



Indiana Medicaid Therapeutics Committee **Therapeutic Class Review Summary**

Therapeutic Class:

Oral Antifungals

Overview:

Three major types of complications are caused by the approximately 200 known species of fungi that infect humans. These complications are allergies, mycotoxicoses, and mycoses. A few dozen fungi are the etiology for 90% of mycoses. The incidence of superficial and systemic mycotic infections has increased dramatically over the past decade. The two major factors contributing to this shift in epidemiology are related to two specific immunocompromised patient populations: patients undergoing transplantation and chemotherapy and patients with HIV and/or AIDS. In response to the increasing incidence of fungal infections, several oral agents that are effective against systemic fungal pathogens have been developed.

The availability over the past two decades of the azole antifungal agents represents a major advance in the management of systemic fungal infections. The relative broad spectrum of the azoles against common fungal pathogens (*Candida sp.*, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, *Sporothrix schenckii* and *Aspergillus sp*), ease of administration, and limited toxicity are highly attractive features. Fluconazole, itraconazole, ketoconazole, miconazole, voriconazole, and posaconazole are azole antifungals that inhibit the CYT P450 dependent synthesis of ergosterol, the principal sterol in the fungal cell membrane, and are approved to treat systemic mycoses. Griseofulvin is only effective in the treatment of superficial dermatophytes. Terbinafine is a synthetic allylamine derivative that inhibits squalene epoxidase, a key enzyme in sterol biosynthesis in fungi, resulting in a deficiency in ergosterol within the fungal cell membrane and cell death. Terbinafine is approved to treat topical onychomycosis of the fingernails and toenails. Terbinafine oral granules are approved for the treatment of tinea capitis; however, griseofulvin is also effective for this indication. Among the azoles, fluconazole possesses the most desirable pharmacologic properties, including high bioavailability, high water solubility, low degree of protein binding, wide volume of distribution into body tissues and fluids including cerebrospinal fluid and urine, and long half-life. In addition, fluconazole and itraconazole are better tolerated and more effective than ketoconazole. Voriconazole is an azole antifungal agent derived from the structure of fluconazole. It was designed to enhance the potency and spectrum of activity of fluconazole. The indications of voriconazole include invasive aspergillosis, esophageal



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candidiasis, serious fungal infections caused by *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and *Fusarium* spp., in patients intolerant of, or refractory to, other therapy and candidemia in nonneutropenic patients. Posaconazole is the newest of the systemic azole antifungals and is indicated for prophylaxis of invasive fungal infections, treatment of oropharyngeal candidiasis, and treatment of oropharyngeal candidiasis refractory to itraconazole and/or fluconazole. One potential limitation of the azole antifungals is the drug interactions, which are more significant with itraconazole and ketoconazole. Miconazole buccal tablet is a new once daily localized/topical oral therapy for oropharyngeal candidiasis. It is active against *Candida albicans*, *C. parapsilosis* and *C. tropicalis* and may be an alternative to systemic antifungal agents as there is minimal systemic absorption and therefore, less risk of CYT P450-mediated drug interactions.

Though the incidence of mycosis has increased, there remains a limited population in which head-to-head comparative trials for the most common fungi can be conducted. Hence, comparative efficacy data are limited. Studies are available for topical infections such as onychomycosis and systemic infections in the HIV population. Importantly, duration of treatment is based on the severity of the patient's underlying disease, level of immunosuppression, and clinical response.

GENERIC NAME	TRADE NAME	MANUFACTURER	GENERIC
Fluconazole	Diflucan [®]	Pfizer, various	Y
Itraconazole	Sporanox [®]	Janssen	Y
Ketoconazole	Nizoral [®]	Janssen	Y
Miconazole	Oravig [™]	Strativa, division of Par Pharmaceutical	N
Terbinafine	Lamisil [®]	Novartis	Y (tablets only)
Voriconazole	Vfend [®]	Pfizer	N
Griseofulvin	Gris-PEG [®] , Grifulvin [®] V	Various	Y
Posaconazole	Noxafil [®]	Schering Corp	N

Summary:

Selection of an agent for the preferred drug list should be based on spectrum of activity, efficacy, cost and safety. Posaconazole, the newest of the systemic azole antifungals, is indicated for prophylaxis of invasive fungal infections, treatment of oropharyngeal candidiasis, and treatment of oropharyngeal candidiasis refractory to itraconazole and/or fluconazole. Miconazole buccal tablet is a new oral antifungal that provides once daily localized/topical therapy and is only indicated for oropharyngeal candidiasis. Since it has minimal systemic absorption, there is less risk of CYT P450-mediated drug



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interactions. Lamisil oral granules are approved for the treatment of tinea capitis; however, griseofulvin is also effective for this indication. Among the systemic azole antifungals, fluconazole has the most favorable profile. Other oral antifungal agents for topical infections should be reserved for patients who fail topical antifungal agents.