EXPERT REVIEWS

Sertaconazole: an antifungal agent for the topical treatment of superficial candidiasis

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Sertaconazole is a useful antifungal agent against mycoses of the skin and mucosa, such as cutaneous, genital and oral candidiasis and tinea pedis. Its antifungal activity is due to inhibition of the ergosterol biosynthesis and disruption of the cell wall. At higher concentrations, sertaconazole is able to bind to nonsterol lipids of the fungal cell wall, increasing the permeability and the subsequent death of fungal cells. Fungistatic and fungicidal activities on *Candida* are dose-dependent. The antifungal spectrum of sertaconazole includes deramophytes, *Candida*, *Cryptococcus*, *Malassezia* and also *Aspergillus*, *Scedosporium* and *Scopulariopsis*. Sertaconazole also shows an antimicrobial activity against streptococci, staphylococci and protozoa (*Trichomonas*). In clinical trials including patients with vulvovaginal candidiasis, a single dose of sertaconazole produced a higher cure rate compared with other topical azoles such as econazole and clotrimazole, in shorter periods. Sertaconazole has shown an anti-inflammatory effect that is very useful for the relief of unpleasant symptoms

Keywords: antifungal • azole • *Candida* • candidiasis • mycoses • onychomycoses • oral • sertaconazole • thrush • vulvovaginal

Superficial fungal infections of skin, hair, nails and oral and genital mucosa are among the most widespread human diseases, and their incidence continues to rise, with *Candida* and the dermatophytes being the principal etiological agents [1]. More than a quarter of healthy persons harbor *Candida* in their oral, digestive, skin or genital microbiota. *Candida* colonization of human surfaces begins at birth and can remain asymptomatic until some factors or diseases, such as antibiotic treatment, dentures, diabetes, obesity, occlusive clothing and so on induce or increase the susceptibility of the host to candidiasis. Oral, skin and gynecological candidiasis are frequent medical problems and finding an effective topical treatment has become an important challenge in dentistry, dermatology, gynecology and primary care [2–5].

Oral candidiasis is a significant source of morbidity, as it can cause chronic buccal pain or discomfort upon mastication, limiting nutrition intake in the elderly or immunodeficient patients. There are mulitple clinical presentations of oral candidiasis (Table 1). Most cases of oropharyngeal and esophageal candidiasis are caused by *Candida albicans*, either alone or in mixed infection. Symptomatic infections caused by *Candida glabrata*, *Candida tropicalis* and *Candida krusei* have been described. Most patients are treated with topical antifungal agents, such as amphotericin B, nystatin or miconazole, which are useful for the initial episodes. Inadequate management of oral candidiasis is related with relapse episodes and higher recurrence rates of oral candidiasis. This can contribute to chronic infection and cause significant disability and morbidity. These complications are more frequent in HIV-infected patients, where symptomatic relapses may occur, antifungal resistance may develop or emergent species, such as *Candida dubliniensis*, are implicated [6,7].

Vulvovaginal candidiasis (VVC) is a very common disease presenting with pruritus, irritation, vaginal soreness, external dysuria and dyspareunia, often accompanied by a change in vaginal discharge. Signs include vulvar edema, erythema, excoriation, fissures and a white, thick, curd-like vaginal discharge. VVC is usually

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Table 1. Clinical manifestations of superficial candidiasis and *Candida*-associated lesions.

Location	Clinical manifestation	Main species implicated	Ref.
Oral mucosa	Acute oropharyngeal candidiasis: pseudomembranous candidiasis or oral thrush; erythematous candidiasis; hyperplastic candidiasis	*Candida albicans*; *Candida glabrata*; *Candida tropicalis*; *Candida dubliniensis*†	[3,6,84,85]
	Denture stomatitis or chronic atrophic stomatitis	*C. albicans*	
	Angular cheilitis or perlèche	*C. albicans*	
	Candida leukoplakia or chronic hyperplastic candidiasis	*C. albicans*	
	Midline glossitis or median rhomboid glossitis	*C. albicans*	
Genital mucosa	Acute vulvovaginal candidiasis (uncomplicated and complicated)	*C. albicans*; *Candida glabrata*	[3,8,85]
	Recurrent vulvovaginal candidiasis	*C. albicans*	
	Candidal balanitis and balanoposthitis	*C. albicans*; *C. glabrata*	
Skin	Intertrigo and *Erosio interdigitalis blastomycetica*	*C. albicans*; *C. tropicalis*	[9,10,85]
	Candida folliculitis	*C. albicans*	
	Candida paronychia and onychomycosis	*C. albicans*; *Candida parapsilosis*; *C.tropicalis*	
	Generalized cutaneous candidiasis	*C. albicans*; *C. tropicalis*	

†In HIV-infected patients suffering from recurrent episodes of oropharyngeal candidiasis.

caused by *C. albicans*, but it can also be caused by other species of *Candida* that are less susceptible to azoles, such as *C. glabrata* or *C. tropicalis*. Recurrent VVC is defined as more than four episodes of symptomatic VVC within 1 year and is usually caused by azole-susceptible *C. albicans*. VVC can be effectively treated with either single-dose or short-course therapy using topical antifungal drugs. Complicated VVC requires daily topical therapy administered intravaginally for weeks, or multiple doses of oral fluconazole. Azole-resistant *C. albicans* infections are extremely rare. However, after the control of contributing factors, induction therapy with 2 weeks of a topical or oral azole followed by a suppressive regimen for months can be helpful [3,5,8]. Moreover, onychomycosis and other superficial candidiasis are common causes of morbidity (Table 1) [9,10]. Although miconazole and econazole are frequently used for the management of oral and genital candidiasis, there are new antifungal agents for topical use, such as sertaconazole, which offers clinical advantages over these older drugs. There are many questions to be solved on the selection of the most proper agent for the treatment of superficial candidiasis. For these reasons, this review focuses on the efficacy of sertaconazole as topical antifungal agent for the management of *Candida* infections, especially for superficial candidiasis, such as vulvovaginitis, with a high prevalence and a high rate of recurrence.

Sertaconazole

Sertaconazole nitrate (FI-7045; nitrate salt of 7-chloro-3-[1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethoxy-methyl] benzo[b]thiophene; $C_{20}H_{16}O_4N_3Cl_3S$; molecular weight 500.8 Da; CAS 99592-32-2) is a broad-spectrum topical antifungal agent that belongs to the azole class of drugs, having a benzothiophene-associated radical and high lipophilia as differential characteristics [11,12]. Sertaconazole penetration of the keratinized layers of the skin is due to its synthesis reaction with lipophilic benzothiophene ether [13]. In the same way, these procedures assess a molecule without systemic absorption [13]. In addition, molecular changes to the imidazole ring of sertaconazole nitrate improve its *in vitro* antifungal activity obtained against *Aspergillus*, *Candida*, dermatophytes and Gram-positive cocci in comparison with other molecules from the same antifungal class [11,12]. The high stability of sertaconazole nitrate was demonstrated under different physical and chemical conditions [12].

Mechanisms of action of sertaconazole

There are three main antifungal drug targets in *Candida*: the cell membrane, cell wall and nucleic acids (Figure 1) [14]. The azoles interfere with the ergosterol biosynthetic pathway by inhibiting the cytochrome P450-dependent 14α-lanosterol demethylase or Erg11p, encoded by the *ERG11* gene. Inhibition of 14α-lanosterol demethylase reduces the ergosterol content in the fungal cell wall membrane and results in the accumulation of toxic sterol pathway intermediates, which inhibit cell growth. In addition, azoles are usually fungistatic.

Sertaconazole inhibits the ergosterol biosynthesis and also, as an additional effect, binds to nonsterol lipids in the cell membrane as other azoles do, altering the cell viability [15]. The inhibition of ergosterol biosynthesis is determined by inhibiting the P450-dependent Erg11p enzyme. In this way, the P450-dependent Erg11p enzyme is not able to catalyze the methylation of lanosterol to ergosterol, resulting in a damaged fungal cell membrane without the main bioregulator of fluidity, asymmetry and integrity [16–20]. Sertaconazole interacts with its biosynthetic route, depleting the levels of ergosterol and affecting the integrity of the cell producing lanosterol which damages the cellular architecture, fluidity and membrane permeability [19,20]. Interaction between the azole molecule and the iron atom of the hemo group leads to the inactivation of the enzyme 14α-lanosterol demethylase. Under these conditions the blockade of yeast mycelium transformation has been described. This action could prevent the adhesion of the fungus to the human surfaces, considered an essential step to start the infection [21,22]. Even at lower MICs, sertaconazole is able to produce the inhibition of the hypha development and the accumulation of shorter, less developed and clustered blastoconidia [19,20,22,23].

Additionally, sertaconazole binds directly to nonsterol lipids in the membrane without relation to ergosterol synthesis, interfering with the regulation of its permeability and producing leakage

of intracellular components, particularly ATP, in a similar way to that observed in miconazole action and over that obtained with ketoconazole [24]. Both mechanisms are sertaconazole dose-dependent which can be an effective fungistatic and also fungicidal drug by direct interaction with the cell membrane and disrupting the fungal growth [21,24,25]. In *C. albicans*, the direct damage to cell membrane is produced at sertaconazole IC_{50} of 1.15×10^{-7} mol/l [2,15,21,24–26]. This fungicidal effect also depends on the cell growth phase and takes place after 1 h of cell–drug contact at concentrations higher than sertaconazole MIC requiring between 5 and 10 h of contact [21,22,24–26]. The fungicidal activity is achieved at high concentrations of sertaconazole driving to an increased cell permeability and causing intracellular ATP leakage, damage to the cytoskeleton and lysis of cell organules, thus reducing the number of viable cells by up to 90% [2,19–22,24,27]. This fungicidal action seems to be higher than those observed in other azoles. ATP leakage due to the action of 500 µg/ml of sertaconazole (84.3%) was higher than obtained by 500 µg/ml of miconazole (76.9%). A similar ATP leakage (77.1%) was obtained using 1000 µg/ml of ketoconazole [24]. Other azoles, such as bifonazole, clotrimazole or ketoconazole, only showed a fungistatic activity with the same contact times and drug concentrations [27,28].

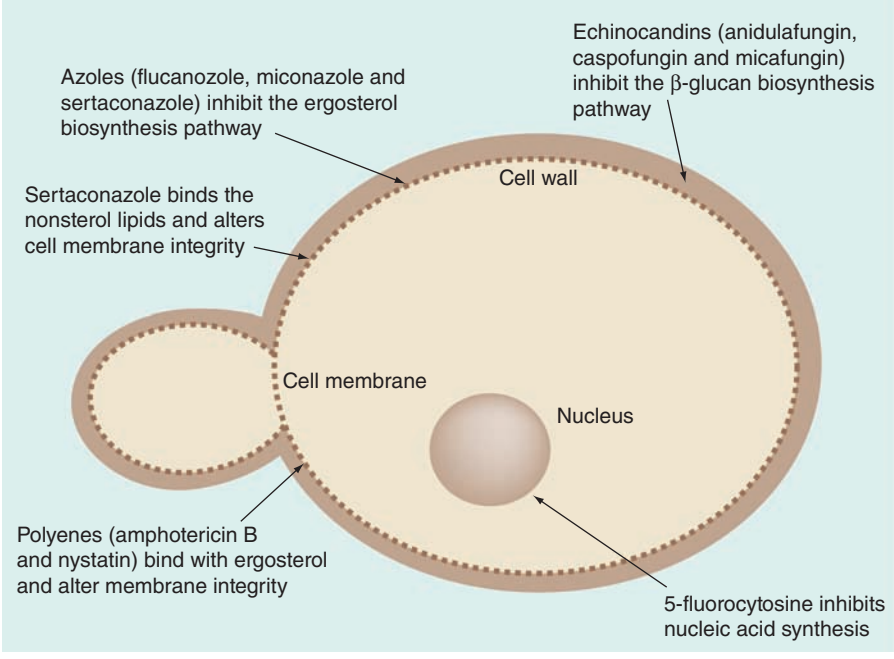

Figure 1. Site of action of antifungal drugs in yeast-like cells.

Antimicrobial spectrum of sertaconazole

Sertaconazole has been demonstrated to be active *in vitro*, compared with other antifungal agents used in the treatment of superficial candidiasis (Table 2) [2,26,29]. Some references from unstandardized and standardized studies showed the *in vitro* activity of sertaconazole as a fungistatic and fungicidal antifungal by using pathogenic *Candida* clinical isolates, providing low MIC and minimal fungicidal concentration (MFC) values, joined with rapid time-kill curves [2,12,20,22,25,26,28–42]. In these comparative studies, the rank order of described *in vitro* fungicidal effect was sertaconazole > miconazole > clotrimazole > ketoconazole. In time-kill curve studies, sertaconazole concentrations of 8 µg/ml, were able to develop a 90% of fungicidal effect, while ketoconazole was not fungicidal at concentrations as high as 64 µg/ml without these efficacy [27]. Ketoconazole did not demonstrate any fungicidal action at drug concentrations as high as 64 µg/ml, although it developed a 90% efficacy [27]. The fungistatic activity of sertaconazole against other azoles and 5-fluorocytosine-resistant isolates of *C. albicans* was achieved at 0.09 µg/ml at 24 h. Sertaconazole showed MIC values of 2.27 ± 4.02 µg/ml, concentrations readily achieved by topical application, against yeast-like isolates resistant to miconazole and ketoconazole [2]. Carrillo-Muñoz and Torres-Rodriguez studied the *in vitro* activities of sertaconazole, econazole and bifonazole against 150 clinical isolates of *Candida*, including 73 *C. albicans* isolates. They observed that the MIC for sertaconazole was threefold lower than that of econazole [39]. In a posterior study, Carrillo-Muñoz and Tur-Tur observed that sertaconazole was found to be five- and ten-fold more potent than bifonazole and terbinafine against 81 isolates of *C. albicans* and 99 isolates of other yeasts. The mean MICs for *C. albicans* and the rest of isolates tested were 1.14 and 1.24 µg/ml for sertaconazole, 3.51 and 6.54 µg/ml for bifonazole and 9.59 and 12.61 µg/ml for terbinafine, respectively [38].

Imidazoles exhibit different antifungal actions depending on the species of *Candida*: *C. glabrata*, *C. krusei* and *C. tropicalis* seem to be less susceptible to miconazole and clotrimazole than to sertaconazole (Table 2) [2,22,26,28,31,42]. There is a low percentage of *in vitro* resistance to sertaconazole in comparison with bifonazole, clotrimazole and miconazole, which only exhibits a lower fungicidal activity [20,26,28]. Something similar is observed when sertaconazole is compared with econazole, fluconazole, itraconazole, ketoconazole or tioconazole [20,32,43]. There is no evidence of induced *in vitro* resistance of *C. albicans* or *C. tropicalis* when exposed to repeated subinhibitory concentrations of sertaconazole [22,25]. Clinical failure has been associated in some cases with discontinued treatments after clinical improvement without mycological cure within the first weeks. In these cases, the dual fungistatic and fungicidal activity of sertaconazole could improve the compliance and reduce the possibility of recurrence of superficial candidiasis [28].

Sertaconazole is also active against other fungi, being more active than other imidazole derivatives, such as miconazole, which shows partial inhibition concentrations <0.04 µg/ml, although this activity depends on the fungal species studied [22,25–27,32,34,44]. Of special interest is the additional fact that sertaconazole also has an *in vitro*

Table 2. Comparison of *in vitro* antifungal activities of sertaconazole and other antifungal agents against clinical isolates of different species of *Candida*.

Species	Geometric mean MIC (μg/ml) of antifungal drug									Ref.
	n	*STZ*	*BFZ*	*FLZ*	*TRB*	*CIC*	*AMR*	*ECZ*	*NAF*	*MNZ*	
Candida albicans	5	0.15	16	1	4.29	0.77	2.41				[35]
	81	1.14	3.51		9.54						[38]
	73	1.02	3.6					2.24			[39]
	65	0.34	13.2						16.3		[40]
	10	4.64								5.66	[22,27]
	20	0.21								0.41	[25]
	30	0.06†		4							[43]
	10	4.64								5.6	[11]
Candida glabrata	3	0.63	0.65	5.04	6.35	1	16				[35]
	22	0.66	4.15		19.9						[38]
	16	0.78	4.09					2.39			[39]
	13	0.4	10.6						23.9		[40]
	5	0.09								0.09	[25]
	11	0.25†		64							[43]
Candida guilliermondii	4	0.54	10.37	1.09	0.65	2	7.34				[35]
	5	0.41	3.25			7					[38]
	5	0.51	3.87								[39]
	4	13	14						23.7		[40]
Candida krusei	3	0.03	8.98	2.44	0.48	0.79	3.18				[35]
	14	0.77	1.87			12.89					[38]
	13	0.38	2.20					0.91			[39]
	9	1.27	14.2						18.2		[40]
	3	0.18								0.18	[25]
	15	1†		64							[43]
Candida parapsilosis	30	0.27	12.26	0.68	1.62	1.72	4.87				[35]
	25	0.26	3.05			2.53					[38]
	22	0.31	3.76					0.75			[39]
	25	0.3	6.73						3.43		[40]
	18	0.25†		8							[43]
Candida tropicalis	3	1.41	16	5.65	11.31	1.59	12.7				[35]
	27	1.49	8.93			11.89					[38]
	21	1.67	9.51					3.14			[35]
	18	0.44	18.8						9.05		[40]
	20	2†		64							[43]

†Value corresponds to 90% inhibited isolates.
AMR: Amorolfine; BFZ: Bifonazole; CIC: Ciclopyrox olamine; ECZ: Econazole; FLZ: Fenticonazole; MNZ: Miconazole; NAF: Naftifine; STZ: Sertaconazole; TRB: Terbinafine.

activity against *Streptococcus*, *Staphylococcus*, *Listeria monocytogenes*, *Gardnerella vaginalis* and *Trichomonas vaginalis*, which are microorganisms involved in skin and mucosal infections [20,22,26,45]. The activity of sertaconazole against Gram-positive bacteria is observed with a lower geometric MIC (0.88 μg/ml) than with miconazole (0.97 μg/ml) and clotrimazole (1.44 μg/ml) and this azole can be considered for the treatment of genital infections caused by two or more pathogens [20,22]. These *in vitro* antifungal, antibacterial and antiprotozoal activities are obtained at concentrations lower than those reached after the topical administration of sertaconazole. In addition, sertaconazole does not inhibit lactobacilli and other frequent members of the healthy vaginal microbiota, avoiding the interference with the host defense mechanisms [20].

Some experimental studies performed in mice and guinea pigs confirmed the antifungal usefulness and *in vivo* efficacy of topical formulations of sertaconazole nitrate (doses of 2%) in some mycoses [27,46,47]. In the case of the model of vaginal candidiasis, those studies revealed a therapeutical improvement of the clinical and microbiologic symptoms when sertaconazole was used over rates obtained by other imidazole derivatives. The treatment during 3 days with sertaconazole in an animal model of vaginal candidiasis demonstrated a better prophylactic and curative effect than with miconazole, with a greater recovery of viable yeast cells (97.7 and 77.5%, respectively) [46,47].

Pharmacokinetics & pharmacodynamics of sertaconazole

Some factors affect the clinical efficacy of an antifungal agent, especially in the treatment of a superficial fungal infection. Drug concentration in the horny layer of the skin (*stratum corneum*),

where the pathogenic yeasts and dermatophyte fungi can multiply, is associated to the retention time at this location to eradicate the fungal growth [48]. MIC and MFC values can be indicative in establishing the reliable susceptibility of fungi to antifungal agents but are not sufficient to predict the clinical outcome for topical antifungals. Only pharmacokinetic data, such as the C_{max} and the area under the curve of a given antifungal drug in humans and MIC/MFC values can be predictive of the clinical outcome. Nevertheless, a good index of the best prediction of clinical outcome is provided by the ratio of the area under the curve or C_{max} achieved in the *stratum corneum* and the MIC for the infecting organism [49].

Sertaconazole is available under different formulations (tablets, pessaries, 2% solution and 2% cream) that have been adapted to the main clinical manifestations of superficial candidiasis and other mycoses and do not show significant differences in terms of clinical efficacy or mycological cure [50]. Sertaconazole penetrates well into the *stratum corneum* and this enhanced ability could be related to the synthesis procedure of the molecule and the presence of lipophilic benzothiophene ether [28]. The cutaneous absorption after topical application at increasing doses varied from 5 to 9.2% after 1 h to 46.5% at 2 h, while values of 50% of the applied dose are obtained at 4 h and of 71% at 24 h [13,51]. Penetration of sertaconazole is achieved just after administration (at baseline, 0 h) in the upper and middle skin layers up to 1% of the dose applied, and these concentrations are increased to a saturation of the drug in the upper layers at 30 min and at 3 h in the lower layers, verifying a gradient of concentrations from outside to inside of skin (100–120 µg in the upper skin layer, 20–30 µg in the middle layer and 5–15 µg in the lower layer) [51].

Sertaconazole is retained in the skin without absorption into the plasma after topical administration of 2% sertaconazole cream in healthy volunteers [20,52]. Pharmacokinetic studies performed with healthy volunteers with administration of 100 mg of 2% sertaconazole nitrate cream, concentrations in the *stratum corneum* offered values of 1409 µg/ml (0 h) and 14,550 µg/ml with a peak absorption at 24 h (C_{max}) [20,52]. Susilo *et al.* reported *stratum corneum* concentrations higher than those required to inhibit the growth of most species of *Candida*; 1409 µg/ml at baseline, 7030 µg/ml at 30 min and a C_{max} of 9029 µg/ml at 3–48 h after administration [51].

Sertaconazole is retained in the skin for long periods of time (half-life of 60 h) [20,51,52]. Values of recovered sertaconazole from the skin surface after administration (0 h) can reach a mean of 88.9% of the administered dose of 2103 µg, while these values are progressively reduced to 82.5% at 30 min and to 52.4% at 48 h [51]. These absorption and retention rates allow a good clinical response even with one application per day [26,28]. These concentrations are higher than the MICs required to inhibit fungal growth *in vitro* and a short course of sertaconazole for 4 weeks will give ratios of C_{max}/MIC >1000 for *Candida*. These drug concentrations are enough to obtain a successful mycological cure of most superficial candidiasis, although no high concentrations of sertaconazole can be achieved in the lower layers of skin, thus avoiding the potential risk of systemic absorption [2,26,28]. Plasma concentrations in preclinical studies obtained with radioactively marked sertaconazole were below 0.011% (5 h) after dermal application of 2% cream, but some different available formulations of sertaconazole could produce differences in this parameter [13,53]. Nevertheless, some differences can be noticed under different available formulations of sertaconazole [13,53]. No hematological, cardiac or body temperature changes were observed after 13 days of treatment, nor were any alteration of blood testosterone levels, thus proving a good safety profile for sertaconazole [13]. The fecal and renal routes are the main routes of elimination of the product (61 and 4%, respectively, for endovenous administration; 30 and 0.4% for administration and 17 and 0.6% for skin) [53].

A poor compliance usually produces reduced antifungal efficacy, treatment benefits and increasing healthcare costs, so adherence to treatment is very important. The duration of antifungal treatment and the number of applications required each day are higher in dermatomycoses, particularly once symptoms have disappeared, so adherence to treatment decreases. Sertaconazole has pharmacokinetics that are considered favorable for once-daily therapy and it is hypothesized that its prolonged dermal retention may translate into the need for less frequent application for successful treatment [54].

Finally, sertaconazole has shown an anti-inflammatory effect after topical application on skin and mucosa. This effect can improve the unpleasant symptomatology, such as edema and pruritus, associated with candidal vulvovaginitis and skin infections. Sertaconazole also reduces the severity of erythema, desquamation or the formation of pustules. Therapeutic antifungal agents that have anti-inflammatory activity have the potential to provide clinical benefit beyond fungus eradication [28,45,55–58]. In this way, the topical administration of 2% sertaconazole to rats was able to reduce the edema [58].

The antipruritic activity is mediated by the induction of prostaglandin-D2 synthesis. Prostaglandin D2 has antipruritic activity by suppressing histamine release. Sertaconazole nitrate mitigated degranulation of rat basophilic leukemia-2H3 mast cells and augmented prostaglandin-D2 synthesis in mast cells and macrophages. In a murine model of pruritus Kaur *et al.* observed that the scratching behavior induced by compound 48/80, a pruritogenic agent known to promote the release of histamine, was mitigated by topical application of sertaconazole [59]. This effect was reversed by the addition of the cyclooxygenase inhibitor, ibuprofen or MK0524, a prostanoid D2-receptor antagonist [28,55,59]. This anti-inflammatory activity is better than those produced by other topical antifungals, such as butoconazole, ciclopiroxolamine, fluconazole, terconazole, tioconazole, ketoconazole and miconazole. On the basis of this action, sertaconazole is able to reduce the release of cytokines from activated lymphocytes [60]. Sertaconazole also mitigates the inflammation process as it was demonstrated in animal models with induced irritant contact dermatitis and also inhibited contact hypersensibility in animal models [60]. The anti-inflammatory properties of sertaconazole are added to the antifungal activity of this drug, contributing to the efficacy in the management of cutaneous fungal infections [60].

This anti-inflammatory activity was greater when it was compared with other antifungal agents [60]. In stimulated human keratinocytes and peripheral blood mononuclear cells, sertaconazole was found to suppress the release of cytokines. Sur *et al*. found that sertaconazole stimulated the proinflammatory p38 mitogen-activated protein kinase [56]. Treatment with sertaconazole resulted in the induction of cyclooxygenase-2 and the subsequent release of prostaglandin E_2. Knocking down p38 in keratinocytes using small interfering RNA resulted in an inhibition of sertaconazole-induced prostaglandin E_2 release, confirming that activation of p38 was required for prostaglandin E_2 production. Treatment with antiprostaglandin E_2 antiserum or the cyclooxygenase-2 inhibitor NS398 reversed the inhibitory effects of sertaconazole on the release of proinflammatory cytokines, linking endogenous prostaglandin E_2 with the anti-inflammatory effects. These authors concluded that the activation of the p38 cyclooxygenase-2-prostaglandin-E_2 pathway by sertaconazole provides anti-inflammatory therapeutic benefits [56].

Safety profile of sertaconazole

Animal studies

The tolerability profile of sertaconazole has been determined by using animal models and healthy volunteers, in which the absence of associated adverse effects was demonstrated [13,61]. The median lethal dose (LD_{50}) of sertaconazole was considered indeterminable because at the maximum administered dose of 8000 mg/kg mortality (single doses of sertaconazole were administered by oral, subcutaneous and intraperitoneal routes to rats and mice), the median did not allow the LD_{50} calculation [62]. Toxic effects were not detected after single administration, they were determined by subacute toxicity and maximum tolerated dose studies of repeated administration over a period of 28 days. Sertaconazole did not induce hepatomegalia in dermal-administered rabbits [53]. Due to reduced sertaconazole absorption, its administration is safe even in the event of accidental overdose or ingestion [62]. No differences have been found between the effects produced by sertaconazole administration and other azole derivatives for topical treatment, determined in chronic toxicity studies after oral administration. In the case of sertaconazole, a low increase in body weight has been reported in animals treated with 300 mg/kg of drug over 5 weeks (rats) and 150 mg/kg over 11 weeks (ferrets) [63]. Additionally, other actions in such inhibition synthesis of adrenal steroidal hormones are common to other azole antifungal derivatives and were only detected after the administration of very high doses at no case achievable under topical administration of sertaconazole. The resulting effects consist of changes in the ovaries and ductal hyperplasia of the mammary gland and endometrium of treated female ferrets [63]. The administration of sertaconazole is not associated with necrogenic, inflammatory nor degenerative changes, whereas the available data for miconazole and clotrimazole effects demonstrate a worse toxicity [63,64]. Sertaconazole also demonstrates a low toxicological risk, in comparison with ketoconazole, bifonazole or miconazole in reproduction, without the signs of promutagenicity, mutagenicity, clastogenicity nor interference with the process of chromosomal segregation caused by DNA damage in studies performed with prokaryotic and eukaryotic cells [65–67].

Human data

Sertaconazole is generally well tolerated in patients with dermatological and gynecological candidiasis, and frequency of adverse events did not differ from that obtained with placebo vehicle-treated patients; its safety has even been demonstrated in children [68]. Described adverse effects associated with skin topical application of sertaconazole were contact dermatitis, dry or burning skin, application-site reaction, eczema, itch and skin tenderness. No evidence of sensitizing action in causing contact dermatitis was noticed in healthy volunteers after sertaconazole topical administration or vaginal suppository [61]. Vaginal tablet administration is characterized by absence of severe adverse events and, where reported, included only local irritation after insertion without biochemical alterations [61]. Econazole, ketoconazole, bifonazole, clotrimazole and miconazole, produced some minor adverse reactions consisting of the formation of vesicles after the application on the skin of their topical formulations [13]. Tolerability studies performed with women, after the application of 2% cream and/or 300 mg ovules for the management of *Candida* vulvovaginitis, reported values of general local tolerability that were classified as excellent in 95% without any local adverse effect, and only five patients had a local burning while the general clinical tolerability was excellent in 100% of patients [51,69]. Similar studies show a reduced percentage of local irritation, itching and burning after the application of sertaconazole (8.7%) and econazole (13.4%) in the same patients offering a good toleration [70]. Sertaconazole does not induce contact dermatitis at therapeutic doses under its 2% cream formulation or solution and only 1.1% of the patients involved in a comparative study with sertaconazole cream and solution revealed adverse events that were considered to be possibly related to study medication [13,50,70,71]. Allergic contact dermatitis to sertaconazole has been observed in patients who had previously presented sensitivity to some azole derivatives, such as miconazole and econazole, while miconazole sensitized two out of 78 volunteers [72]. Sertaconazole may be administered without photosensibility reaction nor degradation byproducts caused by direct sunlight [13,62,67].

Clinical efficacy of sertaconazole

The broad spectrum of fungi susceptible to sertaconazole included those that cause superficial mycoses. As a result, sertaconazole is licensed by European, Asiatic, South American, Middle East and African agencies for the treatment of superficial dermatomycoses as *tinea pedis*, *cruris*, *manuum*, *corporis* and superficial infections by *Candida* and *Malasezzia*. In the USA, sertaconazole topical cream has been approved for the management of *tinea pedis*. Two different vaginal formulations have been approved in several countries for the treatment of VVC. Different clinical trials performed with sertaconazole nitrate have shown efficacy in the treatment of seborrheic dermatitis and cutaneous and mucosal candidiasis, with an antifungal activity greater than that obtained by other topical azole drugs and also by terbinafine [2,73,74].

The efficacy of sertaconazole in VVC has been demonstrated in comparative clinical studies with econazole, clotrimazole and omoconazole (Table 3). Most authors have observed that treatment with sertaconazole improved the clinical symptomatology [28,45,55,69–76]. Different available formulations of sertaconazole (cream, ovules and tablets) for vaginal infection management can provide antifungal concentrations that are maintained in vaginal secretions for several days after a single administration [20,77,78]. No systemic absorption has been detected [20,77,78]. High sertaconazole concentrations in vaginal fluids persist over 72 h but are different for different formulations (1.44, 572 and 186 µg/ml for 2% cream at 24, 48 and 72 h, respectively; and 56.01, 105.87 and 39.36 µg/ml for 500-mg tablets at 24, 48 and 72 h, respectively). The recovered percentage of sertaconazole in vaginal fluids after a single dose of 300-mg ovule were obtained in 100% of treated women after 3 days, 77% after 4 days and 50–75% after 1 week [77,79].

The eradication of *Candida* with sertaconazole (single-dose 300 mg vaginal ovule or 500-mg tablet) was successful in 65–100% of women with VVC when clinical and mycological cure rates were evaluated up to 1 year after the last treatment [80]. Furthermore, clinical and mycological cure rates obtained with sertaconazole (single-dose 500-mg tablet) were significantly greater than that of triple-dose econazole (150 mg) in the eradication of *C. albicans*. Sertaconazole was generally well tolerated in patients with dermatological and gynecological mycoses [26]. Similar rates of efficacy and safety between sertaconazole and econazole in the treatment of VVC have been described, although percentage of recurrence in favor of sertaconazole. In a multicenter, randomized, double-blind study, Dellenbach *et al*. compared the efficacy and safety of sertaconazole and econazole sustained-release pessaries in the treatment of 310 women with symptoms and signs of vulvovaginitis and a positive isolation of *Candida* in culture; 160 women were treated with sertaconazole (300-mg pessary) and 150 with econazole (150-mg pessary) [70].

No differences between the treated groups were obtained when clinical recovery or *Candida* eradication was studied, although differences were obtained in favor of sertaconazole over econazole: 62.1 and 67.7%, respectively, 1 week after the first application, 72.3 and 80.6%, respectively, 1 week after the second application, 65.3 and 62.0%, respectively, for all patients 1 month after the last application. Nevertheless, in the same study, the recurrence

Table 3. Comparison of efficacy of sertaconazole and other antifungals in the treatment of superficial candidiasis.

Infection	Patients (n)	Treatment	Results	Ref.
Cutaneous mycoses (dermatophytes, *Candida* spp. and opportunistic filamentous fungi)	317 and 314	STZ 2% (cream) vs MNZ 2% (cream) Two applications/day	95.6% STZ and 88.1% MNZ clinical outcome. 98.6% STZ and 91.7% MNZ of mycological cure	[82]
Cutaneous candidosis (6.4%) and dermatophytosis (91.1%)	313	STZ cream 2% (n = 153) vs STZ 2% solution (n = 160). Two applications/day for 28 days	STZ solution (90.6% clinical cure and 91.1% mycological cure) vs STZ cream (88.9% clinical cure and 91.8% mycological cure)	[50]
Superficial candidiasis	10	STZ cream 2%	95% of clinical and mycological cure	[61]
Vulvovaginal candidiasis	369	Suppository STZ 300 mg vs ECZ suppository 150 mg 1 week	62.1 vs 67.7% of clinical and mycological cures respectively (after 1 week). 65.3 vs 62% of clinical and mycological cures respectively (after 1 month)	[70]
Vulvovaginal candidiasis	77	Monodose STZ (ovules 300 mg) combined with 2% STZ cream (n = 39) vs STZ monodose (300 mg ovules; n = 38)	100 versus 80% of clinical and mycological cures, respectively	[69]
Vulvovaginal candidiasis	40	Single dose STZ vaginal tablets 500 mg vs ECZ three-dose vaginal tablet 150 mg	100 vs 72.2% on day 7 of significantly better clearance	[55]
Vulvovaginal candidiasis	62†	One 300-mg STZ vaginal suppository before sleep vs 100-mg CLZ tablet intravaginally before sleep for 7 days	93.4% of clinical recovery with mycological cure for STZ versus 71.9% for CLZ	[81]
Vulvovaginal candidiasis	30†	STZ tablets (twice at 7-day intervals) vs OMZ (twice for 6 days)	90% of mycological cure with STZ and 76.7% with OMZ	[45]
Vulvovaginal candidiasis	327	600 mg FTZ vaginal pessary (136 cases) with a 500 mg vaginal tablet of STZ (191 cases) as a single dose	Clinical outcome 83.7%, recurrence 16.2% and side effects 1.5% for STZ. Clinical resolution in 84.5%, recurrence in 15.4% and side effects in 1.4% for FTZ	[80]

†Pregnant women.
CLZ: Clotrimazole; ECZ: Econazole; FTZ: Fenticonazole; MNZ: Miconazole; OMZ: Omoconazole; STZ: Sertaconazole.

rate after one week in the sertaconazole treated patients was significantly lower that the one of the econazole treated group (19.8 vs 32.7%; p = 0.035) [70]. No serious adverse effects were described and only local irritation was reported [70].

These authors concluded that not only did sertaconazole offer a better cure rate than econazole but also a lower incidence of mycological recurrence was observed one month after treatment with sertaconazole [69]. Wang *et al*. evaluated in an open, randomized, comparative study, including 40 symptomatic patients with VVC, the efficacy, acceptability and safety of a 500 mg single-dose sertaconazole vaginal tablet treatment compared with three-dose 150 mg econazole vaginal tablet treatment. The group treated with sertaconazole showed a significantly better clearance rate for candidiasis than the group treated with econazole (100 vs 72.2% on day 7, p = 0.013; 100 vs 77.8% on day 14, p = 0.030), a fact probably related to the fungicidal capacity of sertaconazole. Women treated with a sertaconazole tablet showed a more rapid response for symptom relief than women treated with econazole on day 7, but there was no difference in overall symptom relief between both groups on day 14. Authors concluded that single-dose sertaconazole proved to be a more convenient and symptom-relieving treatment for VVC [55].

Sertaconazole reached a cure rate higher than 80%, being at the same level as clotrimazole (clinical and mycological cure), of the 582 patients studied after the application of a single dose 500-mg vaginal tablet [55]. Sertaconazole and clotrimazole shown the same tolerability and produced the same adverse effects, consisting of pruritus, erythema ahead of irritation, sensitization, edema, rubor, leucorrhoea and maceration [70]. Egorova *et al*. compared the clinical efficacy of sertaconazole (receiving one intravaginal suppository in a 7-day period, twice) and omoconazole (receiving one intravaginal suppository in a 6-day period), twice in pregnant women. They studied clinical manifestations, microbiological changes and curation and also bacterial stained vaginal smears [45]. Other studies show the absence of pruritus and burning after the administration of sertaconazole. The same dose was intravaginally administered to 30 pregnant women (14–26 and 27–40 weeks of gestation) at two 7-day intervals and compared with an other similar group of 30 pregnant women treated with omoconazole with doses of 1 intravaginal suppository in a 6-days period [45]. Lutsevich *et al*. reported a higher efficacy sertaconazole (at a single use) to a 7-day course of the comparator clotrimazole. Clinical recovery (7 days after the treatment with sertaconazole) with complete mycological sanation was observed in 28 (93.4%) and clotrimazole in 23 (71.9%) pregnant women [81]). Mycological recovery, 28 days after the treatment with sertaconazole, was found in 96.7%, and with clotrimazole, in 78.1% of cases [81].

In other prospective, multicentric and randomized open study, Quereux *et al*. assessed the efficacy and speed of action of a 300-mg monodose sertaconazole vaginal pessary administered as a single treatment at night or combined with sertaconazole cream applied to the vulvar area for 7 days in 77 women with VVC confirmed by mycological examination [69]. Clinical cure rates were higher in the group treated with the suppository combined with sertaconazole cream than in the group of women treated with the vaginal pessary only at day 7 (76 vs 68%), and at day 14 (100 vs 80%) [69]. The efficacy on symptoms was faster in the group treated with the pessary plus the cream, with 78% of the patients relieved of pruritus as early as day 2 versus 61% in the other group, although these differences were not significant. Clinical local tolerance was approximately 95% of the patients not experiencing any local side effects [69].

There are also clinical studies validating the efficacy of treatment of cutaneous candidiasis with sertaconazole (**Table 3**). Alomar *et al*. evaluated, in a double-blind, controlled, multicenter trial with parallel groups, the efficacy and tolerance of sertaconazole 2% dermatological cream in two daily applications compared with miconazole 2% cream in two daily applications in 631 patients suffering from superficial cutaneous mycosis, including candidiasis (sertaconazole: n = 317; miconazole: n = 314) [82]. The rate of clinical cures for both treatments after 4 weeks was 95.6% for sertaconazole and 88.1% for miconazole. Patients treated with sertaconazole were cured earlier and in a higher proportion than those treated with miconazole, with the difference being significant. The negative result of the microscope examination and culture test confirmed the superiority of sertaconazole over miconazole after 14 days of treatment. At the end of the follow-up, 98.6% of the patients in the sertaconazole group obtained a negative culture test result, as opposed to 91.7% in the miconazole group, with the difference being highly significant [82]. The percentage of therapeutic failure, recurrence or relapses was below (4.4%) that of miconazole (11.9%) for relapses at 35 days after beginning the treatment (p < 0.001) [81,82]. Similar results were obtained for a comparison of the clinical efficacy of sertaconazole with sulconazole, clotrimazole or bifonazole for the treatment of patients suffering from cutaneous candidiasis [83].

Umbert *et al*. studied the activity of sertaconazole in a randomized parallel double-blind clinical trial on 20 patients suffering from superficial candidiasis caused by *C. albicans*. The patients were divided into two similar groups; one received sertaconazole 1% cream and the other received sertaconazole 2% cream, both over a period of 28 days. The cure was complete in 19 out of the 20 patients. There were no relapses of infection in any of the cured patients and no undesirable effects were recorded [61].

Borelli *et al*. compared in a prospective, open-label, randomized, controlled, parallel-group, multicenter, noninferiority therapy study, the efficacy of a solution containing sertaconazole 2% with a sertaconazole 2% cream formulation in patients with *tinea corporis*, *tinea pedis interdigitalis* or a corresponding candidiasis. Patients received either sertaconazole solution (160 patients) or cream (153 patients) twice daily for 28 days. Efficacy was documented in 90.6% of the patients treated with the solution and 88.9% of those using the cream, without adverse events recorded [50].

Expert commentary

The incidence of skin and mucosa mycoses and, particularly candidiasis, has increased. This clinical trend will continue as there is a rise in the population with chronic exposure or predisposing

conditions, such as denture use, obesity, diabetes, antibiotic use and so on. In otherwise healthy persons, many of these superficial mycoses are caused by *Candida* and dermatophyte moulds and their clinical evolution is uncomplicated. In those clinical presentations of candidiasis where there are relapses, recurrences or other situations that complicate the prognosis, it is important to begin the most appropriate therapeutic approached based upon clinical data and the specific *in vitro* antifungal activity against the specific etiologic agent. For this target, sertaconazole offers a dual (fungistatic and fungicidal) broad antifungal activity that can be achieved at drug concentrations that are reached after topical administration on skin and mucosa. Moreover, sertaconazole is characterized by its affinity for specific targets higher than those of other topical azoles, such as econazole or miconazole, with a extremely low frequency of resistant strains recovering. Dermal and gynecological formulations of sertaconazole have additional qualities, such as good tolerance and safety profiles, and their antibacterial, antiprotozoal and anti-inflammatory activities that are helpful for the management of cutaneous and VVC and mixed infections. Successful results have been reported with sertaconazole dermal and gynecological formulations in several clinical studies [26,68–70,76,77,80,82,83]. Among the most interesting observations are that single-dose sertaconazole has proved to be a convenient and symptom-relieving treatment for VVC and that sertaconazole has an excellent efficacy in comparative clinical studies with econazole, clotrimazole, miconazole and omoconazole, suggesting it should be a first-line drug.

Five-year view

In the next 5 years, candidiasis will continue to be a frequent medical challenge. Although invasive candidiasis will remain an important cause of morbidity and mortality, the most common clinical presentations will be, as nowadays, those affecting the skin and mucosa. Among these conditions, vulvovaginitis and *Candida*-associated conditions, such as denture stomatitis, related to new habits and human advances, could experience an important increase. New trends for solving these challenges are focused on the development of new antifungals, of new formulations or combinations of the current drugs, together with finding new genomic and structural targets and adjuvant immunotherapies. Although the need for new drugs is obvious, progress in this area is always slow and unpredictable. Sertaconazole, one of the latest imidazoles, has increased antifungal, antibacterial and antiprotozoal activities, excellent safety and toxicological profile and good pharmacokinetics. Tineas (specially *tinea pedis*), seborroheic dermatitis and VVC are the main clinical targets for sertaconazole, and several studies have shown its usefulness in the single-dose treatment of uncomplicated candidal vulvovaginitis and its promising role in the therapy of recurrent vulvovaginitis. On the basis of this criteria, there is a wide field for the expansion of the use of sertaconazole in clinical practice for the therapy of the different presentations of oropharyngeal candidiasis; from the common and unpleasant denture stomatitis to the severe recurrent pseudomembranous candidiasis in HIV-infected patients. Moreover, many patients suffering from superficial candidiasis are treated with oral therapy with different antifungals with more adverse effects compared with the topical administration of sertaconazole.

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Key issues

- Sertaconazole nitrate is a broad-spectrum topical antifungal agent that belongs to the azole drug class, having as differential character of a benzothiophene-associated radical and high lipophilia.
- Sertaconazole penetration of the keratinized layers of the skin is due to its synthesis procedure.
- Sertaconazole inhibits ergosterol biosynthesis and also binds nonsterol lipids in the cell membrane as other azoles do, altering the cell viability.
- Sertaconazole is available under different formulations that have been adapted to the main clinical manifestations of superficial candidiasis and other mycoses.
- Sertaconazole is retained in the skin without absorption into plasma after topical administration, demonstrating a good pharmacokinetic profile.
- The anti-inflammatory effect after topical application of sertaconazole on skin and mucosas can improve unpleasant symptomatology, such as edema and pruritus, associated with candidal vulvovaginitis and skin infections.
- The tolerability profile of sertaconazole has been determined by using animal models and healthy volunteers, in which the absence of associated adverse effects was demonstrated.
- Sertaconazole is well tolerated in patients with dermatological and gynecological candidiasis and frequency of adverse events do not differ from that obtained with placebo vehicle-treated patients, its safety has even been demonstrated in children.
- The efficacy of sertaconazole in vulvovaginal candidiasis has been demonstrated in comparative clinical studies with econazole, clotrimazole and omoconazole.
- Eradication of *Candida* with sertaconazole produced a succesfull outcome at levels of 65–100% of women with vulvovaginal candidiasis when clinical and mycological cure rates were evaluated up to 1 year after the last treatment.

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