CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-980

MICROBIOLOGY REVIEW(S)

JUN 29 1998

Consultative Review for HFD-540
Division of Topical Drug Products
Division of Anti-Infective Drug Products (HFD-520)
Clinical Microbiology Review #1

Requester:	Frank Cross, Project Manager, HFD-540
Date of Request:	4-15-98
Reason for Request:	Clinical Microbiology Review of antifungal activity for Prescription to Over-The-Counter (OTC) switch
IND/NDA Number:	NDA # 20980
Review Date:	6-15-98
Submission/Type:	Original NDA
Document Date:	3-27-98
CDER Date:	3-30-98
Assigned Date:	4-16-98
Applicant:	Novartis Pharmaceuticals Corp. Drug Regulatory Affairs 59 Route 10 East Hanover, NJ 07936-1080
Contact Person:	Christine Babiuk, Ph.D., Associate Director Regulatory Affairs Novartis Consumer Health, Inc. 560 Morris Avenue Summit, NJ 07901-1312 Phone: (908) 598-7816
Drug Product Name:	
Proprietary:	Lamisil® Cream
Nonproprietary/USAN:	Terbinafine Hydrochloride Cream 1%
Code Names/#'s:	None
Chemical Type:	Allylamine derivative
Therapeutic Class:	3S

ANDA Suitability Petition/DESI/Patent Status:
Not Applicable

Pharmacological Category/Indication:
Antifungal—Allylamine derivative/Topical treatment of interdigital tinea pedis, tinea cruris, or tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes*, or *Epidermophyton floccosum*

Dosage Form:	Cream
Strength(s):	1%
Route of Administration:	Topical
Dispensed:	_____ **Rx** __X__ **OTC**

Supporting Documents:
NDA: 20192, 20539, 20749
IND:

REMARKS/COMMENTS:

This microbiological review is concerned with only the clinical aspects of this applications (mechanism of action, *in-vitro* activity, *in-vivo* animal models). A different consulting division reviews the microbiological aspects of the manufacturing controls for this product.

This NDA is for a product, which has previously been approved by FDA for treatment of tinea pedis, tinea cruris, or tinea corporis, due to *Trichophyton rubrum, Trichophyton mentagrophytes, or Epidermophyton floccosum.* The active ingredient is an allylamine derivative, terbinafine, with antifungal activity. Its antifungal activity is derived from inhibition of squalene epoxidase, a key enzyme in ergosterol biosynthesis. The antifungal activity of terbinafine is related to the corresponding accumulation of squalene within the fungal cell wall.

The applicant is seeking approval for switching from Prescription (Rx) to OTC status. There has been no change in the formulation of the drug product. However, the proposed labeling for terbinafine marketed OTC is different from the Rx label in three ways. First, the indications are tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis (ringworm); the moccasin type athlete's foot has remained a Rx indication. Second, the label states the cream is to be applied twice a day (athlete's foot) or once a day (jock itch and ringworm) for one week. The current Rx label states 1 to 4 weeks treatment. Third, in the Rx label it has been emphasized "Depending on the concentration of the drug and the fungal species tested in vitro, terbinafine hydrochloride may be fungicidal; however, the clinical significance of these data is unknown." This concept not only has been lost in the OTC label, but it has been misrepresented as follows:

"Small amounts of Trademark® applied to the affected area for 1 week, kill the fungi that causes athlete's foot, jock itch, and ringworm. Other non-prescription antifungal agents only prevent the growth of the offending fungi and they take 4 weeks for regular usage to completely cure athlete's foot, and 2 weeks for jock itch and ringworm. With Trademark® the treatment period is shortened to 1 week." NOTE: The proprietary name is listed as Trademark® in label pending its selection.

The treatment duration of 1 week for terbinafine hydrochloride 1% cream is being supported by nine clinical trials, four of which were submitted in the original NDA (20192). Dr. Brenda Vaughan is the Medical Officer responsible for the review of these clinical trials and she will determine whether reduction in treatment duration is justified. She will also determine whether the moccasin type athlete's foot should remain under prescription in which case the product label for Rx Lamisil 1% cream must be revised to reflect these indication changes. The Division of Over-The-Counter drug products is responsible for the final review of the label and its contents.

The followings are points that should be addressed in the final label:

1. Depending on the concentration of the drug and the fungal species tested in vitro, terbinafine hydrochloride may be fungicidal, however, the clinical significance of these data is unknown. In the label under the heading "How is Trademark® different from other antifungal products?" The sponsor states that the reason why their product works in one week is because it "kills" the fungi (i.e. it is fungicidal); and the other drug products on the market which work in 2-4 weeks, only "prevent the growth" (i.e. fungistatic) of the fungi. The studies conducted in support of one week treatment duration clearly demonstrate that it take up to 4 weeks before a significant number of patients are adequately treated. The Rx label states: "Improvement is gradual. In many patients with shorter duration of therapy (1-2 weeks), improvement continues during the 2-6 weeks after drug therapy has been completed." For the reasons just stated this reviewer believes the statements made by the sponsor in the OTC label under the heading "How is Trademark® different from other antifungal products?" are inappropriate and should be reworded to reflect the clinical and microbiological data.

2. The sponsor states that the labeling for athlete's foot is distinct from that for jock itch. To this effect the sponsor is proposing a separate carton for each of the tinea pedis (athlete's foot) and tinea cruris (jock itch) indications. The tube wrap in both cartons, however, states that the drug product is for treatment of tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis (ringworm). By doing this, the sponsor is misleading the consumers in believing that they must buy two different products to treat tinea pedis (athlete's foot) and tinea cruris (jock itch) should they occur in the same patient. In addition, the sponsor does not provide a carton for tinea corporis (ringworm) indication. It is this reviewer's opinion that the sponsor should have all three indications listed on the carton jus as they appear on the tube wrap.

CONCLUSION & RECOMMENDATIONS:

With respect to the specific consultation request, form the clinical microbiology viewpoint, the application is approvable. The sponsor should be notified to revise the package insert and the carton as indicated on page 3 of this review.

/S/

Sousan S. Altaie, Ph. D.
Clinical Microbiology Review Officer

cc: Orig. NDA 20-980
HFD-540/Division File
HFD-520/Micro/S. Altaie
HFD-540/MO/B. Vaughan
HFD-540/TL MO/S. Walker
HFD-540/PharmTox/K. Mainigi
HFD-540/TL PharmTox/A. Jacobs
HFD-540/TL Biopharm/D. Bashaw
HFD-540/Chem/J. Vidra
HFD-540/TL Chem/T. DeCamp
HFD-725/Stat/S. Thomson
HFD-725/TL Stat/R. Srinivasam
HFD-160/Micro/D. Hussong
HFD-160/TL Micro/P. Cooney
HFD-560/IDS/N. Mokhtari-Rajali
HFD-560/MO/S. Aurecchia
HFD-560/Dep.Dir./L. Katz
HFD-560/IDS/K. Freeman
HFD-540/PM/F. Cross
HFD-540/SPM/R. Cook
HFD-560/PM/S. Walther

Concurrence Only:
HFD-540/Div Dir./J. Wilkin
HFD-520/TL Micro/A. Sheldon
LD & Final 6/16/98 ATS 6/29/98
HFD-560/Div Dr/D. Bowen
6/29/98

540 Cross

JUL 16 1998

REVIEW FOR HFD-540
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA

July 8, 1998

A. 1. NDA 20-980

SPONSOR Novartis Pharmaceutical Corporation
59 Route 10
East Hanover, NJ 07936-1080

2. PRODUCT NAMES: Terbinafine Hydrochloride Cream, 1%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 15 gram and 30 gram tubes of cream for topical application

4. METHOD(S) OF STERILIZATION: Not sterile (microbial limits tests)

5. PHARMACOLOGICAL CATEGORY: Anti fungal

6. DRUG PRIORITY CLASSIFICATION: 5S

B. 1. DATE OF INITIAL SUBMISSION: March 27, 1998

2. DATE OF AMENDMENT: none

3. RELATED DOCUMENTS: NDA 20-192 (LAMISIL® Cream 1%)

4. ASSIGNED FOR REVIEW: April 22, 1998

C. REMARKS: This is the same product as NDA 20-192 (Rx), but is labeled differently for Over the Counter use. The prescription product has additional indications. NDA 20-192 from Sandoz Pharmaceutical Corporation was approved in December 1992. Sandoz Pharmaceutical Corporation is now Novartis Pharmaceutical Corporation.

D. CONCLUSIONS: The submission is recommended for approval.

/S/ 7-16-98

David Hussong, Ph.D.

Pitc 7/16/98

cc:

HFD 160/Consult File
HFD 540/Division File
HFD 540/CSO/F. Cross
HFD 540/Rev Chemist/ J. Vidra.
HFD 805/D. Hussong

Drafted by: D. Hussong, 07/08/98
R/D initialed by: P. Cooney

Filename, d:\nda\20-980r1.DOC