CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-124

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA:	21-124	**Submission Date:**	5/14/99
Product:	Terbinafine HCL 1% Topical Solution Lamisil®AT™Smart Pump™		
Sponsor:	Novartis Pharmaceutical Corp East Hanover, NJ 07936	**Reviewer:**	Abimbola Adebowale Ph.D.

Review of an Rx to OTC Switch NDA

I. Background

Terbenafine is a synthetic allylamine derivative with a broad spectrum of antifungal activity. It exerts its antifungal activity by inhibiting squalene oxidase, a key enzyme in sterol biosynthesis in fungi. This action results in a deficiency in ergosterol and, a corresponding accumulation of squalene within the fungal cell resulting in fungal cell death. Terbinafine HCL solution, 1% spray form (NDA 20-749) approved on October 17th, 1997, is currently available as a prescription only product on the U.S market. The other prescription only products of terbinafine currently on the market include an oral 250 mg tablet (NDA 20-539) approved on May 10th, 1996 and, a topical emulsion gel (NDA 20-846) approved on April 29th 1998. Terbinafine is also available on the US market as a topical cream prescription product (NDA 20-192) approved on December 30th, 1992 and OTC product (NDA 20-980) approved on March 9th, 1999.

This NDA represents a partial move of terbinafine 1% solution spray from prescription to OTC status for the topical treatment of interdigital tinea pedis (athlete's foot), tinea cruris (jock itch and tinea corporis (ringworm) due to Epidermophyton floccosum, Trichophyton mentagrophytes and, Trichophyton rubrum. These indications are the same as for the approved OTC terbinafine 1% cream. The indication for the topical treatment of tinea versicolor and plantar tinea pedis approved under NDA 20-749 will remain prescriptive indications. The sponsor is also seeking OTC approval for the dropper solution dosage form which, is not currently marketed by Novartis Pharmaceuticals Corporation in the USA, although it was studied.

II. Formulation

The solution formulation for OTC marketing is identical to that approved for the prescription product on October 17th, 1997 under NDA 20-749. The sponsor stated that the

marketed product has remained unchanged since its introduction in the US in early 1998. In this submission the sponsor did not supply any new formulation information except a reference back to the original NDA submission materials and annual reports for the specifications and manufacturing controls.

III. Biopharmaceutics

Lamisil ®1% solution spray (NDA 20-749) was originally reviewed in the Division of Biopharmaceutics by Dennis Bashaw Pharm. D in 1996. In the original NDA the sponsor submitted three human pharmacokinetic studies:

1. SFF 101 E-00
   A bioavailability study of terbinafine HCL 1% solution in subjects with normal skin applied once daily for 7 days.

2. SFF 103-E-00
   A bioavailability study of terbinafine HCL 1% solution in patients with tinea cruris applied once daily for 7 days.

3. SFF 307-E-00
   Dermatopharmacokinetics of the 1% solution, delivered by dropper or spray dispenser, and the 1% cream in healthy subjects applied once daily for 1 or 7 consecutive days.

The synopses from the three human pharmacokinetic studies were included in this submission. There were no biopharmaceutic deficiencies in the original review of these studies. Review of the bioavailability studies in normal and diseased skin, indicated that terbinafine is poorly absorbed into the systemic circulation. The plasma levels were either below or just at the limit of detection in all samples for parent and metabolite. Review of the dermatopharmacokinetics data indicated that there were no statistically significant differences in stratum corneum pharmacokinetics when Lamisil® was delivered using a 1% solution spray or 1% solution dropper dispenser, or as Lamisil® 1% cream following 1 or 7 days treatment. There were no new biopharmaceutics studies included in this submission.

III. Labeling

The proposed labeling for terbanifine HCL solution 1%, to be marketed OTC differs from the Rx label currently in use in three ways:

1. Indications are interdigital tinea pedis (athlete's Foot), tinea cruris (jock itch) and tinea corporis (ringworm)
2. OTC label states that the solution is not to be used in children under the age of 12 years.

3. Labeling is also included for the dropper, which is not currently marketed by Novartis Pharmaceuticals Corporation in the United States.

IV. Comments

1. The OTC indication, strength, duration of use, dose, route of administration and the dosage form are identical to that which was studied for the original Rx 1% spray product (with the exception of plantar tinea pedis and tinea versicolor indications), and, the currently marketed OTC 1% cream.

2. The proposed OTC label for the 1% solution stating that the solution should not be used in children under the age of 12 years is similar to the current Rx and OTC label for the 1% cream. The current Rx label for the 1% spray solution states that the safety and efficacy have not been established in pediatric patients and thus is slightly different. Since the biopharmaceutic studies have indicated that the systemic absorption of the 1% cream and the 1% solution are approximately the same, there does not appear to be a problem related to the extension of use in this population. Also the proposed OTC label for the 1% spray form gives a more definitive age group for the pediatric population.

3. From the biopharmaceutic perspective the inclusion of a label for the dropper does not appear to be a problem. Even though the 1% dropper solution dosage form has never been marketed in the USA, the dropper uses the same formulation of terbinafine 1% solution as the spray (thereby ruling out formulation effects). In addition the dropper dosage form was used in all three biopharmaceutic studies and, in study SFF 307 it was indicated that the systemic absorption of the 1% solution and the 1% spray were approximately the same.

V. Recommendation

This application for OTC marketing represents a partial move of a product from prescription to OTC status. As the population to be treated is identical to that which was originally studied with the prescription product and the OTC 1% cream, and there are no outstanding biopharmaceutic commitments from the 1% solution approval, the marketing of this product is acceptable from a biopharmaceutic perspective.

/S/

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Office of Clinical Pharmacology /Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT signed by Dennis Bashaw, Pharm.D. /S/ - 11/15/99

CC:
NDA 21-124
HFD-540 (Div. File)
HFD-540 (CSO/Cross)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Adebowale)
HFD-340 (Viswanathan)
CDR: ATTN: Barbara Murphy

/S/ 3/17/00