Sertaconazole, an azole derivative (7-chloro-3-[1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethoxy-methyl]benzo[b]thiophene), acts by inhibiting the ergosterol biosynthesis and damaging the cell integrity. It has a broad spectrum of activity against yeasts,
dermatophytes as well as Gram-positive bacteria. The antimicrobial activity and the pharmacology of sertaconazole have been recently review.

MODE OF ACTION

Sertaconazole inhibits the biosynthesis of ergosterol in direct proportion to the antifungal concentration used, this mechanism being similar to that of other azole antifungal agents. However, due to its mixed structure, sertaconazole is capable of causing direct damage to the C. albicans cell membrane. This second, and very important, effect is the basis of its fungicidal effect against C. albicans. The special structure of the cell membrane of fungi is based on the properties of ergosterol, which
is capable of regulating the internal fluidity of the membrane. The interaction at some stage of the biosynthetic route of ergosterol may cause a reduction of the levels of this compound and, as a result, affect the integrity of the cell. An intermediary of the biosynthesis of ergosterol (lanosterol) is produced by the interaction of azole compounds with the cytochrome P450 complex (in mono-oxygenase or hydroxylase 14-α-demethylase enzymes). In general, azole derivatives cause inhibition of the biosynthesis of ergosterol and inhibition of filamentation in C. albicans, as well as in some cases, such as with sertaconazole (direct damage to the cell membrane) The bond between the azole molecule and the iron atom of the hemo group leads to inactivation of the enzyme and the resulting accumulation of lanosterol that damages cellular architecture and membrane fluidity and permeability. Any increase in cell permeability causes the loss of intracellular ATP, destruction of the cytoskeleton and lysis of the cell organelles,
while at the same time reducing the number of viable cells by up to 90%. The result of this is the fungicidal effect of sertaconazole when cells are exposed to high concentrations of this drug. Under these same conditions, it is also possible to detect an interruption in the process of the formation of hyphae, thus preventing invasion of the host tissue.

**Antifungal action spectrum**

The relevant antifungal activity of sertaconazole has already been demonstrated in different preclinical studies against a broad spectrum of pathogenic fungi, including yeasts, fungi
dermatophytes, opportunistic filamentous fungi and Grampositive bacteria (Streptococcus and Staphylococcus) and Trichomonas spp. The species of fungi included potential producers of dermatomycoses, dermatophytosis and genital candidiasis. A complete comparison of the minimum nhibitory concentrations, which would enable establishing the antifungal power of the substance in vitro is complex, as some of the different results were obtained prior to the appearance of the Clinical and Laboratory Standards Institute (CLSI/NCCLS) documents, which established standard experimental conditions and variables. Nevertheless, it can be deduced from data that there is a wide activity spectrum against pathogenic fungi, an activity that takes place at concentrations far below those reached after the topical application of sertaconazole.

Antifungal activity in vitro
The in vitro antifungal activity of sertaconazole has been widely demonstrated by various authors using standard and nonstandard methods under different experimental conditions against pathogenic yeasts, including Malassezia spp. dermatophyte fungi and opportunistic filamentous fungi. Susceptibility testing enables an excellent statistical base to be obtained indicating the tendency of a substance towards activity or inactivity and also serves as a therapeutic guide when making clinical decisions regarding the prediction of susceptibility or resistance of the isolated strain, the selection of the most clinically active antifungal agents, or indicating the reasons for therapeutic failure on the basis of microbiologic criteria. The fungicide activity of sertaconazole has its onset at concentrations of 8–16 μg/ml, whereas at lower concentrations, in ranges equivalent to clotrimazole and miconazole, it develops a fungistatic action mechanism. This antifungal activity of sertaconazole is higher than that of other imidazole derivatives, such as
bifonazole, econazole or fluconazole In the absence of adverse effects as serious as those observed with other imidazoles such as clotrimazole, miconazole, bifonazole or ketoconazole, in comparison, sertaconazole is more active against opportunistic filamentous fungi than miconazole. Sertaconazole also proved to be more active against resistant strains of dermatophytes than fluconazole, a triazole derivative used by oral route in the treatment of some dermatophytoses. Sertaconazole is very active against this group of pathogenic fungi with partial inhibition being detected at concentrations below 0.04 μg/ml. This excellent in vitro antifungal activity of sertaconazole is completed by a low percentage of resistances, placing it in the same range as other topical antifungal agents such as clotrimazole and tioconazole, and lower than those obtained for amphotericin B, itraconazole, fluconazole, econazole, miconazole or ketoconazole. On the other hand, it has not been possible to obtain
evidence of induced resistance in vitro by exposure of C. albicans and Candida tropicalis to subinhibitory concentrations of sertaconazole.

**Antibacterial activity in vitro**
Sertaconazole has demonstrated in vitro antibacterial activity against Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Streptococcus agalactiae, Listeria monocytogenes, Gardnerella spp. and other bacteria involved in mixed infections. The activity of sertaconazole against Gram-positive bacteria was described at concentrations below 0.97 μg/ml and considered to have in vitro therapeutic value.

**Animal models**
Some experimental models in animals (mouse and guinea pig) have been used to prove the
usefulness and efficacy of topical sertaconazole at doses of 2% against vaginal candidiasis and dermatophytosis, when tested in comparison with miconazole (2%) in different treatment regimes [24,27,28]. In the animal model of dermatophytosis, sertaconazole has a proven efficacy after 12 days of treatment similar to that obtained with miconazole. The therapeutic improvement of the clinical and microbiologic symptoms was better for the sertaconazole group treated during 3 days. The same occurred with the model of vaginal candidiasis but with an even better prophylactic and curative effect. In the latter model, there was a greater reduction in the cell count of yeasts with the vaginal administration of sertaconazole (97.7 and 77.5% with sertaconazole and miconazole respectively) promising a good clinical efficacy. Clinical efficacy

Anti-inflammatory effect
Sertaconazole has been shown to have anti-inflammatory activity when administered at a dose of 2%. This effect is useful in the treatment of some inflammatory forms of dermatophytoses.

Dermatology (dermatophytoses & other cutaneous mycoses).

A comparison between different clinical studies to establish the efficacy of antifungal agents is difficult due to the differing numbers of patients assessed in these studies. However, it is possible to review comparative multicentric clinical studies between sertaconazole and other azole derivatives (miconazole, sulconazole, clotrimazole, bifonazole or ketoconazole) that support the clinical efficiency of sertaconazole against superficial mycoses in
all its different formulations. The cream formulation was effective in a double-blind study carried out with parallel groups of patients suffering from different dermatophytoses (tinea cruris, tinea corporis, tinea pedis, tinea manuum, tinea barbae among other locations). The efficacy of the cream formulation of sertaconazole in a Multicenter Phase III, randomized and comparative study with miconazole in patients infected by Microsporum canis, C. albicans and other dermatophyte fungi, reached ranges of 98.3 versus 94.3%, respectively, after 4 weeks of treatment. This was statistically significant [30]. The ranges of clinical cure for sertaconazole were accompanied by similar mycologic cure rates – being the percentage of therapeutic failure, recurrence or relapses being very low (sertaconazole 4.4 vs. miconazole 11.9% of relapses at 35 days after beginning the treatment, p < 0.001). 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 and dermatophytosis. Apart from its antifungal activity, some properties of sertaconazole, such as reduction of the severity of erythema, reduction of desquamation, pruritus or the formation of pustules, were also useful when determining the clinical cure. The good results obtained with sertaconazole in the treatment of superficial mycoses were previously described in Phase II studies, which also enabled characterizing a high safety profile in a group of 20 patients. The effectiveness of the gel formulations (2%) of sertaconazole compared with ketoconazole was demonstrated against seborrheic dermatitis. Clinical signs and the presence of fungal elements were reduced in 61.1% of the 60 patients studied whereas for ketoconazole this occurred in 52.6% of patients. Clinical and mycologic improvement of various superficial infections was achieved with different formulations of sertaconazole in comparison with other compounds belonging to
other chemical families of antifungal agents. Furthermore, its efficacy was demonstrated in children after the application of single doses of the 2% cream formulation of sertaconazole.

**Gynecology (vaginal candidiasis)**

In gynecologic mycoses, such as candidal vulvovaginitis, the excellent efficacy of sertaconazole was also demonstrated in comparative studies with clotrimazole and econazole. The effectiveness of sertaconazole was comparable with that of clotrimazole in terms of clinical and mycologic cure of the 582 patients studied, reaching a cure rate higher than 80% in both groups at 14 days after the application of a single dose of 500 mg as a vaginal tablet. Both antifungal agents were well tolerated with the adverse effect of greatest frequency being the appearance of pruritus and erythema ahead of irritation, sensitization, edema, rubor,
leukorrhea and maceration. Sertaconazole and econazole demonstrated similar rates of efficacy and safety, but the percentage of recurrence was lower among patients treated with sertaconazole. In a comparative study between the application of a single intravaginal dose in 369 patients suffering from vaginal candidiasis (183 sertaconazole; 186 econazole), the clinical and mycologic cure rate was 70.8 and 64.7%, respectively, for sertaconazole and econazole, after 7 days of treatment and the clinical cure rates were 71.6 versus 64.2%, respectively, for each of the treatments. In spite of these results being similar for both imidazole antifungal agents, it was possible to observe statistically significant differences in favor of sertaconazole in regard to the relapse rates (19.8 and 32.7%, respectively, after 30 days; p = 0.035), a fact probably related to the fungicide capacity of sertaconazole. No differences were found between both medicinal products for local tolerability. Another study evaluated the
differences between the treatment of vulvovaginal candidiasis with single intravaginal doses of 300 mg (applied at night) and the combined intravaginal therapy of a single dose of 300 mg together with topical application of sertaconazole cream (2%) to the vulva during 7 days (combined treatment). The results demonstrated an efficacy of close to 99% with regard to clinical improvement in all patients, but the cure was faster in the combined treatment group of pessary plus cream than in the group of pessary alone at 7 days (76 vs. 68%, respectively). Furthermore, annoying symptoms such as pruritus disappeared sooner in the combined treatment group.

SAFETY PROFILE

Acute toxicity studies
The acute toxicity of sertaconazole was determined after the administration of single doses by oral, subcutaneous and intraperitoneal route in rats and mice with the median lethal dose (LD50) being higher than 8000 mg/kg in all cases. Due to its reduced absorption, administration is safe even in the event of accidental overdose or ingestion [38].

Subacute toxicity & maximum tolerated dose
Studies of repeated administration over a period of 28 days with subacute oral and dermal doses of 50, 150 and 300 mg/kg and maximum tolerable doses on a geometric progression of 50, 75, 112.5, 168 and 250 mg/kg of sertaconazole reveal a reduced number of toxic effects that are not possible to reproduce after the administration of single doses. No histopathologic changes were found in any of the cases.
Chronic toxicity studies after oral administration

In this regard, the effects produced by sertaconazole are also common to otherazole derivatives used for the treatment of mycoses, and were detected at a dose of 50 mg/kg in chronic toxicity studies after repeated and sustained administration by oral route doses of 50, 150 and 300 mg/kg in rats and ferrets. The accumulative effect, which did not produce any associated mortality, was observed in the group treated with bifonazole (10 mg/kg), ketoconazole (60 mg/kg) and miconazole (100 mg/kg). There was a low increase in body weight in animals treated with 300 mg/kg of sertaconazole over 5 weeks (rats) and 150 mg/kg over 11 weeks (ferrets). The histopathologic findings are similar to those produced by other imidazoles and consisted of changes in the pattern of microvacuolization in the hepatocyte cytoplasm related to the induction of microsomal enzymes. The inhibitory effect on the synthesis of adrenal
steroidal hormones, also common to other azole antifungal agents and observed after the administration of very high doses, produces changes in the ovaries of treated females (ferrets) and ductal hyperplasia of the mammary gland and endometrium. The effects, although common to other imidazoles, were found at higher concentrations of sertaconazole and this its safety profile is higher, requiring doses of more than 50 mg/kg [40]. The data available for miconazole and clotrimazole show a worse toxicity profile for these substances. In any case, the administration of sertaconazole is not associated with any necrogenic, inflammatory or degenerative changes.

Toxicity studies in reproduction
Compared with ketoconazole, bifonazole or miconazole, the low toxicologic risk associated with the administration of sertaconazole has been demonstrated by teratologic studies in
rats, rabbits and also in peri- and postnatal rats [41].

**Genotoxicity**

There was no evidence of induction of signs of promutagenicity, mutagenicity, clastogenicity or interference with the process of chromosomal segregation caused by DNA damage. Neither have genotoxicity studies carried out with sertaconazole demonstrated any increase in the frequency of bacterial retromutation or lethal mutations in spermatozoa or spermatids [42].

**Skin tolerance & phototoxicity**

It is possible to state that there is no risk of phototoxicity after the administration of the 2% cream formulation of sertaconazole in guinea pigs [43]. Trials carried out to detect skin tolerance demonstrated the absence of any
irritation [43]. This means that sertaconazole may be administered safely without the possible existence of degradation by-products caused by direct exposure to sunlight [43,44]. Sertaconazole does not induce contact dermatitis at therapeutic doses (2% cream) [44,45], although allergic contact dermatitis to sertaconazole was observed in patients who had already presented sensitivity to miconazole and econazole [47].

**Pharmacokinetics**
Sertaconazole penetrates the horny layer of the skin where some pathogenic fungi are capable of developing their effect, and therapeutic concentrations may be found there during a long period of time, which is of interest in clinical practice. However, such high concentrations of sertaconazole cannot be reached in the lower layers, thus avoiding the potential risk of systemic absorption. The
concentrations found in plasma in a preclinical study with radioactively marked sertaconazole were below 0.011% 5 h after beginning application of 2% cream to the skin [48]. The cutaneous absorption in humans has been described after topical application at increasing doses [44]. The results of this study showed that the percentage of cutaneous absorption at 24 h after the application was 72% of the dose applied. Analysis of plasma samples did not reveal concentrations of sertaconazole that were detectable at a quantitation limit of 25 ng/ml. No hematologic, cardiac or body temperature changes were observed at 13 days, neither was there any alteration of the blood testosterone levels, thus proving its good safety profile [44]. The antifungal agent is retained in the skin for long periods of time, reaching antifungal concentrations at 72 h after topical applications of once or twice a day [49]. The different vaginal forms in which sertaconazole is available (tablets, pessaries and cream) for the treatment of vulvovaginitis
make it possible to reach concentrations above those required to inhibit the development of different species of the genus Candida spp. with a dose of 300 or 500 mg. In addition, these concentrations are maintained in vaginal secretion for several days after a single administration without there being any systemic absorption, thus resolving its necessary presence and persistence in the vaginal mucous membrane [50]. Some of the main pharmacokinetic parameters of sertaconazole in preclinical studies are shown in. 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 the skin) [48].

Tolerability studies
Tolerability studies for sertaconazole carried out using animal models and healthy human
volunteers showed the absence of evidence of adverse effects associated with the administration of total amounts of 98 g of antifungal agent during 13 days (1–16 g each) [44]. It was also shown with healthy human volunteers that other therapeutically available antifungal agents such as econazole, ketoconazole, bifonazole, clotrimazole and miconazole, produced adverse reactions consisting of the formation of vesicles after the application of their commercial forms [44]. There were no differences between sertaconazole and placebo in regard to photosensitivity [43].

REFERENCES

3 Raga MM, Moreno-Manas M, Cuberes MR, Palacín C, Castello JM, Ortíz JA. Synthesis and antimycotic activity of (benzo[b]thienyl)methyl ethers of 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)-ethanol and of (Z)-1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethanone oxime. Arzneimittelforschung 42(5A), 691–694 (1992).

4 Albet C, Fernández JM, Sacristán


7 Agut J, Palacín C, Salgado J, Casas E, Sacristán A, Ortíz JA. Direct membrandamaging effect of sertaconazole on Candida albicans as


13 Carrillo-Munoz AJ, Tur C, Torres J. In vitro antifungal activity of


16 Carrillo-Muñoz AJ, Brió S,


19 Carrillo-Munoz AJ,


21 Torres JM, Carrillo-Muñoz JM, Madrenys- Brunet N. Minimal inhibitory concentrations of sertaconazole, miconazole and clotrimazole on 14 strains of Scopulariopsis brevicaulis isolated


30 Alomar C, Bassas S, Casas M et al. Multicentre double-blind trial on the efficacy and safety of sertaconazole 2% cream in comparison with miconazole 2% cream on patients suffering from cutaneous mycoses. Arzneimittelforschung 42, 767–773


33 Pedragosa R, González B, Martín M et al. Therapeutic efficacy and safety of the new antimycotic sertaconazole in the treatment of cutaneous dermatophytosis.
36 Dellenbach P, Thomas JL, Guerin V, Ochsenbein E, Contet-Audonneau N. Topical treatment of vaginal


39 Romero A, Villamayor F, Grau MT, Sacristán A, Ortíz JA. Subacute


45 Romero A, Grau MT, Villamayor F et al. Ocular tolerance of
48 Agut J, Moren M, Rego M, Sacristán A, Ortíz JA. Pharmacokinetic evaluation of