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APPLICATION NUMBER: NDA 20-980

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 20-980
Original

NDA # 20-980

Submission date: 03/30/98
Review completed: 01/29/99

Drug name:	Terbinafine Hydrochloride Cream, 1%
Chemical name:	(E)-N-(6,6-Dimethyl-2-hepten-4-inyl)-N-methyl-1-naphthalenemethanamine hydrochloride
Preferred trade name:	Lamisil®AT Cream
Back-up trade names:	Lamisil®PF Cream or Lamisil®ST Cream
Sponsor:	Novartis Pharmaceuticals Corporation
Pharmacologic Category:	Antifungal
Proposed Indication(s):	For Use Without Prescription of Terbinafine Hydrochloride Cream, 1% for the 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
Dosage Form:	Cream
Route of Administration:	Topical
NDA Drug Classification:	6S
Related NDAs:	20-192 (Lamisil Cream, 1%), 20-749 (Lamisil Solution/Spray, 1%) 20-539 (Lamisil Tablets)
Related INDs:	

Related Reviews:
Chemistry Reviews dated: 07-28-98 and 12-22-98
Statistical Review dated: 01-06-99
Pharmtox Review dated: 06-03-98
Biopharm Review dated: 06-15-98
Microbiology Review dated: 06-29-98 (Clinical) and 07-16-98 (CMC)

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Background

On 27 March 1998, Novartis Pharmaceuticals Corporation submitted New Drug Application 20-980. The application proposes the use without prescription of terbinafine hydrochloride (HCL) cream, 1% (i.e., Rx to OTC switch). Terbinafine HCl cream, 1% (Lamisil® Cream, 1%) is a synthetic antifungal agent of the allyamine class. Lamisil® Cream, 1% is approved for prescription use under NDA 20-192 for topical treatment of interdigital tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis (ringworm) due to *E. floccosum, T. mentagrophytes, or T. rubrum.* NDA 20-192 was approved December 30, 1992. Lamisil® Cream, 1% was approved under NDA 20-192/1S, for topical treatment of plantar tinea pedis (moccasin type) due to *T. mentagrophytes or T. rubrum* on January 21, 1997.

The OTC formulation will be identical to the currently approved prescription cream formulation. Terbinafine hydrochloride would be the first topical antifungal of the allylamine class to be available without prescription. The sponsor's initial proposal was to maintain plantar tinea pedis (moccasin type) as a prescription indication; however, this request was later changed.

A labeling change for the OTC product is also being requested. The proposed label (See FDA Form 356h dated 3/27/98) for the over-the-counter (OTC) terbinafine was different from the prescription label in that the plantar tinea pedis (moccasin type) was not requested for OTC status but requested to remain as a prescription indication. Second, the proposed label would state that the cream should be applied for shorter durations of therapy in all indications. These differences are summarized below:

	NDA 20-192 (Approved 1992)	**NDA 20-980 (March 28, 1998)**
Indication	**Rx treatment regimen**	**Proposed OTC Regimen**
Tinea cruris Tinea corporis	Once or twice daily for one to four weeks	Once daily for one week
Interdigital tinea pedis (athlete's foot)	Twice daily for one to four weeks	Twice daily for one week
TP- Moccasin	Twice daily for two weeks	OTC indication not requested

A teleconference was held with the sponsor on October 1, 1998 in which the agency informed the applicant that the indication of tinea pedis could not be divided into interdigital and moccasin type tinea pedis for an over-the-counter medication unless there was compelling evidence to support such a change from the OTC precedent. The applicant stated their intention to submit revised labeling and a labeling comprehension study. On October 27, 1998 the agency received a label comprehension study and carton labeling, in addition to an FDA 356h which listed the proposed indications as: tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis (ringworm).

The applicant proposed to bifurcate the label with graphic representations of athlete's foot located in the interdigital area and athlete's foot located on the bottom and sides of the foot.

	NDA 20-192/1S7. (January 1, 1997)	NDA 20-980 (October 27, 1998)
Tinea pedis (between toes)	Twice daily for one to four weeks	Twice daily for one week
Tinea pedis (bottom and sides)	Twice daily for two weeks	Twice daily for two weeks

New clinical studies with the exception of Study 2508-01 were conducted in the United Kingdom (UK). The sponsor regards the UK studies as applicable to the US population because the distribution of pathogenic organism is similar, the epidemiology of the treated disease is comparable, the drug is topical without population-based pharmacologic differences, and demographic data for patients are claimed to be comparable.

3 Material Reviewed NDA 20-980 (Volumes 1.1 -1.3 and Vols. 8 - 21), NDA 20-192 Medical Officer's review stamp dated September 25, 1992, NDA 20-192/1S Medical Officer's review stamp dated March 23, 1994, and an amendment dated 09-04-98. The following submissions to NDA 20-980 were reviewed:

Document Identification	Date Received
20-980 BZ	06-17-98
20-980 BC	10-16-98
20-980 BL	10-27-98
20-980 BC	10-28-98
20-980 BL	11-25-98

Memoranda of Teleconferences dated: April 15, 1998; April 30, 1998; and October 1, 1998.

4 Chemistry/Manufacturing Controls *(See Chemistry Review.)*

5 Animal Pharmacology/Toxicology

The sponsor provided nonclinical pharmacology and toxicology summaries for this NDA. Pharmacology and toxicology sections from NDA 20-192 were incorporated by cross reference by the sponsor.

Non-clinical Pharmacology Summary

According to the sponsor, data demonstrates that no relevant central nervous system, cardiovascular/respiratory/autonomic, or immunological effects were observed in response to treatment with terbinafine hydrochloride. Support of these data were extracted from the pharmacology sections contained in the following applications:

- NDA 20-192, Lamisil Cream, 1% , Section V (Vol. 8), approved December 30, 1992
- NDA 20-539, Lamisil Tablets (Vol. 5), approved May 10, 1996
- NDA 20-749, Lamisil Solution, 1% (Vol. 5), approved October 17, 1997

Nonclinical Toxicology Summary

The toxicology summary for NDA 20-539, Lamisil® Tablet, is provided because it contains a more comprehensive overview of rodent carcinogenicity data and a more updated summary from the terbinafine cream application, NDA 20-192 (volumes 8 - 32). The NDA for the 250 mg (base equivalents) tablet of terbinafine HCl was approved on May 10, 1996.

Results of studies in mice, rats, rabbits, dogs, and monkeys with terbinafine HCl (SF 86-327) have demonstrated minimal toxicity and is well tolerated in laboratory animals. The results of these studies, and the evaluation of metabolism and pharmacokinetic data, have demonstrated large safety ratios for oral administration of Lamisil® Tablets to humans. This conclusion is supported by long-term clinical use of the drug without reported serious adverse effects. Based on this information there exist no safety concerns to the general public associated with the over-

the-counter use of terbinafine cream.

6 Clinical Background

6.1 Relevant human experience

The United States is the largest market for sales of terbinafine with approximately tubes being sold since launch in 1993; however, tube size was not specified. World-wide distribution was reported to be units sold through 1996.

A total of 3,550 patients participated in 50 clinical trials conducted by the sponsor in the United States, the United Kingdom, Central America, and South America. During conduct of these trials, terbinafine was received by 2,265 (64%) of the patients, 656 (19%) received placebo, and 629 (18%) received active control.

6.2 Important information from related INDs and NDAs

Studies 2-1, 2-2, 3-1, and 3-2 are being referenced from NDA 20-192. Studies 2509-01 and 2509-02 are being referenced from NDA 20-192/1S.

6.3 Foreign experience

Terbinafine hydrochloride cream was first approved on October 3, 1990 in Great Britain. Terbinafine hydrochloride cream has been approved for use by prescription in 81 additional countries. It has been sold worldwide in 43 non-US countries from 1992 through 1996. Terbinafine hydrochloride cream has not been withdrawn from marketing in any country for reasons related to safety and efficacy.

In June 1992, terbinafine cream was approved for use without a prescription in New Zealand. It is also available over-the-counter with and without prescription in Australia, Denmark, Korea, South Africa, Sweden , and Switzerland.

6.4 Human Pharmacology, pharmacokinetics, pharmacodynamics

For Human Pharmacokinetics and Bioavailability data, reference is made to NDA 20-192 (volumes 35 - 46) for Lamisil ® Cream, 1%, approved December 30, 1992 and to NDA 20-539 (volumes 2.9 - 2.45) for Lamisil ® Tablets approved May 10, 1996.

Topical application of ^{14}C radiolabeled SF 86-327 (Lamisil^{R}, terbinafine, or Sandoz Code SF 86-327) 1% cream to man established absorption at 4%. The oral absorption of SF 86-327 was shown to be at least 70%. Metabolic pathways studies suggest that metabolic patterns are qualitatively similar in man when SF 86-327 is administered by topical and oral routes. Systemic side effects would not be expected to be seen with topical exposure to terbinafine as

observed with Lamisil tablets.

Terbinafine HCl, a member of the allylamine family, lacks affinity for human cytochrome P-450 enzymes. As a result of this lack of affinity for human cytochrome P-450 enzymes, there appears to be little potential for drug interactions or toxicity related to inhibition of these enzymes.

The sponsor asserts that terbinafine HCl cream, 1% is fungicidal. A fungicidal claim does not have clinical significance for this OTC product. The exfoliative nature of the epidermis in addition to decreased fungal replication would have the same effect whether the mechanism of action is fungicidal or fungistatic.

6.6 Directions for Use (NDA 20-980 BL received 10-27-98):

- Open tube by using the top of the cap to puncture the seal.
- Wash the affected area with soap and water and dry completely before applying Lamisil AT Cream.
- For athlete's foot:
  Between the toes only:
  For 1 week apply Lamisil AT Cream between the toes and surrounding areas twice a day (morning and night) or as directed by a doctor.
  On the bottom or sides of the foot:
  For 2 weeks apply Lamisil AT Cream to the bottom or sides of the foot and surrounding areas twice daily (morning and night) or as directed by a doctor.
- If you have athlete's foot, wear well-fitting ventilated shoes and change shoes and socks at least once daily.

For jock itch and ringworm:

- For 1 week apply Lamisil AT Cream to the affected and surrounding areas once a day (morning and night) or as directed by a doctor.
- Do not use on children under 12 years of age and supervise children 12 and over in the use of this product.

7 Description of Clinical Data Sources

Nine clinical studies were submitted in the initial NDA. Four of the nine studies were previously submitted under NDA 20-192 and are identified as original studies. The remaining five studies are identified by the sponsor as new studies. The original studies submitted under NDA 20-192 are interdigital tinea pedis studies (2-1 and 2-2) and tinea corporis/cruris studies (3-1 and 3-2).

With the sponsor's decision to request approval of use without prescription for treatment of moccasin type tinea pedis, additional studies not originally referenced in this NDA are included. Studies 2509-01 and 2509-02 provided evidence of safety and efficacy for approval of treatment with terbinafine HCl cream, 1% for moccasin type tinea pedis at twice daily applications for 2 weeks under NDA 20-192/1S.

The clinical studies reviewed follow with study number, indication, title, and source.

Indication # 1: Tinea pedis (interdigital and moccasin)

A) Original Studies (from NDA 20-192)

Study #	Title
2-1	"A Double-Blind, Parallel, Multicenter Trial Comparing the Efficacy and Safety of 1% Terbinafine Cream and Placebo Cream the in the Treatment of Tinea Pedis Athlete's Foot (Interdigital Lesions)"
2-2	"A Double-Blind, Parallel, Multicenter Trial Comparing the Efficacy and Safety of 1% Terbinafine Cream and Placebo Cream the in the Treatment of Tinea Pedis Athlete's Foot (Interdigital Lesions)"

B) New Studies (interdigital)

Study #	Title
2508-01	"A Double-Blind, Parallel, Multicenter Trial Comparing the Efficacy and Safety of 1% Terbinafine Cream with 1% Clotrimazole Cream the in the Treatment of Tinea Pedis (Interdigital Type) Athlete's Foot"
SF0040	"A Double-Blind, Randomized, Parallel Group Study to Compare Lamisil ® (Terbinafine) 1% Cream Given for One Week with Canesten® (Clotrimazole) 1% Cream Given for Four Weeks in Tinea Pedis (Athlete's Foot Type)."
SF0029	"A Double-Blind, Randomized, Parallel Group Study to Investigate the Safety and Efficacy of Lamisil ® (terbinafine) Cream Applied Once for One Day, Three Days, Five Days, or Seven Days in Patients with Tinea Pedis"

C) Additional Studies (moccasin) referenced from NDA 20-192/1S:

Study #	Title
2509-01	"A Double-Blind, Randomized, Parallel-Group, Vehicle Controlled Multicenter Study in Patients with Tinea Pedis of the Moccasin Type"
2509-02	"A Double-Blind, Randomized, Parallel-Group, Vehicle Controlled Multicenter Study in Patients with Tinea Pedis of the Moccasin Type"

Indication #2: Tinea corporis/cruris

A) Original Studies (from NDA 20-192)

Study #	Title
3-1	"Double-Blind, Multicenter, Clinical Therapeutic Trial of the Efficacy and Safety of Topical Terbinafine 1% Cream Applied Once Daily Compared to Vehicle During One Week in Patients with Tinea Corporis/Cruris"
3-2	"Double-Blind, Multicenter, Clinical Therapeutic Trial of the Efficacy and Safety of Topical Terbinafine 1% Cream Applied Once Daily Compared to Vehicle During One Week in Patients with Tinea Corporis/Cruris"

B) New Studies

Study #	Title
SF2003	"A General Practice Multicenter Double-Blind Therapeutic Trial of the Efficacy and Safety of Topical SF86-327, 1% Cream Applied Once Daily Compared to Its Vehicle During One Week in Patients with Tinea Corporis/Cruris"
SF2030	"A Double-Blind, Randomized, Parallel Group Study to Investigate the Safety and Efficacy of Lamisil® (Terbinafine) 1% Cream Applied Once Daily for One Day, Three Days, Five Days, or Seven Days in Patients with Tinea Corporis/Cruris"

8 Clinical Studies

Indication # 1 Tinea Pedis Indication (interdigital and moccasin)

Studies 2-1, 2-2, 2509-01, and 2509-02 have been identified as pivotal efficacy studies in support of the Rx-to-OTC switch. Statistical analysis in support of a shorter duration of therapy for interdigital tinea pedis was performed using current divisional guidance on efficacy endpoints for antifungal drug products.

Studies 2509-01 and 2509-02, in support of moccasin type tinea pedis, were reviewed under NDA 20-192/1S resulting in an approved drug product at the same proposed OTC frequency and duration of twice daily applications for two weeks. Therefore, these two studies were mainly reviewed for safety and appropriate use in an OTC setting without the intervention of a learned intermediary.

Problems with protocol design were recognized in new studies 2508-01 and SF0040 submitted by the sponsor. These studies were not vehicle controlled studies and were therefore primarily reviewed for safety in support of this application.

Inclusion/exclusion criteria were generally similar for studies submitted for the interdigital tinea pedis indication. Efficacy endpoints were similar for the specific indication (tinea pedis or tinea corporis/cruris). Any significant differences will be addressed under the specific study.

Inclusion Criteria (interdigital)

1) Generally healthy outpatients aged 5 years and older.
2) Males and non-pregnant, non-lactating females. Female patients of childbearing age may be included only if they are using reliable contraceptive measures which will be maintained throughout the study.
3) Patients with tinea pedis defined as follows:
   Lesions are localized to the interdigital spaces or lesions are predominantly interdigital, but extend to other areas of the foot (the non-interdigital lesions must not be hyperkeratotic, i.e., characteristic of tinea pedis moccasin).
4) The clinical diagnosis of tinea pedis has been provisionally confirmed by a KOH wet mount positive for dermatophyte at the Baseline Visit. [The diagnosis must be confirmed by a positive culture for dermatophyte from a sample taken at Baseline. A negative result will exclude the patient from the study.
5) The total sum of the scores of the clinical signs and symptoms of the 'Target Lesion' is at least six.
6) Written informed consent must be obtained from each patient. If the patient is a minor, the parent or guardian must give consent and sign the consent form.

Exclusion Criteria (interdigital)

1) Patients who have received systemic, anthelmintic, anti-fungal or anti-inflammatory therapy within one month prior to entry into the study.
2) Patients who have received topical antibiotic, anthelmintic, anti-fungal or anti-inflammatory therapy within two weeks prior to entry into the study.
3) Patients who have taken immunosuppressive medication or radiation therapy either currently or within three months of entering the study or during the study.
4) Patients with concomitant yeast infections or bacterial infections which are systemic or localized to the foot.
5) Patients with concurrent onychomycosis of the toenails of the foot to be evaluated.
6) Patients with signs of systemic fungal disease.
7) Women who are pregnant or breast feeding.
8) Non-pregnant women of child-bearing potential who are not using reliable contraceptive measures (diaphragm, pill or IUD) on a regular basis.
9) Patients with uncontrolled diabetes.
10) Patients with a known allergy to any of the study medications including any of the inactive ingredients.
11) Patients who have been previously enrolled in this study.
12) Patients considered not to be reliable based on the investigator interview in terms of using medication as instructed, compliance in keeping scheduled appointments and adhering to other aspects of the protocol.
13) Patients who have participated in another clinical study within the past month.
14) "Delayed Exclusion". If the culture taken at Baseline proves to be negative for dermatophyte or shows evidence of a significant concomitant yeast or bacterial infection, the patient will be excluded and dropped.