

## A REVIEW ON NOVEL ANTI FUNGAL FORMULATION OF EBERCONAZOLE

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### ABSTRACT

Eberconazole is a broad-spectrum imidazole antifungal agent used as a topical preparation in the management of cutaneous mycoses. In vitro studies have shown that eberconazole is effective against dermatophytes, candidiasis, yeasts (including those which are triazole resistant) and Pityriasis versicolor. It inhibits fungal lanosterol 14 $\alpha$ -demethylase, thereby inhibiting ergosterol synthesis leading to inhibition of fungal growth. In addition to its antifungal activity, it is also effective against Gram-positive bacteria, a property that is useful clinically. It also possesses anti-inflammatory property thus making it a suitable agent in the clinical management of inflamed cutaneous mycoses. Topical application of eberconazole was well tolerated in preclinical studies without any report of delayed hypersensitivity or photosensitivity reactions. There were no phototoxic effects. There was no significant systemic absorption. Animal toxicity studies have shown that it is safe, and the No Observed Effect Level was 2 ml/kg body weight in tested animals. It was not mutagenic and shared similar cytotoxicity profile with other imidazole antifungal products studied. Penetration studies using synthetic membranes revealed that eberconazole intrasets showed less variation as compared to clotrimazole and terbinafine intrasets. Overall amount of eberconazole released was more compared to comparators. In vitro and preclinical studies have demonstrated better therapeutic efficacy with eberconazole than clotrimazole and ketoconazole.

**KEYWORD:** eberconazole, preclinical pharmacology, efficacy, safety, formulation advantages.

### INTRODUCTION

Constant exposure to the ubiquitous fungi has made man vulnerable to fungal infections. Fungal infections of the skin are prevalent globally, with 20-25% of the world's population being affected.<sup>[1]</sup> Life-time risk of acquiring a dermatophytic infection is estimated to be 10-20%.<sup>[2]</sup> Climatic conditions, cultural and socioeconomic factors not only contribute to the increased prevalence in tropics but also influence the type of fungal infection in a particular geographic area.<sup>[3]</sup>

Dermatophytosis is superficial skin infection caused by dermatophytes (specifically Trichophyton, Epidermophyton and Microsporum species), which attach to keratin, colonize the keratinized tissue using keratin as nutrition.<sup>[4]</sup> Since the infection is limited to the superficial layers of skin, topical application of antifungal agents is helpful in the treatment. Selecting a suitable antifungal agent is difficult as the market is flooded with many products. Moreover, treatment has become challenging and complex due to difficulties in diagnosis, deviation from classical clinical presentation, emergence of drug resistance, poor compliance and increase in immuno-suppressed conditions. With

effective treatment, the cure rate is high, even though relapses and exacerbations are common.

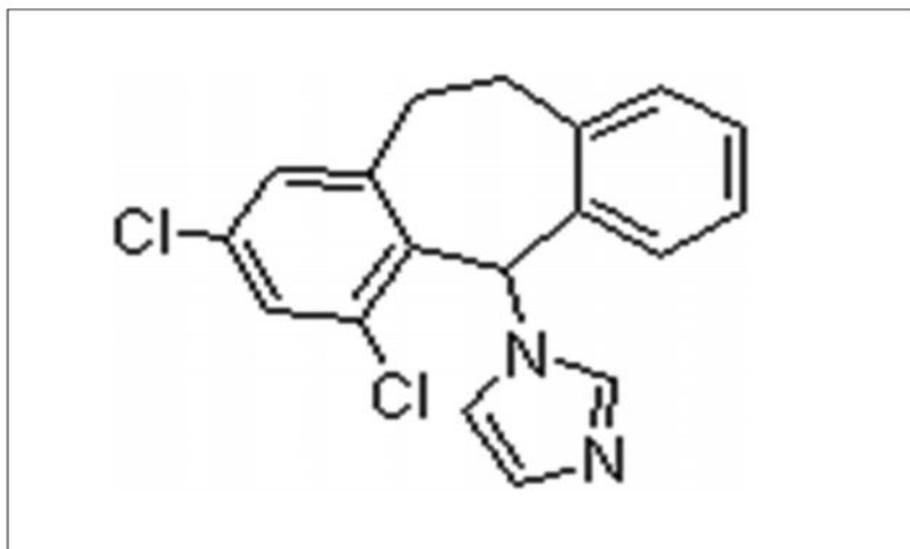
Currently fungal infections are treated with either oral or topical antifungal agents depending upon the site and severity of infection. Oral antifungal agents are used only to treat widespread skin lesions, systemic fungal infections and in cases unresponsive to topical therapy.

Topical preparations with good local bioavailability are the most commonly used and preferred first line agents in the treatment of localized dermatomycosis. Their better efficacy which aims to shorten the treatment period, fewer side effects, minimization of recurrence, and ease of application enhances patient compliance resulting in better therapeutic response.

Eberconazole, a newer antimycotic agent, an imidazole derivative, initially designed and investigated in Spain by the Wassermann investigation centre, later acquired by Laboratories Salvat, was launched in 2005 for the treatment of cutaneous fungal infections. In this article we have reviewed the pharmacology and compared the clinical efficacy of eberconazole with other antifungal agents commonly used in clinical practice.

**EBERCONAZOLE**

Structure Eberconazole

((1-(2,4-dichloro-10,11-dihydro-5Hdibenzo[a,d]cyclohepten-5-yl)-1H-imidazole))<sup>[5]</sup>[Figure 1], with a molecular formula C<sub>18</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>, is a broad-spectrum antifungal agent.

**Figure 1: Molecular structure of Eberconazole** (Source: ChemBlink available from <http://www.chemblink.com/products/128326-82-9.htm> accessed on 10 October 2011)

**Preclinical Pharmacology**

Studies with the strain, *Candida vaginalis* serogroup B have shown that eberconazole binds to the lipid fraction of fungal membrane. The phospholipids sub-fraction of the membrane is responsible for binding and sterol synthesis is the intracellular target.<sup>[7]</sup> A comparative study with clotrimazole has shown that eberconazole showed more inhibitory activity against the phospholipid fraction of membrane protoplasts of *C. albicans* than clotrimazole. This study also showed that eberconazole was active against a wide range of yeast and fungi.<sup>[6]</sup> It has shown to have anti-inflammatory activity in a dose-dependent manner, with an SD50 of 65.5 mg/mL, which was comparable to that with acetyl salicylic acid (70.1 mg/mL) and ketoprofen (41.7 mg/mL).<sup>[7]</sup> In vitro studies have shown that eberconazole is effective against disease causing *Candida* including *C. parapsilosis* (minimum inhibitory concentration 90, MIC<sub>90</sub> = 0.125 µg/ml). In this study, effects of eberconazole on clinical isolates of yeast including *C. krusei*, *C. glabrata*, *C. albicans*, and *C. parapsilosis* was studied. Eberconazole showed lower MIC values and excellent activity against triazole-resistant *Candida* species such as *C. krusei* and *C. glabrata* compared to ketoconazole and clotrimazole, with a statistically significant difference between eberconazole and ketoconazole. Majority of triazole-resistant yeasts (*C. krusei* and *C. glabrata*) and fluconazole-resistant *C. albicans* showed sensitivity to eberconazole. This study demonstrated excellent activity of eberconazole against *C. krusei* and *T. glabrata*; comparable efficacy to that of comparators was noted against *C. albicans* and *C. parapsilosis*.<sup>[8,9]</sup> Although

*Cryptococcus neoformans* isolates were less sensitive to eberconazole than to ketoconazole and clotrimazole, lower MIC values (0.162 µg/ml) were observed. The antifungal activity of eberconazole against 124 clinical isolates of *Candida*, which included eight different species and 34 isolates of *Cryptococcus neoformans* was determined and was compared to that of clotrimazole and ketoconazole.<sup>[8,9]</sup> In vitro activity of eberconazole was compared with clotrimazole, ketoconazole and miconazole against 200 strains of dermatophytes. Eberconazole was more active ( $P < 0.05$ ) than the other agents, against the majority of the species tested.<sup>[10]</sup> Similar MICs were observed with eberconazole and clotrimazole in 116 strains of yeast and 45 dermatophytes, whereas bifonazoles produced different results with higher MICs and resistant strains, i.e., growth at concentrations above 40 µg/ml in *C. tropicalis* and *C. albicans*. Eberconazole produced the lowest MICs with *Torulopsis glabrata* although they are only fungicidal in slightly >50% of the cases. It also demonstrated lowest MICs for *T. mentagrophytes* and fungicidal activity was not seen in the majority of strains. In *M. canis* and *T. rubrum*, it also appeared to be the antifungal with the greatest MIC in relation to other comparator imidazoles.<sup>[6]</sup>

**Efficacy**

Efficacy and safety of topical eberconazole have been established by a number of studies. Twice daily application of eberconazole 1% was found to be as efficacious as eberconazole 2% in 60 patients with mycologically proven tinea corporis and tinea cruris, in a

phase II pilot study, but the measured parameters did not show any statistical significance. Overall clinical cure rate post therapy was 73.3-93.3% in different groups. Adverse effects were seen more with eberconazole 2% than with 1%, but without any statistical significance.<sup>[12]</sup>

Further, efficacy of eberconazole has been compared with the widely used topical antifungals in various studies. In a double blind study, eberconazole 1% cream's therapeutic efficacy and safety profile was similar to miconazole. After 4 weeks of therapy, 76.09% patients on eberconazole showed effective response

compared to 75.0% in miconazole group [Table 1].<sup>[11]</sup> Therapeutic effects of eberconazole with clotrimazole and miconazole are compared in [Table 2].<sup>[13]</sup> In another multicentric double blind randomized study, Repiso Montero et al. compared the efficacy of eberconazole 1% cream with miconazole 2% cream in the treatment of dermatophytosis. In this study, eberconazole showed similar efficacy and safety profile with miconazole in the treatment of dermatophyte infection. This study also suggested that eberconazole can be considered a good alternative for the treatment of dermatophytosis as it has good safety and tolerability profile.<sup>[14]</sup>

Parameter	Eberconazole (%)	Miconazole (%)
Therapeutic response rate (cure + improvement) at week 4	76.09	75.00
Complete cure at week 4	69.57	69.32
Mycological cure rate at week 4	86.95	84.09

Eberconazole 1% cream is as effective as Miconazole 2% cream in the treatment of dermatophytosis, \*Source: Data on file. From Innovators (LaboratoriosSalvat, S.A) product information dated 16 Dec 2001

Parameter	Eberconazole	Clotrimazole	Miconazole
Chemical nature	Imidazole	Imidazole	Imidazole
Mechanism of action	Sterol synthesis inhibitor; Alters cell membrane permeability	Sterol synthesis inhibitor; Alters cell membrane permeability	Sterol synthesis inhibitor; Alters cell membrane permeability
Spectrum of activity	Broad spectrum, fungicidal. Active against wide range of clinically relevant dermatophytes, yeasts and <i>Malassezia furfur</i> . Active against most triazole resistant yeasts such as <i>C. glabrata</i> and <i>C. krusei</i> . Active against even fluconazole resistant <i>C. albicans</i> .	Broad spectrum, fungicidal. Active against wide range of clinically relevant dermatophytes, yeasts and <i>M. furfur</i> .	Broad spectrum, fungistatic. Active against wide range of clinically relevant dermatophytes, yeasts and <i>M. furfur</i> .
Therapeutic indications	Cutaneous candidiasis, Tinea versicolor, and dermatophytosis	Dermatophytosis, T. versicolor, and cutaneous candidiasis due to <i>C. albicans</i>	Dermatophytosis, T. versicolor, and cutaneous candidiasis due to <i>C. albicans</i>
Dosing schedule	Twice daily	Twice daily	Twice daily

\*Source: Adapted from High WA, Fitzpatrick J E. Topical antifungal agents. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, editors. Fitzpatrick's Dermatology in General Medicine. Seventh ed: McGraw Hill, 2008 p. 2116-18 and Innovators (LaboratoriosSalvat, S.A) product information. Dated 16 Dec 2001

Another double blind, randomized control study showed that the overall efficacy and safety of eberconazole cream in patients with cutaneous mycoses including dermatophytosis, candidiasis and pityriasis versicolor, was slightly higher (Per protocol (PP): 74.3% intention to treat (ITT): 61.7%) in comparison to clotrimazole (PP: 67.8% ITT:58.4%) at week 10, though the differences were statistically not significant. However, eberconazole

showed a significantly greater (P=0.011) efficacy than clotrimazole in the treatment of dermatophytosis. Of 94.5% culture-positive patients (eberconazole 95.4%, clotrimazole 93.8%) at baseline, only 25.9% at week 4 and 23.9% at week 10 remained culture positive (eberconazole 21.5%, clotrimazole 24.3%). There was no statistically significant difference between the rate of reinfection and relapse in both the groups.<sup>[15]</sup> Subgroup

analysis of the same study showed that in ITT population, clinical efficacy (defined as the percentage effective response at week 4 of treatment) was higher with eberconazole (66.17%) than with clotrimazole (60.63%). In patients with pityriasis versicolor and candidiasis, no significant difference in therapeutic efficacy was noted with both agents [Table 3].<sup>[15],[16]</sup> Secondary analysis which included symptomatology, time to cure, results at week 4 and the investigators impression, did not show any statistically

significant differences.<sup>[14]</sup> In another study, eberconazole was more effective against dermatophytosis with a response rate of 61% (for clotrimazole 46%) than candidiasis (effective response for clotrimazole 73% and eberconazole 50%). Overall efficacy was 72% for eberconazole and 61% for clotrimazole. There was no significant difference in relapse in both groups, 4% in clotrimazole and 1% relapse in eberconazole was noted.<sup>[17]</sup>

Clinical condition	Eberconazole (%)	Clotrimazole (%)
<b>Dermatophytosis</b>		
Effective response to therapy at 4 weeks	66.17	60.63
Effective response to therapy at the end of 10 weeks	61.70	58.4
<b>Candidiasis</b>		
Effective response to therapy at 4 weeks	63.64	80.77
Effective response to therapy at the end of 10 weeks <sup>†</sup>	63.64	84.62
<b>Pityriasis versicolor</b>		
Effective response to therapy at 4 weeks	84.09	80.95
Effective response to therapy at the end of 10 weeks	81.82	78.57

(Considering missing values as failures), <sup>†</sup>The percentage effective response was the same in those treated with Eberconazole at week 4 and week 10, \*Source: Innovators (LaboratoriosSalvat, S.A) product information dated 16 Dec 2001

A phase III Indian study (n=92) with a treatment duration of 4 weeks followed by another 4 weeks follow-up, confirmed the earlier findings that eberconazole 1% is significantly effective against cutaneous dermatomycoses. The therapeutic efficacy was 97.44%; cure rate defined as negative microscopy and culture and reduction in total symptom score  $\leq 1$  was 84.62% and improvement defined as negative microscopy and culture and reduction in total symptom score=2 was 12.82%. Only one patient failed to respond to treatment (failure to respond was defined as negative microscopy and culture and reduction in total symptom score  $> 2$  or microscopic

and/or culture positive, independent of total symptom score). Clinical improvement was seen within 2 weeks of therapy indicating an early response with eberconazole. Its good safety profile was confirmed as only one patient reported mild burning sensation over the site of application, which disappeared with continued treatment (Data on file).<sup>[18]</sup>

#### Safety

In a phase I study of single and multiple doses of topical eberconazole 2% use, no significant and evaluable changes were noted in vital signs, blood or urine

biochemical parameters of the volunteers. Eberconazole was not detected either in plasma or urine indicating no significant systemic absorption.<sup>[19]</sup>

Another phase I study demonstrated that topical eberconazole 1% (0.1 g), does not induce photosensitivity and phototoxicity indicating its good tolerability.<sup>[19]</sup>

On topical application, safety, tolerability and adverse event (AE) profile of eberconazole was similar to that of placebo. On single dose application, mild symptoms which were common to eberconazole and placebo were reported within the first hour. On multiple dose application, mild pruritus, occasional burning sensation, and mild skin dryness were seen with eberconazole and placebo as well, without showing a dose effect relationship. In the objective evaluation, the only change observed was slight erythema that appeared for the first time on day 3 (lasting 3 days). Later on day 9, two volunteers reported reddening (zone covered with eberconazole 2%) with light granulation associated with a mild pruritus and burning sensation of 1 and 3 days duration, and on day 10 one volunteer presented with light erythema that lasted 12 hours.<sup>[14]</sup>

Further, in a phase II study, eberconazole shared similar safety profile with clotrimazole, as there was no significant difference in the occurrence of AEs. Erythema and pruritus were the commonly seen AEs in this study [Table 4]. Mild irritation was seen in three of 60 patients and two patients withdrew from the study due to severe skin irritation.<sup>[22]</sup> In a phase III study, 20% patients in eberconazole group and 26% in clotrimazole group withdrew prematurely due to AEs in patients with candidiasis.<sup>[23]</sup> In another phase III study, local cutaneous irritation was seen in 6.1% of patients in eberconazole group and in 3.7% in clotrimazole group without any systemic or serious events and the difference between the two groups was not significant.<sup>[14]</sup>

In two studies which evaluated eberconazole for its a) topical and general tolerability, b) eventual development of sensitization, c) local availability, and d) degree of systemic absorption, the only change observed was slight redness in a few volunteers after both active and placebo applications. This remitted spontaneously without intervention and the study was continued with the administration of repeated increasing doses. A few participants described mild side effects which occurred in areas where placebo or eberconazole were applied, mainly within the first hour of application. The most frequent adverse effect after the first application was coldness, and after repeated increasing-doses was itching. No signs or symptoms of skin reactivity were observed following re-exposure to the product. Vital signs (systolic and diastolic blood pressure, heart rate and body temperature), ECG, or analytical parameters (clinical hematology and biochemistry) did not show any clinically significant or relevant changes. The quantity of

compound collected through washing gauzes decreased progressively over time. Plasma and urine concentrations of eberconazole were below the quantification limits of the analytical method at all times. This study has confirmed that eberconazole cream is a topical anti-mycotic drug having good local and general tolerability. It also showed acceptable topical availability without detectable systemic drug levels, and did not appear to cause skin sensitivity.<sup>[24]</sup> No phototoxicity or photosensitivities were seen with topical application of eberconazole 1% cream.<sup>[11]</sup>

#### Formulation advantage

Eberconazole has been marketed as a cream with a characteristic lipophilic-hydrophilic molecular structure for better penetration of fungal cell membrane and prolonged duration of action. The galenic components of this topical azole favor and optimize the drug's action in the skin, fatty acid esters facilitate penetration in the skin and make the cream easy to spread, while polyacrylamides produce a filmogenous effect and facilitate the continuance of the active principle in the skin.<sup>[12]</sup>

#### DISCUSSION

Eberconazole's broad spectrum of anti-mycotic activity against yeast and fungi, high efficacy in the preclinical studies led to its clinical development to explore safety and efficacy in humans. Its anti-inflammatory action and efficacy against gram positive bacteria can add to its efficacy in inflamed cutaneous mycoses and in secondary infections, favoring the regression of inflammatory symptoms and treatment compliance. Eberconazole is clinically effective in the treatment of topical fungal infections, with a good safety profile and good tolerability. It has acceptable topical availability with no detectable systemic drug levels, and does not appear to cause skin sensitivity.<sup>[24]</sup>

Eberconazole was more active *in vitro* against a broad range of dermatophyte species than the other topical drugs tested suggesting that it may be a good alternative for the topical treatment of dermatophytosis.<sup>[15]</sup> Various clinical studies have documented its efficacy in the treatment of dermatophytosis. Eberconazole showed greater therapeutic efficacy than clotrimazole 1% and equivalent efficacy with miconazole 2% in the management of dermatophytosis and was similar in efficacy in the management of cutaneous candidiasis and pityriasis versicolor.<sup>[16]</sup>

The results of study in Indian patients<sup>[21]</sup> has confirmed the earlier findings that eberconazole 1% is significantly effective against cutaneous dermatomycoses and the reported AEs were similar to that seen in other studies indicating that it is well tolerated in majority of patients. Data, available on eberconazole, is quite limited. Data on its metabolism and excretion are still not available<sup>[11]</sup> thereby requiring further studies. Although it is effective against triazole resistant yeasts<sup>[12]</sup> it is found to be less

effective clinically compared to clotrimazole 1%<sup>[20]</sup> thereby limiting its use in this condition. Moreover, comparative efficacy is yet to be established with allylamines and other new antifungal agents.

The rise in fungal infections due to increase in incidence of immunocompromised states, change in socioeconomic and cultural states is demanding an effective antimycotic agent for the treatment and cure. Superficial fungal infections being more prevalent in tropical countries, an antimycotic agent having good safety profile and better efficacy with less chance of developing drug resistance such as eberconazole is always welcome.

With newer antifungal agents flooding the market, eberconazole's effectiveness in the treatment of a wide range of cutaneous fungal infection in comparison with the existing and newer agents has to be established to determine its place in the topical therapy of fungal infections in future.

## CONCLUSION

Complexities in the treatment of dermatomycosis have compelled the invention of newer antifungal agents with better efficacy and safety profile. Proven better efficacy, good safety and tolerability profile of eberconazole along with lack of sensitizing ability make it an attractive and suitable alternative in the management of dermatomycosis. However, further comparative studies with other commonly used agents are required to position eberconazole among topical antifungals.

## REFERENCES

- Havlickova B, Czaika VA, Friedrich M. Epidemiological trends in skin mycoses worldwide. *Mycoses*, 2008; 51: 2-15.
- Drake LA, Dinehart SM, Farmer ER, Goltz RW, Graham GF, Hardinsky MK, et al. Guidelines of care for superficial mycotic infections of the skin: tinea corporis, tinea cruris, tinea faciei, tinea manuum, and tinea pedis. *J Am Acad Dermatol*, 1996; 34: 282-6.
- Charles AJ. Superficial cutaneous fungal infections in tropical countries. *Dermatol Ther*, 2009; 22: 550-9.
- Nelson MM, Martin AG, Heffernan MP. Superficial fungal infections: Dermatophytosis, Onychomycosis, Tinea Nigra, Piedra. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, editors. *Fitzpatrick's Dermatology in General Medicine*. 6th ed. New York: McGraw Hill, 2003; 1989.
- Eberconazole [internet]. North Carolina: ChemBlink Inc.; Available from: <http://www.chemblink.com/products/128326-82-9.htm>. [last cited on 2011 Oct 10].
- Tomás JM, Camprubí S, Merino S, Parés R, Llauredó X, Julve J. Inhibition of two imidazole antimycotics, eberconazole and clotrimazole, by different components of *Candida albicans* serotype B membrane protoplasts. *Int J Antimicrob Agents*, 1993; 3: 61-4.
- Information from Data on file; from Innovators (Laboratorios Salvat, S.A) product information. Part III. Vol. 2. dated 16 Dec 2001.
- Torres-Rodríguez JM, Madrenys-Brunet N, Montsant L. Topical treatment with eberconazole of the experimental guinea pig cutaneous candidosis. *Rev Iberoam Micol*, 1999; 16: 43-5.
- Eberconazole (Eberconazol, Eberconazole nitrate, WAS 2160). *Drugs R D*, 2002; 3: 352-4.
- Fernández-Torres B, Inza I, Guarro J. In vitro activities of the new antifungal drug Eberconazole and three other topical agents against 200 strains of dermatophytes. *J Clin Microbiol*, 2003; 41: 5209-11.
- Thomson Reuters Pharma™ [Internet]. Drug report: Eberconazole. Thomson Reuters Pharma™. Updated on 12/ Aug/2010.
- Font E, Freixes J, Julve J. Profile of a new topical antimycotic, eberconazole. *Revista iberoamericana De Micologia*, 1995; 12: 16-7.
- Rubin AI, Bagheri B, Scher RK. Six novel antimycotics. *Am J Clin Dermatol*, 2002; 3: 71-8.
- Laboratorios Salvat, S.A (Innovators). Product information, 2001
- Fernández-Torres B, Inza I, Guarro J. In vitro activities of the new antifungal drug eberconazole and three other topical agents against 200 strains of dermatophytes. *J Clin Microbiol*, 2003; 41: 5209-11.
- Martin-Gonzalez B, Vilata-Corell JJ, Linares ML, Laguna-Argente C, Roche-Gamon E. Treatment in superficial cutaneous mycoses with eberconazole [Spanish]. *Med Clin*, 2006; 126: 47-50.
- del Palacio A, Cuétara S, Rodríguez Noriega A. Topical treatment of tinea corporis and tinea cruris with eberconazole (WAS 2160) cream 1% and 2%: a phase II dose-finding pilot study. *Mycoses*, 1995; 38: 317-24.
- High WA, Fitzpatrick JE. Topical antifungal agents. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, editors. *Fitzpatrick's Dermatology in General Medicine*. 7th ed. New York: McGraw Hill, 2008; 2116-8.
- Repiso Montero T, López S, Rodríguez C, del Rio R, Badell A, Gratacós MR. Eberconazole 1% cream is an effective and safe alternative for dermatophytosis treatment: multicenter, randomized, double-blind, comparative trial with miconazole 2% cream. *Int J Dermatol*, 2006; 45: 600.
- High WA, Fitzpatrick JE. Topical antifungal agents. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, editors. *Fitzpatrick's Dermatology in General Medicine*. 7th ed. New York: McGraw Hill, 2008; 2116-8.
- Fonseca Capdevila E. Effectiveness of Eberconazole 1% cream as opposed to Clotrimazole 1% cream in patients with cutaneous mycosis. *Skin*, 2004; 19: 480-4.
- del Palacio A, Ortiz FJ, Pérez A, Pazos C, Garau M, Font E. A double blind randomized comparative

trial: eberconazole 1% cream versus clotrimazole 1% cream twice daily in *Candida* and dermatophyte skin infections. *Mycoses*, 2001; 44: 173-80.

23. Dr. Reddy's Laboratories Ltd. Efficacy and safety evaluation of Eberconazole in cutaneous dermatomycoses. CT report 2006.
24. Rius-Tarruella J, López-Bertran R, Viayna-Cardona C. A phase I photosensitivity/phototoxicity study of eberconazole cream in twelve healthy subjects. *Publicadona Piel*, 2005; 20: 314-6.