontinue if signs of liver dysfunction occur.

No dosage adjustment of ibrexafungerp is required in patients with mild hepatic impairment (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B). Administration of ibrexafungerp in patients with severe hepatic impairment (Child-Pugh Class C) has not been studied.

Isavuconazonium does not require dose adjustment with mild or moderate hepatic impairment but has not been studied in the presence of severe liver impairment; therefore, use with caution in patients who have a Child-Pugh Class C rating.

Ketoconazole oral therapy is contraindicated in persons with hepatic impairment. Assess and monitor patients for new and/or worsening of hepatic damage at baseline and weekly during therapy.

Oral terbinafine is contraindicated for patients with chronic or active liver disease.

Oteseconazole is not recommended for use in patients with moderate or severe hepatic impairment based on lack of data for this population. Dosage adjustment is not suggested in those with mild hepatic impairment (Child-Pugh A).

Renal Impairment

Fluconazole is excreted renally as unchanged drug, there is no need to dose-adjust with single dose therapy for vaginal candidiasis, but for renally impaired persons who will receive multiple doses, an initial loading dose of 50 mg to 400 mg should be administered followed by a daily dose based on creatinine clearance. Patients on dialysis should be administered 100% of the recommended dose after each session. On non-dialysis days, administer the dose based on creatinine clearance.

There is limited data available with itraconazole (Sporanox, Tolsura) in patients with renal impairment, therefore use with caution.

Monitor posaconazole oral suspension and delayed-release tablets closely for breakthrough fungal infections in those patients with severe renal impairment.

The use of oral terbinafine in patients with renal impairment (creatinine clearance ≤ 50 mL/min) has not been adequately studied.

Orally-administered voriconazole dosing is not affected by renal impairment; no dosing adjustment is necessary with oral dosing. Avoid IV administration in adult patients with moderate to severe renal impairment (estimated creatinine clearance [CrCl], < 50 mL/min). Dosage adjustment for pediatric patients with renal impairment has not been established.

Oteseconazole is not recommended to be used in those with severe renal impairment (estimated glomerular filtration rate [eGFR], 15 to 29 mL/min) or end-stage renal disease (eGFR < 15 mL/min) based on lack of data in those populations. Adjusting dosage is not suggested in patients with mild to moderate renal impairment (eGFR, 30 to 89 mL/min).

DOSAGES[134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149]

Adult Dosing

Drug	Oral Dosage Forms	Adult Dosage
clotrimazole	10 mg troche	▪ Treatment: One troche (10 mg) 5 times per day for 14 consecutive days ▪ Prophylaxis: One troche (10 mg) 3 times per day
fluconazole (Diflucan)	50 mg, 100 mg, 150 mg, 200 mg tablets; 10 mg/mL, 40 mg/mL suspension	▪ Oropharyngeal candidiasis: 200 mg X 1 dose, then 100 mg daily for at least 2 weeks ▪ Esophageal candidiasis: 200 mg X 1 dose, then 100 mg daily. Doses up to 400 mg/day may be used based on medical judgement. Treat for a minimum of 3 weeks and for at least 2 weeks following resolution of symptoms ▪ Vaginal candidiasis: 150 mg orally X 1 dose ▪ Urinary tract infections and peritonitis: 50 mg to 200 mg daily ▪ Systemic candida infections: optimal dosage and duration have not been established; doses up to 400 mg/day have been studied in small numbers of patients ▪ Cryptococcal meningitis: 400 mg X 1 dose, then 200 mg daily. Dosages up to 400 mg daily have been used. Recommended duration is 10 to 12 weeks. ▪ Undergoing bone marrow transplant: 400 mg daily until neutrophils > 1,000 cells/m^3 for 7 days ▪ Renal impairment for multiple dosing based on creatinine clearance. Loading dose of 50 to 400mg followed by: – Creatinine Clearance > 50 = 100% recommended dose – CrCl ≤ 50 (no dialysis) = 50% of recommended dose – CrCl ≤ 50 (dialysis session) = 100% recommended dose
flucytosine (Ancobon)	250 mg, 500 mg capsules	▪ 50 to 150 mg/kg/day in divided doses every 6 hours
griseofulvin	Microsize: 125 mg/5 mL suspension; 500 mg tablets Ultramicrosize: 125 mg, 250 mg tablets	Microsize: ▪ Onychomycosis: 1 g orally once a day for at least 4 months (fingernails) or at least 6 months (toenails) ▪ Tinea barbae: 500 to 1,000 mg orally once a day until infection has cleared ▪ Tinea capitis: 500 mg orally once a day for 4 to 6 weeks ▪ Tinea corporis: 500 mg orally once a day for 2 to 4 weeks ▪ Tinea cruris: 500 mg orally once a day until infection has cleared ▪ Tinea pedis: 1 g orally once a day for 4 to 8 weeks Ultramicrosize: ▪ Onychomycosis : 750 mg orally in divided doses for at least 4 months (fingernails) or at least 6 months (toenails) ▪ Tinea barbae: 375 mg orally once a day or 375 to 750 mg in divided doses until infection has cleared ▪ Tinea capitis: 375 mg orally once a day or in divided doses for 4 to 6 weeks ▪ Tinea corporis: 375 mg orally once a day or in divided doses for 2 to 4 weeks ▪ Tinea cruris: 375 mg orally once a day or in divided doses until infection has cleared ▪ Tinea pedis: 750 mg orally in divided doses for 4 to 8 weeks

Adult Dosing (continued)

Drug	Oral Dosage Forms	Adult Dosage
ibrexafungerp (Brexafemme)	150 mg tablet	▪ In adult females and pediatric post-menarchal females the dose is 2 tablets (300 mg) twice a day for 1 day (total; 600 mg) ▪ If taking with a strong CYP3A4 inhibitor, reduce dose to 150 mg twice a day for 1 day (total 300 mg)
isavuconazonium (Cresemba)	186 mg capsule (equivalent to 100 mg isavuconazole) (also available as 372 mg vial for IV administration)	▪ Take 2 capsules orally every 8 hours for a total of 6 doses (48 hours) as a loading dose, then take 2 capsules once daily (with or without food); Swallow whole, do not chew or crush ▪ Start the maintenance dose 12 to 24 hours after the last loading dose ▪ Switching between oral and IV is acceptable and does not require a repeat loading dose ▪ Injectable formulation may be reconstituted for nasogastric tube administration; administer within 1 hour of reconstitution
itraconazole (Sporanox)	100 mg capsule; 10 mg/mL solution	▪ Onychomycosis (toenail): 200 mg daily for 12 weeks ▪ Onychomycosis (fingernail): 2 treatment pulses, which consist of 200 mg twice daily for 1 week; The pulses are separated by a 3-week period without itraconazole ▪ Treatment of blastomycosis or histoplasmosis: 200 mg once daily; If no evidence of improvement or progressing disease, the dose can be increased by 100 mg, up to 400 mg daily; Doses greater than 200 mg should be given in 2 divided doses ▪ Treatment of life-threatening situations should include a loading dose of 200 mg 3 times daily for the first 3 days; continue treatment for a minimum of 3 months and until clinical parameters and laboratory tests indicate active fungal infection has subsided ▪ Treatment of aspergillosis: 200 mg to 400 mg daily ▪ Take the capsules with a full meal, swallow whole
itraconazole (Tolsura)	65 mg capsule	▪ Blastomycosis and histoplasmosis: 130 mg (2 tablets) once daily; if no obvious improvement, the dose may be increased in 65 mg increments to a maximum of 260 mg/day (doses > 130 mg/day should be given in 2 divided doses) ▪ Aspergillosis: 130 mg once or twice daily ▪ Treatment of life-threatening situations should include a loading dose of 130 mg 3 times daily for the first 3 days; continue treatment for a minimum of 3 months and until clinical parameters and laboratory tests indicate active fungal infection has subsided. Swallow whole; do not chew, crush, or break. Must be taken with food
ketoconazole	200 mg tablet	▪ 200 mg to 400 mg daily
miconazole (Oravig)	50 mg buccal tablets	▪ One 50 mg buccal tablet to the upper gum region (canine fossa) once daily for 14 consecutive days; Buccal tablet is applied after brushing teeth in the morning; Alternate gum site each day ▪ If the buccal tablet does not adhere or falls off within the first 6 hours, the same tablet should be repositioned immediately; If the tablet still does not adhere, a new tablet should be placed; If the buccal tablet is swallowed within the first 6 hours, the patient should drink a glass of water and a new tablet should be applied only once; If the buccal tablet falls off or is swallowed after it was in place for 6 hours or more, a new tablet should not be applied until the next regularly scheduled dose ▪ Chewing gum should be avoided ▪ Do not chew, crush, or swallow the tablets

Adult Dosing (continued)

Drug	Oral Dosage Forms	Adult Dosage
nystatin	500,000 unit tablets; 100,000 units/mL and 500,000 units/mL suspension	▪ Gastrointestinal candidiasis: 500,000 to 1,000,000 units 3 times daily ▪ Oral candidiasis: 400,000 to 600,000 units 4 times daily
oteseconazole (Vivjoa)	150 mg capsule	▪ 600 mg as a single dose on day 1, then 450 mg as a single dose on day 2, then beginning on day 14: 150 mg once per week for 11 weeks. ▪ If taking with fluconazole: on days 1, 4, and 7 take fluconazole 150 mg; then on days 14 through 20 take oteseconazole 150 mg once daily for 7 days; then on day 28 take oteseconazole 150 mg once per week for 11 weeks
posaconazole (Noxafil)	40 mg/mL oral suspension (brand only); 100 mg delayed-release tablet	▪ Prophylaxis of invasive *Aspergillus* and *Candida* infections: – *Oral suspension:* 200 mg (5 mL) 3 times daily during or immediately following (within 20 minutes) a full meal or with a liquid nutritional supplement or with an acidic carbonated beverage in patients who cannot eat a full meal; for patients who cannot eat nor tolerate a supplement or an acidic carbonated beverage, alternative therapy should be considered – *Delayed-release tablets:* Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day; maintenance dose of 300 mg (three 100 mg tablets) once a day, starting on the second day; tablets should be taken with food to enhance oral absorption; the tablets provide higher plasma drug exposure than does the suspension under both fed and fasted conditions, therefore, the tablet form is the preferred oral formulation – For both dosage forms, duration of therapy is based on recovery from neutropenia or immunosuppression ▪ Oropharyngeal candidiasis *(oral suspension)*: Loading dose of 100 mg (2.5 mL) twice daily on day 1 then 100 mg once daily for 13 days ▪ Oropharyngeal candidiasis refractory to fluconazole and/or itraconazole *(oral suspension)*: 400 mg (10 mL) twice daily; duration to be determined by patient's severity of underlying disease and clinical response ▪ Dosage is not interchangeable between the delayed-release tablets and the oral suspension
terbinafine	250 mg tablet	▪ Onychomycosis (toenail): 250 mg daily for 12 weeks ▪ Onychomycosis (fingernail): 250 mg daily for 6 weeks

Adult Dosing (continued)

voriconazole (Vfend)	50 mg, 200 mg tablets; 40 mg/mL suspension; (also available as 200 mg powder for IV administration, 10 mg/mL following reconstitution)	▪ IV load is required to initiate therapy for all infections except esophageal candidiasis ▪ Invasive aspergillosis, candidemia in nonneutropenic patients and other deep tissue candida infections, or scedosporiosis, or fusariosis: 6 mg/kg every IV 12 hours for the first 24 hours ▪ After the first 24 hours, for invasive aspergillosis, or scedosporiosis or fusariosis: 4 mg/kg IV every 12 hours or 200 mg orally every 12 hours ▪ After first 24 hours for candidemia in nonneutropenic patients and other deep tissue candida infections: 3 to 4 mg/kg IV every 12 hours or 200 mg orally every 12 hours ▪ If the patient's response is inadequate, oral dose may be increased to 300 mg every 12 hours (see Prescribing Information for more details) ▪ For adults weighing < 40 kg, the oral maintenance dose is 100 mg orally every 12 hours; may increase to 150 mg every 12 hours if response is inadequate for maintenance ▪ For concurrent phenytoin or efavirenz therapy, oral and IV dosing should be increased (see Prescribing Information for details) ▪ Oral voriconazole should be taken 1 hour before or 1 hour after a meal

Pediatric Dosing

Drug	Oral Dosage Forms	Ages	Pediatric Dosage
clotrimazole	10 mg troche	> 3 years	▪ Oropharyngeal candidiasis: One troche (10 mg) 5 times per day
fluconazole (Diflucan)	50 mg, 100 mg, 150 mg, 200 mg tablets; 10 mg/mL, 40 mg/mL suspension	6 months to 13 years	▪ Oropharyngeal candidiasis: 6 mg/kg X 1; then 3 mg/kg daily for at least 2 weeks ▪ Esophageal candidiasis: 6 mg/kg X 1; then 3 mg/kg daily for at least 3 weeks; doses up to 12 mg/kg may be used based on medical judgement ▪ Cryptococcal meningitis: 12 mg/kg X 1; then 6 mg/kg once daily; doses up to 12 mg/kg daily have been used ▪ Systemic infections: 6 to 12 mg/kg daily ▪ Pediatric dose should not exceed 600 mg daily ▪ Equivalent dosing

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 Dosing (continued)

griseofulvin	Microsize: 125 mg/5 mL suspension; 500 mg tablets Ultramicrosize: 125, 250 mg tablets	> 2 years	Microsize: ▪ Pediatrics: 10 to 20 mg/kg daily (max: 1 g) given in 1 to 2 divided doses ▪ Children weighing 30 to 50 pounds: 125 mg to 250 mg daily ▪ Children weighing over 50 pounds: 250 mg to 500 mg daily Ultramicrosize: ▪ Pediatrics: 3.3 to 7.3 mg/kg/day ▪ Children weighing 35 to 60 pounds: 125 mg to 187.5 mg daily ▪ Pediatric patients weighing over 60 pounds: 187.5 mg to 375 mg daily
ibrexafungerp (Brexafemme)	150 mg tablet	Post-menarchal females	▪ 2 tablets (300 mg) twice a day for 1 day (total dosage, 600 mg)
ketoconazole	200 mg tablet	> 2 years	▪ 3.3 to 6.6 mg/kg/day
nystatin	500,000 unit tablets; 100,000 units/mL and 500,000 units/mL suspension	Neonates and older	▪ Oral candidiasis: 100,000 to 600,000 units 4 times daily
posaconazole (Noxafil)	40 mg/mL oral suspension; 100 mg delayed-release tablet	2 years to < 18 years who weigh > 40 kg	▪ Prophylaxis against *Aspergillus* and *Candida* infections *(delayed-release tablet):* Loading dose is 300 mg twice daily on day 1; followed by a maintenance dose of 300 mg once daily; duration is dependent on recovery from neutropenia or immunosuppression.
		13 to < 18 years (regardless of weight)	▪ Prophylaxis against *Aspergillus* and *Candida* infections *(oral suspension)*: 200 mg (5 mL) three times a day; duration is based on recovery from neutropenia or immunosuppression ▪ Oropharyngeal *Candidiasis (oral suspension)*: 100 mg (2.5 mL) twice daily on day 1, followed by 100 mg (2.5 mL) once daily; duration of therapy is 13 days ▪ Oropharyngeal *Candidiasis* refractory to itraconazole and/or fluconazole *(oral suspension)*: 400 mg (10 mL) twice daily; duration is based on the severity of the underlying disease and clinical response ▪ Treatment of invasive aspergillosis (*delayed-release tablet*): Loading dose is 300 mg (three 100 mg tablets) twice daily on day 1; followed by a maintenance dose 300 mg (three 100 mg tablets) once daily; recommended total duration of therapy is 6 to 12 weeks; Switching between the IV and delayed-release tablets is acceptable (no loading dose is required when switching) ▪ Dosage is not interchangeable between the delayed-release tablets and the oral suspension

Pediatric Dosing (continued)

Drug	Oral Dosage Forms	Ages	Pediatric Dosage
voriconazole (Vfend)	50 mg, 200 mg tablets; 40 mg/mL suspension; 200 mg powder (10 mg/mL) for IV administration following reconstitution	> 2 years	For patients ages ≥ 15 years, refer to adult dosing; for patients ages 12 to 14 and body weight ≥ 50 kg, refer to adult dosing Initiate therapy with an IV infusion regimen; only consider an oral regimen after there is significant clinical improvement The following dosing is for patients 2 to < 12 years of age or 12 to 14 years of age with body weight < 50 kg: ▪ IV load is required to initiate therapy for all infections except esophageal candidiasis ▪ Invasive aspergillosis, scedosporiosis, fusariosis, and candidemia in non-neutropenics and other deep tissue *Candida* infections: 9 mg/kg every 12 hours for the first 24 hours ▪ Maintenance: 8 mg/kg IV every 12 hours or 9 mg/kg orally every 12 hours (not to exceed 350 mg orally every 12 hours) ▪ Esophageal candidiasis 4 mg/kg IV every 12 hours or 9 mg/kg orally every 12 hours (maximum of 350 mg orally every 12 hours)

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% 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.

Safety and efficacy for the treatment of aspergillosis, blastomycosis, and histoplasmosis with itraconazole (Tolsura) were established in open-label trials.[150]

Aspergillosis

isavuconazole (Cresemba) versus voriconazole (Vfend)

A randomized, double-blind, non-inferiority active-controlled trial which evaluated the safety and efficacy of isavuconazole versus voriconazole for the primary treatment of invasive fungal disease caused by *Aspergillus* species or other filamentous fungi was conducted.[151] Each treatment group included 258 patients. Patients randomized to receive isavuconazole treatment were administered an IV loading dose of 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) every 8 hours for the first 48 hours. Beginning on day 3, patients received IV or oral therapy of 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) once daily. Patients randomized to receive voriconazole treatment were administered voriconazole IV with a loading dose of 6 mg/kg every 12 hours for the first 24 hours followed by 4 mg/kg IV every 12 hours for the following 24 hours. Therapy could then be switched to an oral formulation of voriconazole at a dose of 200 mg every 12 hours. In this trial, the protocol-defined maximum treatment duration was 84 days. Mean treatment duration was 47 days for both treatment groups, of which 8 to 9 days was by an intravenous route of administration. Results for overall success at end of treatment were 35% of isavuconazole treated patients compared to 38.9% of voriconazole-treated patients.

posaconazole (Noxafil) versus voriconazole (Vfend)

A multinational, double-blind study compared safety and efficacy of posaconazole injection and delayed-release tablets to voriconazole for the treatment of proven, possible, or probable invasive aspergillosis infection.[152,153,154] Patients were stratified by mortality risk or high risk for poor outcome (e.g., prior allogeneic bone marrow transplant or liver transplant, or current treatment for relapsed leukemia). Among the 585 patients enrolled, 5 were adolescents 14 to 16 years of age. In the majority of patients (80%), the infection was limited to the lower respiratory tract. Other organs were affected in 11% to 13% of patients. *A. fumigatus* and *A. flavus* were the most commonly identified pathogens. Patients were randomized 1:1 to posaconazole or voriconazole. Those allocated to posaconazole were administered a dose of 300 mg once daily (after a loading dose of 300 mg twice daily on day 1) IV or tablet. Patients who received voriconazole were given a dose of 6 mg/kg twice daily day 1 followed by 4 mg/kg twice daily IV, or oral 300 mg twice daily day 1 followed by 200 mg twice daily. The recommended initial route of administration was IV, but therapy could be initiated via the oral route if the patient was clinically stable and able to tolerate oral dosing. The primary endpoint of all-cause mortality through day 42 in the intent-to-treat population (n=475; who received at least 1 dose) was 15.3% with posaconazole compared to 20.6% with voriconazole (adjusted treatment difference, -5.3%; 95% confidence interval [CI], -11.6% to 1%). In patients with proven or probable invasive aspergillosis (n=334), all-cause mortality through day 42 was 19% with posaconazole and 18.7% with voriconazole (adjusted treatment difference, 0.3; 95% CI, -8.2 to 8.8]).

Esophageal Candidiasis

fluconazole (Diflucan) and voriconazole (Vfend)

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.[155] Patients were on therapy for at least 7 days after clinical signs and symptoms resolved or for a maximum of 6 weeks. Patients underwent endoscopy at

day 43 to determine efficacy. Endoscopy-documented success (98.3% versus 95.1%, respectively), as well as symptomatic success (88% versus 91.1%, respectively), was similar between voriconazole and fluconazole. Visual disturbances were reported in 18% of voriconazole patients compared to 5% with fluconazole. More patients discontinued voriconazole due to laboratory abnormalities or treatment-related adverse effects.

Infection Prophylaxis in Immunocompromised Patients

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.[156] 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 2% of the posaconazole group and 8% in the fluconazole or itraconazole group (absolute reduction, 6%; 95% CI, -9.7 to -2.5; p<0.001). Invasive aspergillosis was significantly lower in the posaconazole group (1% versus 7%, p<0.001). Survival was significantly higher in the posaconazole group (16% mortality) than in the fluconazole/itraconazole group (22% mortality, p=0.04). Serious adverse effects were significantly more common in the posaconazole group (6% versus 2%; 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.[157] Six hundred allogenic 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%, respectively; odds ratio [OR], 0.56; 95% CI, 0.3 to 1.07; p=0.07). Posaconazole was superior to fluconazole in preventing proven or probable invasive aspergillosis (2.3% and 7%; OR, 0.31; 95% CI, 0.13 to 0.75; p=0.006). Overall mortality was similar in the 2 groups; however, the number of deaths from invasive fungal infections was lower in the posaconazole group (1% and 4%, p=0.046). Treatment-related adverse effects were similar in both groups (36% for posaconazole and 38% for fluconazole).

Onychomycosis

terbinafine versus itraconazole (Sporanox)

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.[158] The study included 496 patients diagnosed with toenail onychomycosis caused by a dermatophyte. Patients were randomly assigned to 4 parallel groups: terbinafine 250 mg per day for 12 or 16 weeks or itraconazole 400 mg per day for 1 week in every 4 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% in the 12-week terbinafine group and 80.8% in the 16-week terbinafine group, compared with 38.3% in the itraconazole 12-week study group and 49.1% 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 5-year, blinded, prospective follow-up study to the aforementioned study, the long-term effectiveness of terbinafine was compared to itraconazole in 151 patients.[159] At the end of 5 years, mycologic cure achieved with 1 treatment course was found in 46% and 13% 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% and 48%, respectively, compared to the terbinafine-treated group, 23% and 21%, respectively.

A prospective, investigator-blinded, long-term follow-up (1.25 to 7 years) study comparing 4 treatment regimens with itraconazole and terbinafine was conducted.[160] The 4 regimens were either terbinafine continuous, intermittent, combination with itraconazole, and pulsed itraconazole. Recurrence rate of onychomycosis was the outcome used to determine which of the 4 regimens was the most effective at decreasing the rate of re-infection. Although no statistical significance was found between the dosing regimens, it was determined that itraconazole therapy was associated with higher rates of recurrence (59%) than was terbinafine regimens (32% recurrence rate for continuous and 36% for intermittent). Combining the 2 drugs did not reduce the rate of recurrence of the infection as compared to monotherapy (57% rate of recurrence of infection for combination therapy).

Oropharyngeal Candidiasis

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 5 times daily for 14 days in 577 HIV-positive patients with oropharyngeal candidiasis.[161,162] 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 to 22). Clinical cure was achieved in 61% of miconazole patients compared to 65% of clotrimazole patients (p=NS) in the intent to treat population. Clinical relapse occurred in 27.3% and 27.8% of patients, respectively. Mycological cure (eradication of *Candida* on days 17 to 22) occurred in 27.2% and 24.7% of patients, respectively. Adverse events were similar between treatments.

posaconazole (Noxafil) versus fluconazole (Diflucan)

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.[163] Patients (n = 350) were randomized to posaconazole or fluconazole 200 mg on day 1 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% for posaconazole and fluconazole groups, respectively (95% CI, -6.61 to 5.04). Mycological success was 68% in both arms on day 14, but mycological success on day 42 was 40.6% and 26.4% for posaconazole and fluconazole, respectively (p=0.038). Clinical relapse rates were 31.5% for posaconazole and 38.2% for fluconazole. Adverse effects were similar.

Vulvovaginal Candidiasis

ibrexafungerp (Brexafemme) versus placebo

Non-pregnant, post-menarchal females ≥ 12 years of age with a diagnosis of VVC were enrolled in 2 randomized, placebo-controlled clinical trials to evaluate the safety and efficacy of ibrexafungerp.[164,165,166] A diagnosis of VVC was defined as a vulvovaginal signs and symptoms (VSS) score of ≥ 4 with ≥ 2 signs or symptoms scoring ≥ 2; positive microscopic examination with 10% potassium hydroxide (KOH) in a vaginal sample revealing yeast forms or budding yeasts; and vaginal pH ≤ 4.5. Patients were randomized 2:1 to receive oral ibrexafungerp 300 mg or placebo twice daily for 1 day. The primary endpoint was percentage of patients with clinical cure (complete resolution of signs and symptoms) at the test-of-cure (TOC) visit (day 8 to 14). Secondary endpoints were percentage of patients with mycological eradication (negative culture for *Candida* spp.) at the TOC visit and percentage of patients with complete resolution of symptoms at the follow-up visit (day 25). Trial 1 enrolled 376 patients in the US. Trial 2 enrolled 366 patients in the US and Bulgaria. The modified intent to treat (mITT) population (trial 1: n=290; trial 2: n=278) included only randomized patients with a baseline positive *Candida* culture who received ≥ 1 dose. In both trials, patients receiving ibrexafungerp experienced higher percentages of clinical cure at TOC (trial 1: 50% versus 28%, p=0.001; trial 2: 63.5% versus 44.9%, p=0.009), mycological eradication at TOC (trial 1: 49.5% versus 19%; trial 2: 58.7% versus 29.2%; p<0.001 for both), and complete clinical response at the follow-up visit (trial 1: 59.5% versus 44%, p=0.007; trial 2: 72.5% versus 49.4%, p=0.006) compared to placebo, respectively.

Recurrent vulvovaginal candidiasis (RVVC)

oteseconazole (Vivjoa) versus placebo

Safety and efficacy were established in 3 randomized, double-blind, placebo-controlled trials where RVVC was defined as ≥ 3 acute episodes of VVC in the previous 12 months.[167]

The triple-masked Trial 1 (NCT03562156) and Trial 2 (NCT03561701) were identical in design and enrolled a total of 863 female patients aged ≥ 12 years with RVVC. Pregnant patients were excluded from both trials. The trials consisted of a 2-week induction phase where patients received fluconazole 150 mg orally on days 1, 4, and 7. On day 14, patients who achieved resolution of the acute VVC episode were randomized 2:1 to receive oteseconazole 150 mg once daily for 7 days (n=435) or placebo (n=217), followed by oteseconazole or placebo once weekly for 11 weeks. The primary efficacy endpoint was the proportion of patients with ≥ 1 culture-verified acute VVC episode during the maintenance phase of the study through week 48. In both Trial 1 and Trial 2, treatment with oteseconazole reduced the proportion of patients with ≥ 1 culture-verified acute VVC episode compared to placebo, respectively (Trial 1: 6.7% versus 42.8%; Trial 2: 3.9% versus 39.4%; p<0.001).[168,169]

In the triple masked UltraVIOLET trial (NCT03840616), female patients aged ≥ 12 years with RVVC were randomized 2:1 to receive oteseconazole (n=147) 600 mg on day 1, then oteseconazole 450 mg on day 2, or fluconazole (n=72) 150 mg orally on days 1, 4, and 7. After the 2-week induction phase, patients who achieved resolution of the acute VVC episode moved to the maintenance phase where they received oteseconazole 150 mg or placebo once weekly for 11 weeks. Pregnant patients were excluded from the trial. The primary efficacy endpoint was the proportion of patients with ≥ 1 culture-verified acute VVC episode during the maintenance phase of the study through week 48, including a patient who failed to clear the initial acute VVC episode during the induction phase. Treatment with oteseconazole

reduced the proportion of patients with ≥ 1 culture-verified acute VVC episode compared to fluconazole/placebo (5.1% versus 42.2%, respectively; p<0.001).[170]

META-ANALYSES

A meta-analysis determined mycological cure rate in randomized clinical trials is consistently 76% for terbinafine and 63% for pulse dose itraconazole (Sporanox).[171] Thirty-six randomized, controlled trials evaluated the efficacy of terbinafine, itraconazole, fluconazole (Diflucan), and griseofulvin in the treatment of dermatophyte toenail onychomycosis. 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 ± 3% (18 studies), itraconazole pulse 63 ± 7% (6 studies), itraconazole continuous 59 ± 5% (7 studies), fluconazole 48 ± 5% (3 studies), and griseofulvin 60 ± 6% (3 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.

A meta-analysis completed in 2011 reviewed itraconazole recurrence rates as compared to terbinafine recurrence rates. This analysis concluded that itraconazole had a higher rate of onychomycosis recurrence than did terbinafine.[172]

A Cochrane review found very few comparative trials on which to evaluate efficacy of prophylaxis of oropharyngeal candidiasis in HIV-positive patients.[173] 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.[174] Five additional studies were identified. Only 1 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.

A systemic review with meta-analysis of posaconazole compared to other antifungals for the prevention of invasive fungal infections in immunocompromised patients identified 5 randomized controlled trials (n=1,617) from Embase, Cochrane Central Register of Controlled Trials, and Medline through June 2020.[175] The studies included patients of any age who were at risk of prolonged neutropenia (receiving chemotherapy for hematologic malignancies or transplant recipients on immunosuppressants). Prophylaxis with posaconazole led to a significant 57% lower risk of invasive fungal infections compared to other antifungals (RR, 0.43; 95% CI, 0.28 to 0.66, p=0.0001) as compared to other antifungal agents. In a subgroup analysis, posaconazole was favored over fluconazole (RR, 0.44; 95% CI, 0.28 to 0.7, p=0.0004). No significant difference was detected between posaconazole and other antifungal agents regarding common adverse events reported, such as nausea, vomiting, diarrhea, and liver function abnormalities.

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 for a variety of *Candida* infections, lacking concerns about pH-dependent absorption such as that seen with ketoconazole. Effective therapy for oropharyngeal candidiasis includes fluconazole, itraconazole (Sporanox), nystatin, and clotrimazole. 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. Intravenous loading doses are required during the first 24 hours of voriconazole therapy for all infections except esophageal candidiasis. Posaconazole (Noxafil) oral suspension has an indication for treatment of oropharyngeal candidiasis when refractory to itraconazole and/or fluconazole. Posaconazole delayed-release oral tablets are indicated to treat invasive aspergillosis. Both the posaconazole delayed-release tablets and oral suspension are approved for the prophylaxis of invasive *Aspergillus* and *Candida* infections in patients at high risk for these infections. Nystatin is also used to treat intestinal candidiasis and may be used in infants and children. A new entrant in the oral antifungal class is ibrexafungerp (Brexafemme), but it is only indicated for post-menarchal females with vulvovaginal candidiasis (VVC). Oteseconazole (Vivjoa) is the first and only FDA-approved product for recurrent VVC specifically. Due to the embryo-fetal toxicity risk, use is limited to females not of reproductive potential.[176]

In comparative trials, terbinafine demonstrated higher treatment success rates of toenail onychomycosis in immunocompetent patients compared to itraconazole (Sporanox). 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, isavuconazonium (Cresemba), posaconazole (Noxafil), flucytosine (Ancobon), voriconazole (Vfend), itraconazole (Sporanox, Tolsura), and fluconazole are indicated for treatment and/or prophylaxis.

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