Autobiography of
SERTACONAZOLE

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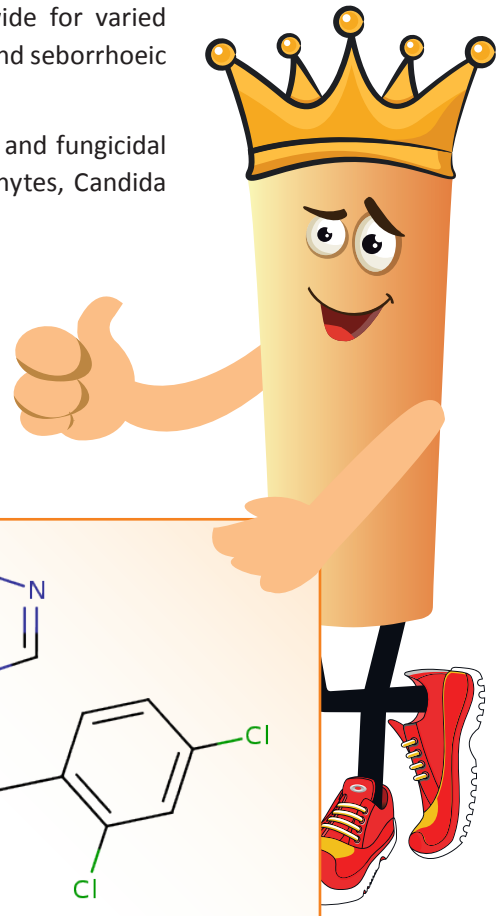
PREFACE

Dermatophytosis or tinea infection is an extremely common dermal fungal infection occurring throughout the world. It is caused by dermatophytes belonging to genera of Trichophyton, Microsporum and Epidermatophyton. Almost three-fourth of the population worldwide is most frequently affected by a dermatophyte infection, usually tinea pedis. The fungal infections of the skin are more frequently reported in tropical countries like India due to environmental factors, such as heat and humidity.

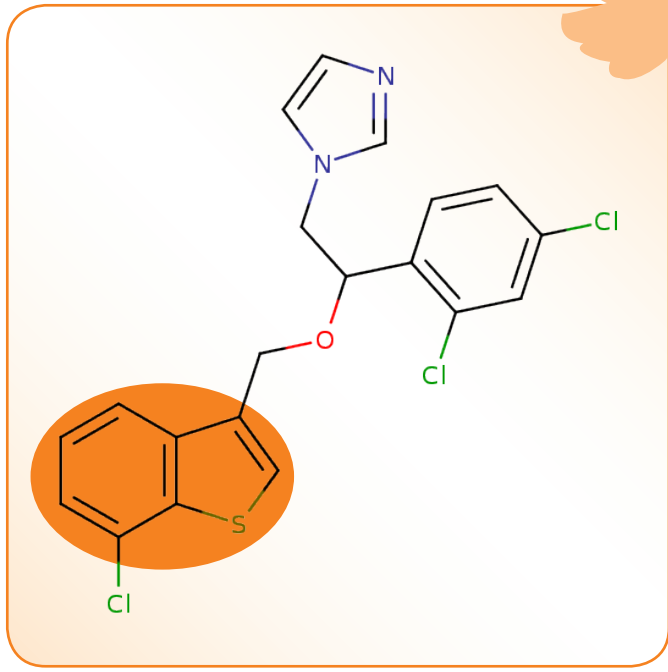
A number of azole antifungal agents are frequently used to treat these superficial fungal infections. However, over the past few decades, an increase in the use of immunosuppressive agents for autoimmune diseases and other medical conditions have led to a dramatic increase in the incidence and severity of fungal infections. This has also added to the common problem of drug resistance. Therefore, the need of hour is an antifungal agent that possesses effective antifungal activity and at the same time has comparatively better resistance profile. Sertaconazole nitrate is one such antifungal agent that was approved by the US FDA for treating tinea pedis in 2003. A large body of evidence accrued from emerging clinical reports suggests that it is a truly unique and effective agent for the management of various dermatophyte infections. It offers a favorable safety profile that makes it a more suitable treatment option.

"Autobiography of Sertaconazole" aspires to update the busy medical professionals with the recent clinical reviews and researches on the drug enabling them to apply the latest knowledge to their practice. The premise is to bring to light its safety and efficacy, and encourage its rational use in individuals with various dermal fungal infections including tinea infections. The information in this journal is expected to be of interest and value to the readers and help them in their daily practice.

About me: A molecule with unique structure and dual mechanism of action



- I am a broad-spectrum antifungal agent that is being used worldwide for varied indications including tinea infections, candidiasis, pityriasis versicolor, and seborrhoeic dermatitis of scalp.[1,2]
- Chemically, I am an imidazole derivative that exhibits both fungistatic and fungicidal activity against a wide range of micro-organisms including dermatophytes, Candida spp., Aspergillus, and Cryptococcus fungi.[1,3,4]
- I am structurally unique from other azole antifungals as I contain a benzothiophene ring, which mimics tryptophan and increases my ability to penetrate and form pores in the fungal cell membrane.[4,5]
- In addition, my unique structure offers higher lipophilicity and aids in prolonged dermal retention for up to 48 hrs, without increasing systemic absorption.[1,4,5]
- This leads to greater mycological cure rates and lesser chance of relapse.[1]
- I have a dual mechanism of action:
  - Firstly, I inhibit the synthesis of ergosterol by blocking the enzymatic pathway of cytochrome P450, leading to increased cell wall permeability
  - Secondly, I bind directly to non-sterol lipids on the fungal cell membrane and interfere with ligands from the intra-cellular contents, thus leading to their rapid leakage and ultimately resulting in cell death.[1,4,6,7]
- In fact, I am the only azole with a fungicidal action due to my ability to cause direct fungal cell membrane damage; this is made possible by my unique chemical structure.[5]



I am a potentially useful antifungal agent in the era of rising drug resistance

- Interestingly, I am also effective against dermatophyte isolates that are resistant to other azoles.[5]
- In a study[8] conducted to compare my in vitro antifungal activity against 250 strains belonging to 15 species of clinically important dermatophytes and Scopulariopsis against various other antifungal agents, I was associated with 4% resistance as compared to 48% observed for fluconazole (Figure 1).[8]
- In another study[1] that compared my efficacy and safety against terbinafine and luliconazole in patients with dermatophytoses, it was observed that greater proportion of patients in my group (85%) had resolution of pruritus as compared to terbinafine (54.6%); and luliconazole (70%); Figure 2.
- Moreover, patients in my group had a greater reduction (97.1%) in mean total composite score (pruritus, erythema, vesicle and desquamation) as compared to terbinafine (91.2%) and luliconazole (92.9%).

Figure 1: Resistance to sertaconazole and fluconazole in various clinically important dermatophytes[8]

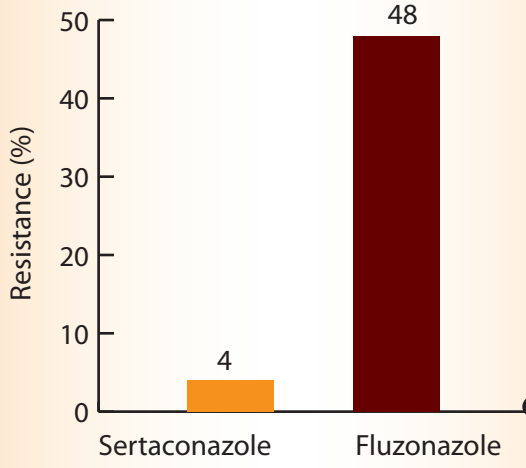
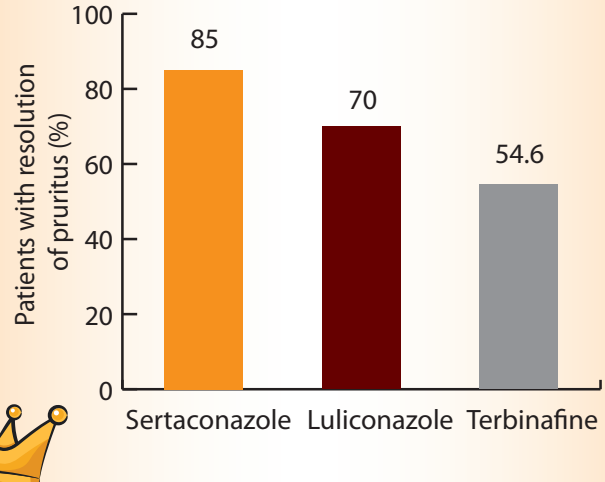
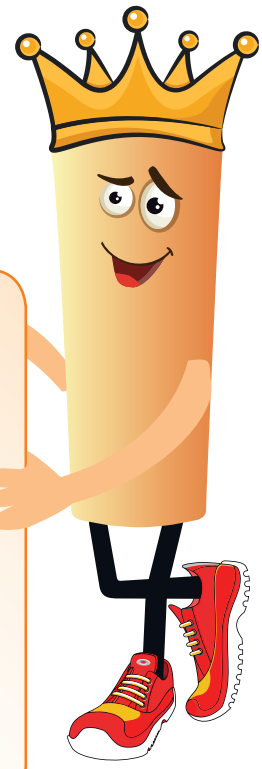


Figure 2: Efficacy of sertaconazole versus luliconazole and terbinafine in resolution of pruritus in patients with dermatophytoses[1]



A brief on my effective pharmacokinetic profile

- An important aspect in the successful treatment of mycotic infections is rapid action of the antifungal agent at the site of infection, which requires the drug to attain therapeutically effective concentrations without substantial systemic absorption.[9]
- After cutaneous application, my systemic absorption is negligible, with no detectable presence in serum or urine.[9]
- My unique lipophilic benzothiophene ring enhances my ability to penetrate the stratum corneum and enhances cutaneous retention.[9]
- Therefore, I attain effective fungicidal concentration in the stratum corneum after cutaneous application.[5]
- Importantly, therapeutic concentrations persist in the skin after application, and it has been found that the percentage of cutaneous absorption 24 hours post-application was 72% of the dose applied.[9]
- My rapid appearance in the stratum corneum and prolonged dermal retention translate into the need for less frequent applications in clinical practice and allows for just once-daily application contrary to most other topical azoles.[5,9]
- In a study involving 400 adult patients with tinea of glabrous skin, I (as 2% cream), used once daily for three weeks resulted in a higher cure rate (82%) as compared to vehicle (61%). This also improves patient compliance and lowers treatment cost.[9,10]
- Of note, I am also available as a vaginal tablet for the treatment of vulvovaginal candidiasis (VVC). Evidence suggests that I am a more convenient (single-dose) and symptom-relieving option for VVC than the conventional 3-dose econazole vaginal tablet.[11]
- Sertaconazole mouth paint dosage in pediatrics: 10-20 drops gently applied to all lesions in the mouth; preferably with cotton bud, 3-4 times/day.



Effective pharmacokinetic profile of sertaconazole[9,10]

- Negligible systemic absorption post-cutaneous application
- No detectable presence in serum or urine
- Enhanced ability to penetrate the stratum corneum
- Rapid appearance in the stratum corneum post-administration
- Prolonged dermal retention
- Need for less frequent applications
- Favorable for once-daily antimycotic therapy

I am a highly effective antifungal agent

- I provide faster and superior cure rates as compared to other azoles.[5] This has been substantiated by a large pool of studies.
- My safety and efficacy in the treatment of tinea pedis was assessed by 2 randomized, multicenter, double-blinded, parallel group, vehicle-controlled studies.[12] I (2% cream), or vehicle, was randomly assigned to 383 patients for twice daily application for 4 weeks. Improvements in symptoms were reported at week 1 in the active treatment group. At week 4, I brought about mycologic cure in 70.3% of patients as compared to 36.7% of vehicle-treated patients. Moreover, at week 6, 46.7% of patients treated with me had successful treatment outcomes compared with 14.9% of vehicle-treated patients (Figure 3).
- Findings of the study substantiate that I, as 2% cream, am well-tolerated, offer rapid relief of symptoms, and achieve high rates of mycologic cure.
- Interestingly, the stability of the mycologic cure rates through weeks 5 and 6 (2 weeks after cessation of therapy) suggest that I also protect against reinfection.[12]
- In another study[2] involving 92 patients with tinea pedis interdigitalis, 88.8% (79/89) of evaluable patients treated with me (for 4 weeks) achieved success on the primary end points (eradication of the pathogen and reduction in total clinical score of at least 2 points).
- The rate of reported adverse events was low (8.7% [8/92]), and none were considered serious. These findings suggest that I am effective and well-tolerated in the treatment of tinea pedis interdigitalis.

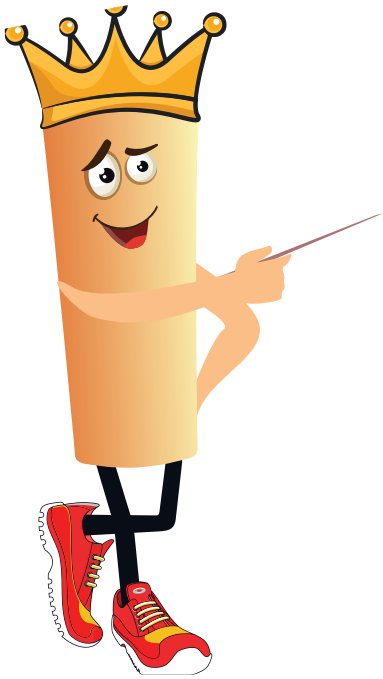
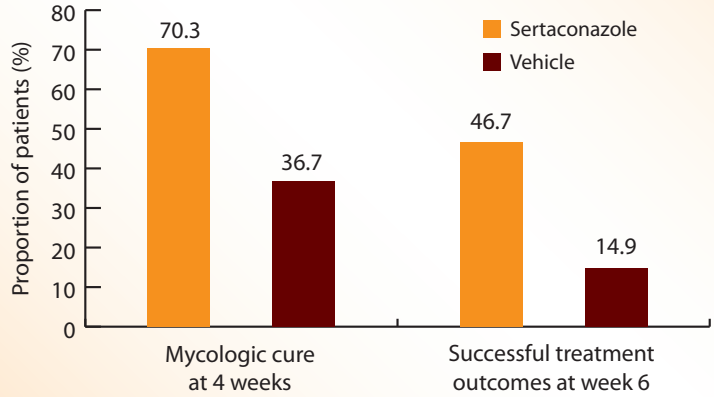
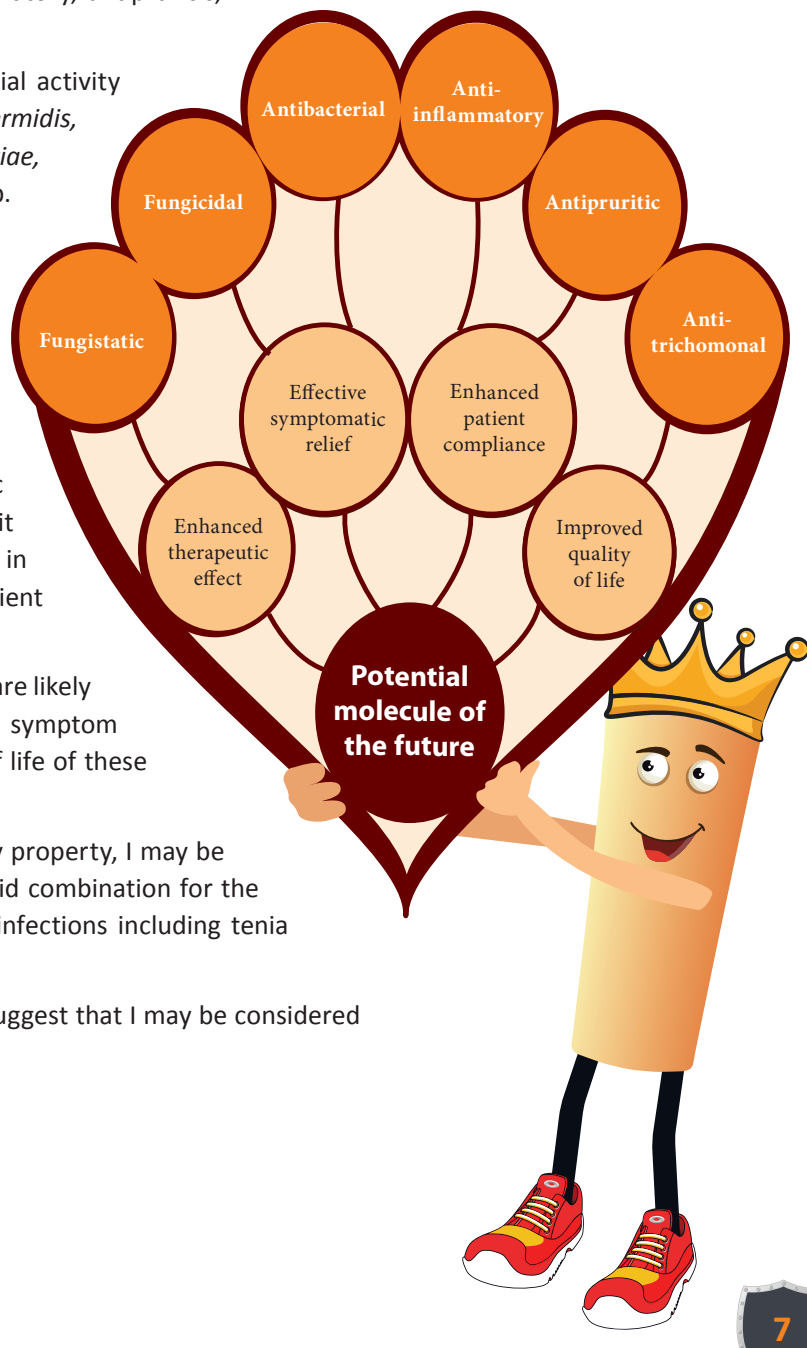


Figure 3: Efficacy of topical sertaconazole nitrate cream 2% in the treatment of tinea pedis[12]



My pleiotropic effect: Antibacterial, Anti-inflammatory, antipruritic and antitrichomonal activity

- Besides having antifungal activity (fungistatic and fungicidal), I also possess antibacterial, anti-inflammatory, antipruritic, and antitrichomonal activity.[3,5,6]
- I have demonstrated in vitro antibacterial activity against *Staphylococcus aureus, S. epidermidis, Streptococcus pyogenes, S. agalactiae, Listeria monocytogenes*, Gardnerella spp. and other bacteria that are likely to cause secondary infection.[1,13]
- Cutaneous fungal infections are usually associated with an inflammatory component including irritated skin, itching and stinging/burning.[14]
- My anti-inflammatory and anti-pruritic properties provide clinical benefit beyond fungus eradication, resulting in symptomatic relief and adding to patient benefit.[1,14]
- These ancillary properties that I possess are likely to make an impact on the concomitant symptom control and therefore improve quality of life of these patients with dermatophytoses.[1]
- Since I possess potent anti-inflammatory property, I may be a better option than an antifungal-steroid combination for the treatment of various cutaneous fungal infections including tenia pedis.[15]
- The aforementioned data convincingly suggest that I may be considered molecule of the future.



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