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Review of in vitro activity of sertaconazole nitrate in the treatment of superficial fungal infections

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Abstract

The evaluation of susceptibility patterns of clinical and laboratory isolates of dermatophytes and *Candida* to sertaconazole nitrate has been determined using macrodilution and microdilution test methods in laboratories worldwide. Antimycotics that have been compared to sertaconazole nitrate include itraconazole, clotrimazole, miconazole, and terbinafine. A comparison of the minimum inhibitory concentrations clearly shows differences in potency and spectrum among the various agents. This article reviews the antifungal activity of sertaconazole nitrate against major fungal pathogens that cause and complicate tinea pedis. In light of the new topical formulation of sertaconazole nitrate, this compilation of data from the literature is helpful for relating in vitro data to the tissue concentrations required for effective eradication of cutaneous fungal infections.

Keywords: Dermatophytes; *Candida*; Tinea pedis; Sertaconazole nitrate; ERTACZO®; Antimycotics; Cutaneous fungal infections; Microdilution; In vitro susceptibility; Imidazoles; Resistance; Fungicidal

1. Introduction

Effective topical treatment of superficial fungal infections is an important challenge in dermatology, primary care, and podiatric care settings (Cohn, 1992; Drake et al., 1996). Topical antifungal treatments often have a broad spectrum of action on dermatophytes and yeast, but the high relapse rates and recurrence of symptoms after stopping treatments are common clinical concerns. Untreated or improperly treated superficial cutaneous fungal infections may become chronic and cause significant disability and morbidity. A study by the National Center for Health Statistics found fungal infections to be the most common skin disease in patients aged 1–74 years (Johnson, 1978). Cutaneous *Candida* spp. are ubiquitous: about 18% of healthy people carry the yeast in their oral flora. Candidal colonization of the skin begins at birth and remains asymptomatic until host factors (e.g., obesity, occlusive clothing, antibiotic use) or disorders (e.g., diabetes) induce or increase susceptibility to infection (Hay, 1996). The American Academy of Dermatology estimates that 10–20% of the population is affected by dermatophytes. Of these infections, tinea pedis is the most common, occurring in up to 70% of adults (Drake et al., 1996).

Notably, imidazoles, allylamines, and triazoles are the most effective agents for the topical treatment of fungal infections. The methods to assign clinical relevance to the in vitro measures of fungal susceptibility and resistance to these and other fungicides are not uniformly understood or used by the clinical and research communities, respectively (Rex et al., 2001). To help elucidate the scientific results that affect clinical decisions, this review focuses on the in vitro susceptibility patterns for sertaconazole nitrate, a broad-spectrum imidazole agent that has been used in Europe to treat a wide variety of skin infections caused by dermatophytes, *Candida* spp., and *Malassezia furfur* (Umbert et al., 1992; Torres et al., 2000; Zsolt, 2002) and was recently approved in the United States for the treatment of tinea pedis, which is caused primarily by *Trichophyton mentagrophytes*, *Trichophyton rubrum*, and *Epidermophyton floccosum* (ERTACZO® prescribing information, 2003).

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2. Sertaconazole, novel antimycotic therapy

Sertaconazole nitrate is a new topical broad-spectrum antifungal that was developed to provide an additional agent for the treatment of superficial cutaneous and mucosal infections. Sertaconazole has been tested in vitro against clinical and laboratory isolates of the most common fungi present in superficial tinea and *Candida* infections. Consistent with other imidazoles, 2 modes of action, fungicidal and fungistatic, have been described (Agut et al., 1992a). To enhance the potential of sertaconazole nitrate for antimycotic efficacy (Raga et al., 1992), it was synthesized with a lipophilic benzothiophene ether (Fig. 1) to aid in penetration of the keratinized layers of the skin without absorption into systemic circulation (Farré et al., 1992; Zsolt, 2002; Day, 2005). In addition, molecular changes to the imidazole ring of sertaconazole nitrate has resulted in improved activity against aspergillus, dermatophytes, and Gram-positive bacteria relative to other azoles (Raga et al., 1992; Prats and Mirelis, 1995).

2.1. Dual mechanisms of action

Sertaconazole has 2 primary effects on cell function. First, it inhibits ergosterol synthesis by blockade of the P450-dependent enzyme pathway that catalyzes the methylation of lanosterol to ergosterol, a major constituent of fungal cell wall membranes (Fig. 2) (Elewski, 1993). Second, it binds directly to nonsterol lipids in the membrane, which interferes with the regulation of the permeability of fungal cell membranes. Inhibition of ergosterol synthesis interferes with fungal cell growth, whereas direct interaction with the membrane produces subsequent leakage of intracellular components, particularly adenosine triphosphate, thereby contributing to immediate cell death. As a result, sertaconazole is an effective fungicidal and fungistatic agent (Agut et al., 1992a, Agut et al., 1992b).

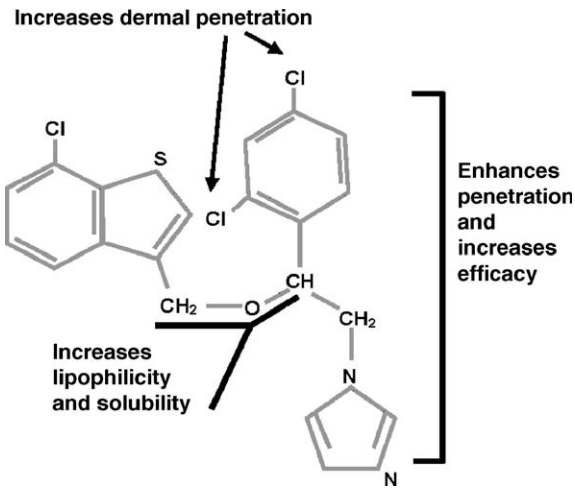

Fig. 1. Molecular structure of sertaconazole. Sertaconazole is a new imidazole that contains a 1-(2-aryl-2-substituted-ethyl) azole group for antifungal action and a lipophilic benzo[*b*]thiophene group that increases penetration of the stratum corneum (Raga et al., 1992).

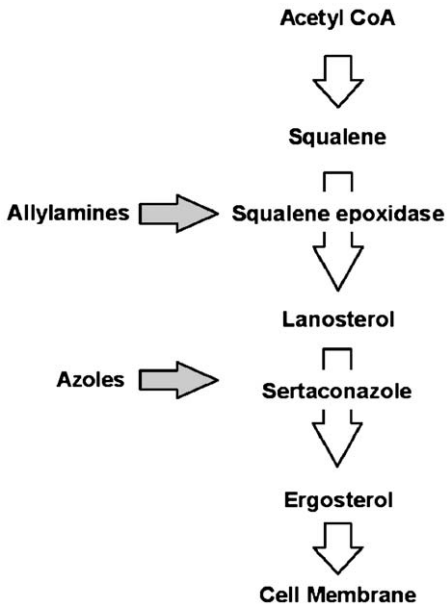

Fig. 2. Mechanism of action of cell wall-specific antifungals: inhibition of cell lipid synthesis and direct effect on cell wall. Imidazoles block the P450-dependent enzyme that catalyzes the methylation of lanosterol to ergosterol, which serves as a major constituent of fungal cell wall membranes. At higher concentrations, imidazoles bind to sterols in the membrane, which produces subsequent leakage of intracellular components and ultimately leads to cell death (Elewski, 1993).

2.2. Clinical use

Sertaconazole is effective against a broad spectrum of organisms that cause superficial cutaneous fungal infections. In the years since the development of sertaconazole, clinical indications have been granted by European and US agencies for fungal infections caused by dermatophytes (*T. rubrum, T. mentagrophytes*, and *E. floccosum*) and for specific infections such as mucocutaneous candidiasis (*Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, and *Candida tropicalis*), and pityrosporosis (*M. furfur*). Secondary indications include treatment of *Trichomonas* infections and complications of fungal infections caused by Gram-positive bacteria (*Staphylococcus*, *Streptococcus*). Clinical trials with sertaconazole nitrate cream 2% show efficacy in the treatment of superficial cutaneous fungal infections (Zsolt, 2002). In clinical studies of tinea pedis in the United States and Europe, sertaconazole was shown to be superior to other topical azoles (bifonazole, miconazole, fluconazole, and clotrimazole) (Product Monograph, 2004; Alomar et al., 1992; Contet-Audonneau et al., 1994; Zsolt, 2002). Furthermore, in European clinical studies of other dermatomycoses caused by *Candida* spp., sertaconazole was shown to be superior to other azoles and terbinafine.

3. In vitro susceptibility of dermatophytes and *Candida* spp. to sertaconazole

Sertaconazole nitrate has been tested with a variety of in vitro methods, all of which show fungistatic activity against

Table 1
Arithmetic mean and ranges of MIC values for sertaconazole, bifonazole, and terbinafine against 53 strains of dermatophytes (Carrillo-Muñoz and Tur-Tur, 1997)

Species (no. tested)	Antifungal Agent	MIC (μg/mL)	
		Range	Mean
T. mentagrophytes (14)	Sertaconazole	0.03–1.25	0.77
	Bifonazole	0.62–2.5	1.19
	Terbinafine	0.03	0.03
T. rubrum (17)	Sertaconazole	0.03 – 0.62	0.09
	Bifonazole	0.03–2.5	0.18
	Terbinafine	0.03	0.03
M. canis (9)	Sertaconazole	0.03–1.15	0.27
	Bifonazole	0.03–2.5	1.73
	Terbinafine	0.03–0.31	0.17
M. gypseum (5)	Sertaconazole	0.31–1.25	0.93
	Bifonazole	0.03–5	2.25
	Terbinafine	0.03	0.03
M. audouinii (1)	Sertaconazole	0.62	0.31
	Bifonazole	2.5	2.5
	Terbinafine	0.03	0.03
E. floccosum (7)	Sertaconazole	0.03–0.62	0.11
	Bifonazole	0.03–1.25	0.2
	Terbinafine	0.03	0.03
All dermatophytes (53)	Sertaconazole	0.03–1.25	0.41
	Bifonazole	0.03–5.0	1.04
	Terbinafine	0.03–0.31	0.05

dermatophytes and fungicidal and fungistatic activity against yeasts (Carrillo-Muñoz and Torres-Rodriguez, 1995; Carrillo-Muñoz and Tur-Tur, 1997; Carrillo-Muñoz et al., 2003; Drouhet and Dupont, 1992; Palacín et al., 1992a). Numerous studies have shown that sertaconazole has potent activity against the most common dermatophytes: *T. rubrum, T. mentagrophytes*, and *E. floccosum* (Carrillo-Muñoz and Tur-Tur, 1997; Carrillo-Muñoz et al., 2003; Carrillo-Muñoz et al., 2004; Drouhet and Dupont, 1992; Palacín et al., 1992a). In comparison studies, sertaconazole inhibited dermatophyte growth as well as or better than the other azoles (e.g., clotrimazole, bifonazole, and miconazole) (Carrillo-Muñoz and Tur-Tur, 1997; Carrillo-Muñoz et al., 2004; Drouhet and Dupont, 1992; Palacín et al., 1992b). When studied in vitro for fungicidal and fungistatic activity against *Candida albicans* and other yeasts, sertaconazole was found to be more potent than terbinafine, clotrimazole, bifonazole, and econazole (Carrillo-Muñoz and Torres-Rodriguez, 1995; Carrillo-Muñoz and Tur-Tur, 1997; Drouhet and Dupont, 1992).

3.1. Sertaconazole in vitro activity against dermatophytes

Palacín et al. (1992a), among the first to report on the susceptibility of fungal species to sertaconazole nitrate, determined the activity of sertaconazole and that of miconazole against several species of dermatophytes. These included *T. mentagrophytes* (7 strains), *T. rubrum* (5 strains), *Microsporum gypseum* (5 strains), and *Microsporum canis* (6 strains). The MIC end point was read at days 7 and 14. The data indicated a rank order for potency of sertaconazole = miconazole for *M. gypseum*, *T. mentagrophytes*, and *M. canis*, and sertaconazole > miconazole for *T. rubrum* (Palacín et al., 1992a). The MIC for *T. rubrum* was 3-fold lower for sertaconazole than miconazole (0.24 versus 0.71 μg/mL, respectively).

Carrillo-Muñoz and Tur-Tur (1997) reported a rank order of potency of terbinafine > sertaconazole > bifonazole against 53 strains of dermatophytes when tested using a broth microdilution method. The average MIC for sertaconazole was lower than that found for bifonazole (mean MIC for 53 strains: 0.41 and 1.04 μg/mL, respectively; Table 1). Each of the dermatophytes in this study was more susceptible to sertaconazole than bifonazole (Carrillo-Muñoz and Tur-Tur, 1997). The susceptibility profiles of the dermatophytes to terbinafine overlapped at the lower ends of the ranges reported for sertaconazole. At 0.03 μg/mL, 5 of the 6 dermatophytes species tested were susceptible to both sertaconazole and terbinafine. However, the overall mean MIC for 53 strains of dermatophytes tested was approximately 8-fold lower for terbinafine than sertaconazole (0.05 and 0.41 μg/mL, respectively; Table 1) (Carrillo-Muñoz and Tur-Tur, 1997).

Despite the excellent activity of terbinafine in vitro, resistance is beginning to emerge as a clinical problem. In a clinical study of tinea pedis in Brazilian patients, 9%

Table 2
MIC for sertaconazole against 114 strains of dermatophytes with resistance to fluconazole (MIC ≥16 μg/mL) (Carrillo-Muñoz et al., 2003)

Species (no. tested)	MIC (μg/mL)			
	MIC range	MIC_{50}	MIC_{90}	GMIC
T. mentagrophytes (41)	0.06–2	0.5	1	0.62
T. rubrum (12)	0.06–2	0.125	0.5	0.19
Trichophyton schoenleinii (1)	1.000	–	–	1.00
Trichophyton tonsurans (4)	0.125–1	–	–	0.35
Trichophyton verrucosum (1)	0.25	–	–	0.25
Trichophyton violaceum	0.5	–	–	0.5
M. canis (16)	0.125–1	0.25	0.5	0.27
M. gypseum (12)	0.125–1	0.5	1	0.5
Microsporum audouinii (6)	0.5–2	–	–	0.89
Microsporum ferrugineum(1)	0.125	–	–	0.125
E. floccosum (4)	0.01–1	–	–	0.07
All dermatophytes (114)	0.01–2	0.5	1	0.41

of *T. rubrum* (2 strains) and 18% of *T. mentagrophytes* (6 strains) isolates tested were not inhibited by terbinafine at concentrations as high as 4 μg/mL (Soares and Cury, 2001). Furthermore, a case of terbinafine-resistant *T. rubrum* was reported in the United States (Mukherjee et al., 2003), suggesting that clinical resistance to this agent may be emerging.

Carrillo-Muñoz et al. (2004) recently reported the susceptibility and resistance of 250 strains of dermatophytes and *Scopulariopsis brevicaulis* to terbinafine, sertaconazole nitrate, and 8 other imidazoles. The data, which were obtained using a commercial agar diffusion method, indicated that 87.6% of the isolates tested were susceptible to sertaconazole nitrate, the highest rate among the imidazoles evaluated. Slightly more species were susceptible to terbinafine (94%) than to sertaconazole nitrate. However, in the fungal strains tested, the resistance to sertaconazole nitrate and terbinafine was identical: 10 of 250, or 4% (Carrillo-Muñoz et al., 2004).

Fungal cross-resistance to imidazoles has been found with in vitro testing of some strains of dermatophytes and *Candida*. Carrillo-Muñoz used the National Committee for Clinical Laboratory Standards broth microdilution method to evaluate the activity of sertaconazole against 114 dermatophytes with reduced susceptibility to fluconazole (Carrillo-Muñoz, 2003). The MIC value for fluconazole against these dermatophytes was ≥16 μg/mL. The MIC range for all dermatophytes tested with sertaconazole was 0.01 to 2.0 μg/mL with the broadest range obtained for *T. rubrum* and *T. mentagrophytes* (0.06–2 μg/mL; Table 2) (Carrillo-Muñoz, 2003).

3.2. Sertaconazole in vitro activity against Candida

Sertaconazole demonstrated potent in vitro fungistatic and fungicidal efficacy against clinical and laboratory isolates of *Candida* spp. as indicated by its low MIC, minimum fungicidal concentration (MFC), and rapid time-kill curves in comparative studies with other antifungals. In the studies reviewed, the fungicidal activity was defined as the minimum concentration of antifungal required to cause a 90% decline in 1 h of the initial inoculum when added during the exponential growth phase of yeast culture, as determined by standard plate count methods. In initial studies designed to compare the in vitro activity of several imidazoles, the rank order of fungicidal effect was sertaconazole > miconazole > clotrimazole > ketoconazole. In time-kill curves, sertaconazole produced a 90% fungicidal effect at 8 μg/mL. Ketoconazole was not fungicidal at concentrations as high as 64 μg/mL and did not reach 90% efficacy even after 4 h (Palacín et al., 1992b).

The fungistatic activity of sertaconazole against azole- and flucytosine-resistant strains of *Candida albicans* was measured at 0.09 μg/mL at 24 h. Even against strains that were not considered susceptible to azoles (i.e., miconazole and ketoconazole), sertaconazole had an MIC at 2.27 ± 4.02 μg/mL, which is a range readily achieved by topical application (Day, 2005; Sertaconazole Product Monograph, 2004; Zsolt, 2002).

Carrillo-Muñoz and Torres-Rodriguez (1995) investigated the in vitro activity of sertaconazole, econazole, and bifonazole against 150 strains of *Candida*, including 73 strains of *Candida albicans*. Their results show that the MIC for sertaconazole was 3-fold lower than that of econazole, suggesting that sertaconazole may be useful clinically in the treatment of cutaneous and mucosal candidiasis (Carrillo-Muñoz and Torres-Rodriguez, 1995).

In another in vitro study of *Candida albicans* (81 strains) and other yeasts (99 strains), sertaconazole was found to be 5- and 10-fold more potent than bifonazole and terbinafine, respectively (Table 3) (Carrillo-Muñoz and Tur-Tur, 1997). Against *Candida albicans* (81 strains), the mean MIC was 1.14 μg/mL for sertaconazole, compared to 3.51 μg/mL for bifonazole and 9.59 μg/mL for terbinafine. The mean MIC for all 180 yeast strains tested was 1.24 μg/mL for sertaconazole, 6.54 μg/mL for bifonazole, and 12.61 μg/mL for terbinafine.

Table 3
Arithmetic mean and ranges of MIC values for sertaconazole, bifonazole, and terbinafine against 180 strains of yeast (Carrillo-Muñoz and Tur-Tur, 1997)

Species (no. tested)	Antifungal agent	MIC (μg/mL)	
		Range	Mean
Candida albicans (81)	Sertaconazole	0.03–5	1.14
	Bifonazole	0.23–20	3.51
	Terbinafine	0.03 to >40	9.59
Candida famata (1)	Sertaconazole	0.03	
	Bifonazole	10	
	Terbinafine	0.15	
Candida glabrata (22)	Sertaconazole	0.03–3.12	0.66
	Bifonazole	0.32–20	4.15
	Terbinafine	0.17 to >40	19.9
Candida guilliermondii (5)	Sertaconazole	0.03–1.87	0.41
	Bifonazole	1.87–5	3.25
	Terbinafine	0.03–20	7
Candida humicola (1)	Sertaconazole	5	
	Bifonazole	20	
	Terbinafine	20	
Candida intermedia (17)	Sertaconazole	2.5	2.5
	Bifonazole	10	10
	Terbinafine	40	40
Candida krusei (14)	Sertaconazole	0.14–0.93	0.77
	Bifonazole	0.93–5	1.87
	Terbinafine	0.03 to >40	12.89
Candida parapsilosis (25)	Sertaconazole	0.03–2.5	0.26
	Bifonazole	1.25–10	3.05
	Terbinafine	0.03–20	2.53
Candida tropicalis (25)	Sertaconazole	0.23–5	1.49
	Bifonazole	1.87–20	8.93
	Terbinafine	0.11 to >40	11.89
All *Candida* spp. (177)	Sertaconazole	0.03–5	1.36
	Bifonazole	0.23–20	7.20
	Terbinafine	0.03 to >40	13.77
Cryptococcus neoformans (3)	Sertaconazole	0.03–0.31	0.12
	Bifonazole	0.15–1.25	0.67
	Terbinafine	0.31–5	2.18
All yeasts (180)	Sertaconazole	0.03–5	1.24
	Bifonazole	0.15–20	6.54
	Terbinafine	0.03 to >40	12.61

4. Discussion

In vitro susceptibility testing may be useful when comparing the spectrum and potencies of various agents against the species of fungi most likely encountered in selected clinical settings. When considered in relationship to clinical parameters such as retention and absorption by skin, the in vitro potency obtained from susceptibility testing as described by the MIC, MFC, and time-kill curves may be useful to predict the clinical response against specific fungal strains.

The MICs of sertaconazole against clinical and laboratory isolates of dermatophytes and *Candida* have been evaluated with both agar and broth dilution MIC methods. When compared to other azole antifungal agents used in the treatment of dermatophytes and *Candida* in these studies, sertaconazole has proven to be among the most potent irrespective of the in vitro test method used. When compared to the allylamine drug terbinafine, the MICs of sertaconazole were comparable for dermatophytes and lower for *Candida* spp.

The clinical efficacy of a given antifungal agent for the treatment of a superficial fungal infection is determined partly by the level of the drug retained in stratum corneum, where the pathogenic yeasts and dermatophytes reside, and further by the persistence of the drug at the location long enough to eradicate fungal growth (Elewski, 1993). Therefore, values of MICs and MFCs obtained in vitro may be used as indicators for the relative susceptibility of fungi to the tested agents, but these values are not sufficient in and of themselves to predict the clinical outcome for topical antifungals in vivo. Rather, these measurements are more practically linked with therapeutic outcome when integrated with pharmacokinetic data such as the maximum concentration of drug in serum (C_{max}) and area under the curve of a drug in human subjects. The ratio of the area under the curve or C_{max} achieved in the stratum corneum to the MIC for the infecting organism may provide the best prediction of clinical outcome (Rex et al., 2001).

Pharmacokinetic studies of sertaconazole nitrate 2% cream performed in healthy volunteers showed that the drug is retained in the skin without absorption into plasma after topical administration. After application of 100 mg of 2% sertaconazole nitrate cream to healthy volunteers, concentrations in the stratum corneum were measured at 1409 μg/mL at baseline and 14 550 μg/mL (C_{max}) at peak absorption at 24 h (Palacín, 2002). In a similar study, Day (2005) showed that over a 48-h exposure period, approximately 38% of the applied dose, or 800 μg, penetrated the skin. These results are considerably higher than the concentrations (MICs) required in susceptibility studies to eradicate fungal growth in vitro. Thus, a short course of treatment with sertaconazole for 4 weeks will give ratios of C_{max}/MIC >1000 for dermatophytes and *Candida*. This level of exposure should be sufficient to obtain successful mycologic cure rates of the major dermatophytes and yeast that cause superficial fungal infections; however, at present, there is insufficient data relating clinical outcome to drug exposure and MIC to allow us to assign a predictive value to these parameters.

5. Summary

In the past decade, the incidence of fungal infections has increased. As the number of people with chronic exposure or predisposing conditions such as diabetes rises, opportunistic fungal infections will continue to emerge. In immune-competent patients, the majority of uncomplicated, superficial mycoses are yeast and tinea infections, caused mainly by *Candida* spp. and dermatophytes, respectively. Over-the-counter use of clotrimazole, miconazole, and terbinafine is usually effective in this setting. In relapsing, recurring, and worsening cases, however, it is important to curtail the prolonged use of these remedies and commence appropriate therapeutic regimens based upon in vitro antifungal susceptibility data and available clinical data against the specific fungal etiologic agent.

Sertaconazole nitrate is a broad-spectrum antifungal that is capable of penetrating the stratum corneum and producing fungicidal and fungistatic results. Comparison of in vitro susceptibility testing showed that dermatophytes are more susceptible to sertaconazole than to bifonazole or miconazole. Even dermatophytes that are resistant to fluconazole have been shown to be susceptible to sertaconazole. In addition, the fungistatic activity of sertaconazole is superior to that of terbinafine against 180 strains of *Candida* and other yeasts, and specifically *Candida albicans*, with MICs for sertaconazole 10-fold lower than terbinafine (Carrillo-Muñoz and Tur-Tur, 1997).

In clinical use, sertaconazole nitrate cream 2% is highly effective and safe in treating superficial cutaneous mycoses. After its introduction in Europe in 1992, independent clinical studies of sertaconazole demonstrated the drug's efficacy against the major dermatophytes that cause tinea pedis, as well as *Candida*. In the United States, sertaconazole nitrate is indicated for topical treatment of interdigital tinea pedis caused by *T. rubrum, T. mentagrophytes*, and *E. floccosum*.

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