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APPLICATION NUMBER:

21-958

MEDICAL REVIEW(S)

CLINICAL REVIEW (SAFETY)

Application Type NDA
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Reviewer Name Juan Carlos Pelayo, M.D.
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Established Name Terbinafine Gel 1% (Lamisil[®]
DermGel[™])
(Proposed) Trade Name Lamisil^{AT}[®] Advanced[™]
Therapeutic Class Antifungal
Applicant Novartis Consumer Health, Inc.

Priority Designation S

Formulation Emulsion gel (1% terbinafine)
Dosing Regimen Once daily / one week duration
Indication Tinea pedis (athlete's foot),
tinea cruris (jock itch), and
tinea corporis (ringworm)
Intended Population Subjects 12 years of age and older
with dermatophytosis

Table of Contents

1	EXECUTIVE SUMMARY	4
1.1	RECOMMENDATION ON REGULATORY ACTION	4
1.2	RECOMMENDATION ON POSTMARKETING ACTIONS	5
2	INTRODUCTION AND BACKGROUND	5
2.1	PRODUCT INFORMATION	6
2.2	CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS.....	6
2.3	AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES.....	6
2.4	IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS.....	6
2.5	PRESUBMISSION REGULATORY ACTIVITY	6
2.6	OTHER RELEVANT BACKGROUND INFORMATION.....	7
3	SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES	7
3.1	CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE)	7
3.2	ANIMAL PHARMACOLOGY/TOXICOLOGY	7
4	DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY	7
4.1	SOURCES OF CLINICAL DATA	7
4.2	TABLES OF CLINICAL STUDIES	8
4.3	REVIEW STRATEGY	9
4.4	DATA QUALITY AND INTEGRITY	9
4.5	COMPLIANCE WITH GOOD CLINICAL PRACTICES.....	10
4.6	FINANCIAL DISCLOSURES.....	10
5	CLINICAL PHARMACOLOGY	10
5.1	PHARMACOKINETICS	10
5.2	PHARMACODYNAMICS.....	10
5.3	EXPOSURE-RESPONSE RELATIONSHIPS	10
6	INTEGRATED REVIEW OF EFFICACY	10
7	INTEGRATED REVIEW OF SAFETY	11
7.1	METHODS AND FINDINGS	11
7.1.1	Deaths	13
7.1.2	Other Serious Adverse Events	13
7.1.3	Dropouts and Other Significant Adverse Events	14
7.1.4	Common Adverse Events	14
7.1.5	Less Common Adverse Events	18
7.1.6	Laboratory Findings.....	18
7.1.7	Vital Signs	18
7.1.8	Electrocardiograms (ECGs).....	19
7.1.9	Immunogenicity	19
7.1.10	Human Carcinogenicity	19
7.1.11	Special Safety Studies.....	19
7.1.12	Withdrawal Phenomena and/or Abuse Potential.....	19
7.1.13	Human Reproduction and Pregnancy Data	19
7.1.14	Assessment of Effect on Growth.....	20
7.1.15	Overdose Experience	20
7.1.16	Postmarketing Experience.....	21
7.1.17	Additional Submissions, Including Safety Update	28
7.1.18	Explorations for Predictive Factors	29
7.1.19	Causality Determination	32

Clinical Review
Juan Carlos Pelayo, M.D.
NDA 21-958
Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

8	ADDITIONAL CLINICAL ISSUES	32
8.1	DOSING REGIMEN AND ADMINISTRATION.....	32
8.2	DRUG-DRUG INTERACTIONS.....	32
8.3	SPECIAL POPULATIONS.....	32
8.4	PEDIATRICS.....	33
8.5	ADVISORY COMMITTEE MEETING.....	33
8.6	LITERATURE REVIEW.....	33
8.7	OTHER RELEVANT MATERIALS.....	34
8.8	LABELING REVIEW.....	34
8.9	COMMENTS TO APPLICANT.....	34
9	APPENDICES	34
9.1	REVIEW OF INDIVIDUAL STUDY REPORTS.....	35
9.2	LINE-BY-LINE LABELING REVIEW.....	35
	REFERENCES	35

APPEARS THIS WAY ON ORIGINAL

1 EXECUTIVE SUMMARY

Novartis Consumer Health, Inc. submitted NDA 21-958 in support of the switch of Lamisil[®] DermGelTM, 1%, from prescription to non-prescription status. To this regard, Lamisil[®] DermGelTM, 1%, under NDA 20-846 has been approved by the FDA on April, 1998, for prescriptive use for interdigital tinea pedis (athlete's foot), tinea corporis (ringworm) and tinea versicolor, and on July, 1999, for prescriptive use for tinea cruris (jock itch).¹ The cream and the solution/spray formulations of 1% terbinafine hydrochloride received approval from the FDA for prescription as well as nonprescription use on December, 1992 and March, 1999, and October, 1997 and March, 2000, respectively.

The sponsor has requested that Lamisil[®] DermGelTM, 1% terbinafine as the free base, be switched from prescription to non-prescription based on:

1. data previously submitted in NDA 20-846 with no additional either nonclinical or clinical studies.
2. postmarketing safety data from the Novartis worldwide and the FDA SRS and AERS databases for all marketed Lamisil[®] topical formulations.

In essence the regulatory decision regarding the switch from prescription to nonprescription of Lamisil[®] DermGelTM, 1%, hinges on the interpretation of previously reviewed safety data from NDA 20-846 and new supplementary safety data from postmarketing exposure.

As was previously the case, the review of the safety data derived from 5 pivotal clinical trials, 2 in tinea pedis, one in tinea corporis/cruris and two in pityriasis versicolor and four pharmacokinetic trials and 2 studies of cutaneous irritancy and sensitization conducted as part of NDA 20-846 raised no concerns regarding the safety of Lamisil[®] DermGelTM, 1%.

Similarly, the available postmarketing data from terbinafine for topical application, including significant human use experience from postmarketing spontaneous reports worldwide and in the US, provide reassurance of its safety in that no unexpected adverse events were identified.

The proposed formulation is an alcohol and water based gel that the sponsor intends to have available for nonprescription use in tubes from _____ in size. The proposed administration and dosing regimen in the over the counter setting calls for the topical application of the gel, once daily for a period of one week.

1.1 Recommendation on Regulatory Action

Based on the results of the safety review, which didn't raise any concerns, the medical reviewer recommends that the switch of Lamisil DermGel, 1%, from prescription status to nonprescription status be approved.

¹ For the nonprescription use of the gel formulation of terbinafine the sponsor however is not seeking an indication for the topical treatment of tinea versicolor.

Clinical Review
Juan Carlos Pelayo, M.D.
NDA 21-958
Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

1.2 Recommendation on Postmarketing Actions

The safety profile of Lamisil DermGel, 1%, outlined in this medical review doesn't warrant recommendations for postmarketing actions.

2 INTRODUCTION AND BACKGROUND

In accordance with section 505(b)(1) of the act and 21 CFR §314.50, Novartis Consumer Health, Inc. (NCH) submitted this New Drug Application (NDA 21-958) in support of the switch of Lamisil[®] (terbinafine) DermGelTM, 1%, from prescription to non-prescription status. Lamisil[®] (terbinafine) DermGelTM, 1%, under NDA 20-846 has already received approval by the FDA on April, 1998, for prescriptive use for interdigital tinea pedis (athlete's foot), tinea corporis (ringworm) and tinea versicolor, and on July, 1999, for tinea cruris (jock itch).²

The sponsor is now requesting that Lamisil[®] DermGelTM, 1%, terbinafine as the free base, be switched from prescription to non-prescription based on:

3. the data submitted in NDA 20-846 with no additional studies (nonclinical and clinical)
4. safety data from the Novartis worldwide and FDA postmarketing databases for all marketed Lamisil[®] topical formulations, 1% terbinafine as the hydrochloride salt, as well as the free base.

For the nonprescription use of the gel formulation of terbinafine the sponsor however is not seeking an indication for the topical treatment of tinea versicolor.

The approval history of terbinafine in US is summarized in Table ISS-1.³ Terbinafine is approved as a prescription and non-prescription drug for marketing in the United States under the brand name of Lamisil[®] in various topical formulations including gel, cream and solution/spray for the treatment of dermatophytosis and in tablet form for the treatment of onychomycosis. Of note, Lamisil[®] DermGelTM, 1%, was not marketed in the US after its approval in 1998.

Table ISS-1 Terbinafine Approval History in US

Formulation	Strength/Form	Rx Approval	OTC Approval
Cream	1% terbinafine hydrochloride	December 1992	March 1999
Tablet	250 mg	May 1996	
Solution/Spray	1% terbinafine hydrochloride	October 1997	March 2000
DermGel	1% terbinafine base	April 1998	

[Source: NDA 21-958, Vol. 8, pp. 10. Rx = prescription. OTC = non-prescription.]

² According to the sponsor, the treatment of tinea versicolor approved under NDA 20-846 will remain a prescriptive indication.

³ Worldwide regulatory history (NDA 21-958, Vol. 1.2, page 27-28): Lamisil[®] DermGelTM, 1%, was first approved in New Zealand on March 15, 1998. Since that it has been approved for prescriptive use in 37 countries. It is currently available without a prescription in 32 countries. It has both Rx/OTC statuses, depending on the indication, in five countries. It has not been withdrawn from marketing in any country for reasons related to safety and efficacy.

2.1 Product Information

The proposed formulation is an alcohol and water based gel that the sponsor intends to have available for OTC use in tubes from _____ in size. The active ingredient of Lamisil[®] DermGelTM, 1%, is terbinafine, a potent inhibitor of ergosterol biosynthesis that belongs to the allylamines, a class of synthetic antifungal compounds. It blocks the action of fungal squalene epoxidase suggesting that the fungicidal effect of terbinafine may be related to the accumulation of squalene, which may be toxic to the fungus at high concentrations.

2.2 Currently Available Treatment for Indications

At present there are several nonprescription antifungal products available for the sought indications:⁴

- Clotrimazole 1%: Cream, Solution, Lotion, and Jock Itch Cream.
- Miconazole Nitrate 2%: Spray Liquid, Spray Powder, Spray Deodorant, and Powder.
- Butenafine Hydrochloride 1%: Cream.
- Terbinafine Hydrochloride 1%: Cream and Solution.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient of Lamisil[®] DermGelTM, 1%, terbinafine, is readily available in the United States and there seems to be no indication of any potential shortage of it.

2.4 Important Issues with Pharmacologically Related Products

Not new information on the subject was submitted by the sponsor for this NDA.

2.5 Presubmission Regulatory Activity

Reference is made to the Type C Rx-to-OTC (Prescription to Nonprescription) switch meeting held on July 11, 2005 between Novartis Consumer Health, Inc. and representatives of the FDA from the Division of Dermatologic and Dental Drug Products, and the Office of Nonprescription Products and the Division of Nonprescription Clinical Evaluation. Relevant to this submission the following issues were agreed upon by the parties at that meeting:⁵

1. Reference will be made to NDA 20-846 and all corresponding supplements for chemistry, manufacturing, and controls (CMC), nonclinical, biopharmaceutics and clinical data.
2. No new nonclinical, biopharmaceutics or clinical studies will be submitted to NDA 21-958.
3. Switch NDA will be submitted in the same format as NDA 20-846 except for the Nonclinical section which will be provided in the Common Technical Document format.

⁴ PHYSICIANS' DESK REFERENCE – For Non-Prescription Drugs and Dietary Supplements, 24 Edition, 2003.

⁵ For the complete information on the regulatory history of terbinafine the reader is referred to NDA 21-958, Vol. 1.2, pages 25-27.

Clinical Review

Juan Carlos Pelayo, M.D.

NDA 21-958

Lamisil^{AT}® AdvancedTM / Terbinafine Gel 1%

4. Updated worldwide safety data for Lamisil Cream and Lamisil Solution from the Novartis worldwide safety database and the FDA SRS and AERS safety databases will be submitted in NDA 21-958.
5. Worldwide safety data for Lamisil DermGel from the Novartis worldwide safety database will be submitted in this NDA.
6. The proposed OTC labeling for Lamisil DermGel will be consistent with that currently approved for OTC topical antifungal drug products and will follow Drug Facts format.
7. New CMC data will be submitted to support _____ for the drug substance and to support the use of a _____ tube for the drug product.
8. The OTC formulation will be identical to the currently approved terbinafine gel approved for prescription distribution.
9. No actual use study is required for this submission.

2.6 Other Relevant Background Information

Relevant information to this NDA submission has been addressed in the previous sections of this clinical review. Nevertheless, since this NDA represents a switch to OTC availability for an already approved topical formulation, the interested reader is referred to the original NDAs for any additional information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Not new information on the subject was submitted by the sponsor for this NDA. The required data are incorporated by reference from the approved NDAs for oral and topical terbinafine.

3.2 Animal Pharmacology/Toxicology

Not new information on the subject was submitted by the sponsor for this NDA. The required data are incorporated by reference from the approved NDAs for oral and topical terbinafine.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical development program for prescription Lamisil[®] (terbinafine) DermGelTM, 1%, was designed to demonstrate the efficacy and safety of the formulation for the treatment of interdigital tinea pedis, tinea cruris and tinea corporis, and pityriasis versicolor. The clinical safety database consisted of 5 key trials, 2 in tinea pedis, one in tinea corporis/cruris and two in pityriasis versicolor. Four pharmacokinetic trials and 2 studies of cutaneous irritancy and

Clinical Review

Juan Carlos Pelayo, M.D.

NDA 21-958

Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

sensitization were conducted as part of Lamisil[®] DermGelTM, 1%, clinical development program and their safety results will be also discussed.⁶

In addition, to provide data on the postmarketing experience with topical terbinafine, the sponsor included in this submission a summary of spontaneous AE reports from the Novartis Worldwide Safety Database and the FDA's Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS), and a review of the National Library of Medicine's MEDLINE database for citations pertinent to the safety of topical terbinafine.

The sponsor also submitted to NDA 21-958 a 120-Day Safety Update derived from Novartis Worldwide Safety Database consisting of case reports related to topical terbinafine.

4.2 Tables of Clinical Studies

Tables ISS-2 and ISS-3 summarize the studies which comprised the clinical program in support of safety.

Table ISS-2 Lamisil[®] DermGelTM, 1%, Pivotal Clinical Trials for Approved Indications

Study No.	Country	Subjects	Treatment	Blinded F/U	Indication
SFG 102	UK	85 enrolled 84 safety terb 1% 29/30 terb 3% 28/28 veh 27/27	qd x 5 days	Wk 5 + 2 days	T. Pedis
SFG 202	FN/BEL	101 enrolled 100 safety terb 1% 51/51 veh 49/50	qd x 7 days	Wk 7	T. Pedis
SFG 101	ZAF	83 enrolled 82 safety terb 1% 39/40 veh 43/43	qd x 7 days	Wk 7	T. Cruris/corporis
SFG 203	SWE	61 enrolled 58 safety terb 1% 28/31 veh 30/30	qd x 7 days	Wk 7	Pityriasis Versicolor
SFG 302	NOR/SWE	129 enrolled 129 safety terb 1% 87/87 veh 42/42	qd x 7 days	Wk 7	Pityriasis Versicolor

[Source: NDA 21-958, Vol. 8, pp. 47. terb = terbinafine; veh = vehicle]

⁶The results of three additional studies conducted in non-claimed indications, _____ described in the original NDA 20-846 were not submitted by the sponsor in this application.

Table ISS-3 Lamisil[®] DermGelTM, 1%, Clinical Pharmacological Studies

Study No.	Country	Subjects	Treatment	Design	Endpoints/Population
SFG 101	SWE	24 safety	qd x 7 days	Randomized; double-blind; parallel; 1% gel+oral Lamisil or 1% gel + placebo	Plasma/tissue [] of Lamisil; healthy volunteers
SFG 205	UK	36 safety	qd x 1, 5 or 7 days	Randomized; open-label; parallel; 1% gel vs. 1% cream	Skin PK; healthy volunteers
SFW 406	FRA	100 safety	8 x 48-hour patches (induction phase); 1 x 48-hour patch (challenge phase)	Randomized; double-blind; within subject; 1%, 2%, 3% gel vs. vehicle	Skin tolerability; healthy volunteers
SFW 408	FRA	30 safety	1 x 6-hour occlusive 6 x 24-hour occlusive (induction phase) 1 x 24-hour occlusive (challenge phase)	Randomized; multiple-dose; open-label; within subject; 1%, 2%, 3% vs. vehicle	Photosensitizing potential; healthy volunteers
SFW 409	FRA	12 safety	qd x 7 days	Open-label; multiple-dose; non-controlled; 1% gel	Plasma []of Lamisil; healthy volunteers
SFW 410	DEU	12 safety	qd x 7 days	Open-label; multiple-dose; non-controlled; 1% gel	Plasma []of Lamisil; subjects with tinea corporis/cruris

[Source: NDA 21-958, Vol. 8, pp. 48. [] = concentration.]

4.3 Review Strategy

To delineate the safety profile of Lamisil[®] DermGelTM, 1%, adverse events, discontinuations for adverse events and serious adverse events, including deaths, derived from the aforementioned clinical databases were tabulated and analyzed using standard review techniques, i.e., comparison of event rates in the treatment group versus placebo rates, check for consistency of an identified safety signal across databases, etc.

4.4 Data Quality and Integrity

Not having access to the original randomization code in addition to the inability to comprehensively check for the accuracy of data entry hinders the ability of the medical reviewer to unequivocally ascertaining the quality and integrity of the data. Notwithstanding, the medical

Clinical Review

Juan Carlos Pelayo, M.D.

NDA 21-958

Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

reviewer during the safety review did not come across of any substantial discrepancy that could question the quality and integrity of the data submitted in support of NDA 21-958.

4.5 Compliance with Good Clinical Practices

The clinical trials submitted in support of NDA 21-958 and thus the approval of terbinafine gel, 1%, for nonprescription use were conducted in accordance with acceptable ethical standards, i.e., Declaration of Helsinki, monitoring of safety, etc. To this regard, studies' protocols and informed consents were approved by Institutional Review Boards.

4.6 Financial Disclosures

The evaluation of the financial disclosures provided by the sponsor for the pivotal studies revealed no significant financial conflicts suggesting that financial interests of the principal investigators have not influenced the overall conduct of the studies.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Not new information on the subject was submitted by the sponsor for this NDA. The required data are incorporated by reference from the approved NDAs for oral and topical terbinafine.

5.2 Pharmacodynamics

Not new information on the subject was submitted by the sponsor for this NDA. The required data are incorporated by reference from the approved NDAs for oral and topical terbinafine.

5.3 Exposure-Response Relationships

Not new information on the subject was submitted by the sponsor for this NDA. The required data are incorporated by reference from the approved NDAs for oral and topical terbinafine.

6 INTEGRATED REVIEW OF EFFICACY

The efficacy of terbinafine gel, 1%, has been evaluated by the Division of Dermatology and Dental Products and it is not being addressed in this medical review.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In this Integrated Review of Safety the data analyzed include adverse events (AEs), discontinuations due to AEs, and serious AEs including death.

The safety database for Lamisil[®] (terbinafine) DermGelTM, 1%, is comprised of results from pivotal clinical trials, pharmacology and pharmacokinetics studies, and postmarketing experience (Novartis Worldwide Safety database and FDA's SRS and AERS databases).

The safety data for Lamisil[®] (terbinafine) DermGelTM, 1%, from the 5 key clinical trials, i.e., pivotal clinical trials, in approved indications (Table ISS-4) were pooled by the sponsor and will be presented first. Of note, unlike in the other studies, in study SFG 102, patients were treated with 1% or 3% Lamisil[®] for 5 days.

The safety population derived from these clinical studies consists of all patients who were exposed to study medication, regardless of the extent of the exposure. There were a total of 453 subjects in the safety population, 262 and 191 subjects were exposed to terbinafine and placebo, respectively.

Table ISS-4 Safety Population from Pivotal Clinical Trials

Study No.	Country	Subjects	Treatment	Indication
SFG 102	UK	85 enrolled 84 safety terb 1% 29/30 terb 3% 28/28 veh 27/27	qd x 5 days	T. Pedis
SFG 202	FN/BEL	101 enrolled 100 safety terb 1% 51/51 veh 49/50	qd x 7 days	T. Pedis
SFG 101	ZAF	83 enrolled 82 safety terb 1% 39/40 veh 43/43	qd x 7 days	T. Cruris/corporis
SFG 203	SWE	61 enrolled 58 safety terb 1% 28/31 veh 30/30	qd x 7 days	Pityriasis Versicolor
SFG 302	NOR/SWE	129 enrolled 129 safety terb 1% 87/87 veh 42/42	qd x 7 days	Pityriasis Versicolor

[Source: NDA 21-958, Vol. 8, pp. 47. terb = terbinafine; veh = vehicle]

Clinical Review
 Juan Carlos Pelayo, M.D.
 NDA 21-958
 Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

Table ISS-5 summarizes key demographic characteristics for the safety population from the pivotal clinical trials. The population was mainly represented by Caucasian (88.3%) males (63.3%) with a mean age of 38.7 years. Regarding demographics, by and large, the groups were well balanced.

Table ISS-5 Demographic Characteristics for the Safety Population from Pivotal Clinical Trials

Demographic Characteristic	Terbinafine N=262 n (%)	Vehicle N=191 n (%)
Gender		
Male	163 (62.2)	123 (64.4)
Female	99 (37.8)	68 (35.6)
Ethnicity		
Caucasian	234 (89.3)	167 (87.4)
Black	6 (2.3)	7 (3.7)
Oriental	10 (3.8)	7 (3.7)
Other	12 (4.6)	10 (5.2)
	Mean (±SD)	Mean (±SD)
Age (years)	39.4 (16.5)	38.0 (16.0)
Height (cm)	171.7 (10.2)	171.4 (11.8)
Weight (kg)	72.6 (13.4)	72.5 (14.9)

[Source: NDA 21-958, Vol. 8, pp. 55, Table 8-14.]

Patient disposition by group is summarized in Table ISS-6. The safety population represents 98.1% and 99.5% of the enrolled patients in the terbinafine and vehicle groups, respectively. Five patients in the terbinafine group and one in the vehicle group were excluded from the safety population because no safety follow up was available. Significantly more patients in the vehicle group discontinued as compared with the terbinafine group (11.6% vs. 30.2%). This noted discrepancy in the rate of withdrawal was entirely due to the fact that more vehicle-treated subjects discontinued because of treatment failure than terbinafine-treated subjects (24.5% vs. 3.7%). While one patient discontinued in the vehicle group due to an adverse event no patient withdrew from the study because of an adverse event in the terbinafine group. There was only one death reported in the clinical trials which occurred in the vehicle group.

Table ISS-6 Patient Disposition for the Safety Population from Pivotal Clinical Trials

	Terbinafine N (%)	Vehicle N (%)
Patients		
Total randomized	267 (100)	192 (100)
Safety population	262 (98.1)	191 (99.5)
Excluded ^s	5 (1.9)	1 (0.5)
Completed	231 (86.5)	133 (69.3)
Discontinued	31 (11.6)	58 (30.2)
Rx success	1 (0.4)	0 (0.0)

Clinical Review
 Juan Carlos Pelayo, M.D.
 NDA 21-958
 Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

Adverse event	0 (0.0)	1 (0.5)
Death	0 (0.0)	1 (0.5)
Withdrawal of consent	1 (0.4)	1 (0.5)
Protocol violation	2 (0.7)	2 (1.0)
Treatment failure	10 (3.7)	47 (24.5)
Failure to return	13 (4.9)	6 (3.1)
Other	4 (1.5)	1 (0.5)

[Source: NDA 21-958, Vol. 8, pp. 56, Table 8-15. ⁸Patients were excluded from the safety population because of lack of safety follow-up/evaluation.]

7.1.1 Deaths

There was only one death reported for the entire clinical development program of terbinafine gel, 1%. This death was reported in study SFG 202, involving a vehicle-treated patient (#3014). The subject was an 86 year old female, who had a 7 year history of dementia, had been bedridden for 2 years, and had a 12-week history of tinea pedis. She developed bronchopneumonia and was found dead 8 days after completing the 1 week treatment period.

7.1.2 Other Serious Adverse Events

Table ISS-7 provides a summary of AEs reported as serious regardless of cause. Overall there were few patients reporting serious AEs, one patient in the terbinafine-treatment group reported a severe AE, neuralgia. In the vehicle-treated group, five patients reported a total of eight severe AEs as follows: allergic reaction, coughing, pneumonia, pruritus, rash erythematosus, skin exfoliation and sweat gland disorder (n=2).

Table ISS-7 Number of Patients with Serious AEs in Most Frequently Affected Body Systems for the Safety Population from Pivotal Clinical Trials

Severe AEs	Terbinafine N=262 n (%)	Vehicle N=191 n (%)
Allergic reactions	0 (0.0)	1 (0.5)
Coughing	0 (0.0)	1 (0.5)
Neuralgia	1 (0.4)	0 (0.0)
Pneumonia	0 (0.0)	1 (0.5)
Pruritus	0 (0.0)	1 (0.5)
Rash erythematosus	0 (0.0)	1 (0.5)
Skin exfoliation	0 (0.0)	1 (0.5)
Sweat gland disorder	0 (0.0)	2 (1.0)

[Source: NDA 21-958, Vol. 8, pp. 60, Table 8-19.]

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Table ISS-8 lists the number and percentage of patients who discontinued the study because of AEs by treatment group (WHOART preferred term). Only one subject in the safety population was discontinued due to an AE. This discontinuation was due to death in a vehicle-treated patient (#3014) in tinea pedis study SFG 202 who developed bronchopneumonia and was found dead 8 days after completing the seven day treatment period (see 7.1.1 Deaths).⁷

Table ISS-8 Patients Discontinued due to AEs for the Safety Population from Pivotal Clinical Trials

	Terbinafine N (%)	Vehicle N (%)
Patients		
Total randomized	267 (100)	192 (100)
Safety population	262 (98.1)	191 (99.5)
Excluded [§]	5 (1.9)	1 (0.5)
Discontinued Total	31 (11.6)	58 (30.2)
Adverse event	0 (0.0)	1 (0.5)

[Source: NDA 21-958, Vol. 8, pp. 63, Table 8-21.]

7.1.3.2 Adverse events associated with dropouts

As it was previously mentioned the only AE associated with a withdrawal from a clinical trial was death which occurred in a vehicle-treated subject (see section 7.1.3.1).

7.1.3.3 Other significant adverse events

There were no other significant adverse events except for those mentioned above.

7.1.4 Common Adverse Events

For the safety population from pivotal clinical trials, overall, the number of patients reporting AEs and the number of AEs reported were low and weren't significantly different between the groups. Approximately twenty percent of the subjects reported adverse events. The following Table ISS-9 provides a summary of the overall AE rates for all events regardless causality.

⁷ Of note, in the ISS for the original NDA, this case was counted as a death only, not as a discontinuation for a serious AE.

Table ISS-9 Overall AEs for the Safety Population from Pivotal Clinical Trials

	Terbinafine N (%)	Vehicle N (%)
Patients		
Total randomized	267 (100)	192 (100)
Safety population	262 (98.1)	191 (99.5)
Total # of Patients with AEs	53 (20.2)	44 (23.0)
Total no. of AEs	64	57

[Source: NDA 21-958, Vol. 8, pp. 57, Table 8-16.]

Table ISS-10 provides the number and percentage of patients with AEs in the most frequently affected body systems, according to WHOART terminology, using a 2% occurrence rate in either treatment group as a threshold for listing.

Except for the observed difference in the skin and appendages body system, the rate of AEs⁷ reporting by body system was similar between the groups. In the skin and appendages body system, the incidence of reported AEs was almost two-fold higher in the vehicle-treated group than the terbinafine-treated-patients (13.6% versus 6.9%, p=0.024).⁸

Table ISS-10 Number (%) of Patients with AEs in Most Frequently Affected Body Systems for the Safety Population from Pivotal Clinical Trials

	Terbinafine N (%)	Vehicle N (%)
Patients		
Total randomized	267 (100)	192 (100)
Safety population	262 (98.1)	191 (99.5)
Total # of Patients with AEs	53 (20.2)	44 (23.0)
Body system		
Skin and appendages	18 (6.9)	26 (13.6)
Respiratory system	12 (4.6)	6 (3.1)
Body as a whole	9 (3.4)	7 (3.7)
Application site	4 (1.5)	7 (3.7)
Central and peripheral nervous system	6 (2.3)	3 (1.6)

[Source: NDA 21-958, Vol. 8, pp. 58, Table 8-17.]

7.1.4.1 Eliciting adverse events data in the development program

Adverse events during the clinical development program for terbinafine gel 1% were elicited by the principal investigators for each individual studies.

7.1.4.2 Appropriateness of adverse event categorization and preferred terms

The sponsor categorized AEs by body systems and preferred terms according to WHOART terminology. Both approaches are considered to be adequate.

⁸ Sponsor's analysis.

7.1.4.3 Incidence of common adverse events

Table ISS-11, in section 7.1.4.4, provides a listing of the most frequently reported AEs, the threshold for inclusion was at least 2 patients in the terbinafine group reporting same event.

The three most common AEs reported were skin-related events: pruritus, skin disorder and application site reaction. Pruritus and application site reaction were reported more frequently in the placebo group than in the terbinafine group (3.7% versus 1.9% and 3.7% versus 1.5%, respectively). The incidence rates for the remaining AEs were similar between the groups.

Albeit that number of patients reporting AEs is very low, the data on common adverse events suggest that the terbinafine and placebo groups have a similar safety profile.

7.1.4.4 Common adverse event tables

Table ISS-11 Number of Patients with Most Frequent AEs for the Safety Population from Pivotal Clinical Trials

	Terbinafine N (%)	Vehicle N (%)
Patients		
Total randomized	267 (100)	192 (100)
Safety population	262 (98.1)	191 (99.5)
Total # of Patients with AEs	53 (20.2)	44 (23.0)
WHOART preferred term		
Pruritus	5 (1.9)	7 (3.7)
Skin disorder	5 (1.9)	3 (1.6)
Application site reaction	4 (1.5)	7 (3.7)
Headache	4 (1.5)	3 (1.6)
Upper respiratory tract infection	3 (1.1)	3 (1.6)
Accidental trauma	3 (1.1)	1 (0.5)
Skin discoloration	3 (1.1)	1 (0.5)
Abscess	2 (0.8)	1 (0.5)
Arthropathy	2 (0.8)	1 (0.5)
Pneumonia	2 (0.8)	1 (0.5)
Dermatitis	2 (0.8)	0 (0.0)
Fever	2 (0.8)	0 (0.0)
Laryngitis	2 (0.8)	0 (0.0)
Otitis media	2 (0.8)	0 (0.0)
Tonsillitis	2 (0.8)	0 (0.0)

[Source: NDA 21-958, Vol. 8, pp. 59, Table 8-18.]

7.1.4.5 Identifying common and drug-related adverse events

In the 5 key clinical trials in approved indications, the relationship of the event to the study drug was judged by the sponsor based on the following criteria: not related, unlikely, possible, probable or highly probable.

Clinical Review
 Juan Carlos Pelayo, M.D.
 NDA 21-958
 Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

Table ISS-12 provides a complete listing of drug-related AEs for the key safety population.

The sponsor included in the listing any AE with a relationship of possible, probable, or highly probable. Again, the most prevalent reported drug-related AEs were skin disorders and application site reactions. Vehicle-treated subjects by and large were more affected than subjects receiving terbinafine 1% gel.

One subject in the terbinafine group developed taste perversion, albeit an uncommon labeled AE it has been previously associated with the oral formulation of Lamisil.

Because post hoc determination of causality is riddled with flaws plus the rather small number of events reported, the significance of the presented data remains uncertain to this medical reviewer.

Table ISS-12 Summary of Drug-Related AEs for the Safety Population from Pivotal Clinical Trials

	Terbinafine N (%)	Vehicle N (%)
Patients Studied		
Safety population	262 (100)	191 (100)
Total # of Patients with drug-related AEs	15 (5.7)	27 (14.1)
WHOART Organ System and Preferred Term		
Skin and appendages disorders total	11 (4.2)	21 (11.0)
Dermatitis contact	1 (0.4)	1 (0.5)
Pruritus	3 (1.1)	7 (3.7)
Rash erythematous	1 (0.4)	9 (4.7)
Rash maculo-papular	0 (0.0)	2 (1.0)
Rhagades	0 (0.0)	1 (0.5)
Skin discoloration	3 (1.1)	1 (0.5)
Sweat gland disorder	0 (0.0)	1 (0.5)
Skin disorder	5 (1.9)	3 (1.6)
Skin exfoliation	1 (0.4)	6 (3.1)
Application site disorder Total	4 (1.5)	7 (3.7)
Application site reaction	4 (1.5)	7 (3.7)
Body as a whole-general disorder Total	0 (0.0)	1 (0.5)
Condition aggravated	0 (0.0)	1 (0.5)
Special senses other disorders Total	1 (0.4)	0 (0.0)
Taste perversion	1 (0.4)	0 (0.0)

[Source: NDA 21-958, Vol. 8, pp: 62, Table 8-20.]

Clinical Review
Juan Carlos Pelayo, M.D.
NDA 21-958
Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

7.1.4.6 Additional analyses and explorations

The sponsor also analyzed safety data from the clinical pharmacology and sensitization studies in both healthy volunteers and patients. Table ISS-13 lists the AEs which occurred in any of the clinical pharmacology or skin sensitization trials. There were a total of 5 AEs reported by the 214 healthy volunteers and patients who participated in any of the clinical pharmacology or skin sensitization trials. The incidence rate of AEs was extremely low in that only one event was reported in each of the following studies SFG 101 and 205; SFW 406, 409, and 410.

Table ISS-13 Adverse Events in the Clinical Pharmacology and Sensitization Trials

Adverse Event	n (%)	Study
Pleural Pneumonia	1 (0.5)	SFG 101
Rash	1 (0.5)	SFG 205
Itching	1 (0.5)	SFW 406
Headache	1 (0.5)	SFW 409
Tooth Pain	1 (0.5)	SFW 410

[Source: NDA 21-958, Vol. 8, pp. 59, Table 8-24.]

There were no deaths or serious AEs reported in any of the clinical pharmacology or sensitization studies. Likewise, there were no discontinuations due to AEs in any of these studies.

7.1.5 Less Common Adverse Events

The overall low rate of reporting for adverse events prevents the medical reviewer from meaningfully addressing this issue.

7.1.6 Laboratory Findings

7.1.6.1 Overview of laboratory testing in the development program

The sponsor didn't submit new laboratory data for either NDA 21-958 or NDA 20-846. According to the sponsor, "laboratory effects following topical and systemic administration were reported in the original NDAs for Lamisil Cream, 1% (NDA 20-192) and Lamisil Tablets (NDA 20-539)."

7.1.7 Vital Signs

7.1.7.1 Overview of vital signs testing in the development program

As was the case for the clinical laboratory data, no physical examination or vital sign data were presented either for NDA 21-958 or NDA 20-846.

Clinical Review
Juan Carlos Pelayo, M.D.
NDA 21-958
Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

7.1.8 Electrocardiograms (ECGs)

7.1.8.1 Overview of ECG testing in the development program, including brief review of preclinical results

The sponsor didn't submit new ECG data for NDA 21-958. In this regard, no ECG data were presented in the original NDA for Lamisil DermGel, 1% (NDA 20-846).

7.1.9 Immunogenicity

The sponsor provided no new information on the subject.

7.1.10 Human Carcinogenicity

The sponsor provided no new information on the subject.

7.1.11 Special Safety Studies

The sponsor didn't perform special safety studies during the clinical development program of terbinafine gel, 1%.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

Terbinafine has no known potential for producing withdrawal effects. According to the sponsor, studies of daily oral dosing with the 250 mg terbinafine tablet for 12 and 24 weeks did not produce withdrawal effects and worldwide experience with the tablet and topical formulations, estimated to be over 230 million patient exposures, has not produced AE reports suggestive of withdrawal effects.

Therefore it is reasonable to conclude that the OTC availability of Lamisil DermGel, 1 %, should pose no risk concerning withdrawal effects.

7.1.13 Human Reproduction and Pregnancy Data

No pregnancies were reported during the pivotal clinical trials or the clinical pharmacology or sensitization studies.

According to the sponsor, a review of the Novartis Worldwide Safety database for topical terbinafine, regardless of type of formulation, revealed 23 cases (solution 2, spray 3, cream 18) with 32 associated AE terms (MedDRA) related to pregnancy (Table ISS-14).⁹

⁹ According to the sponsor "the majority of the reports were simply queries or expressions of concern by a consumer after finding out she was pregnant after using topical terbinafine. A smaller number (5) related to women realizing after breast feeding that there was a warning against doing so while using the drug."

Clinical Review
Juan Carlos Pelayo, M.D.
NDA 21-958
Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

Table ISS-14 Adverse Event Terms Associated with reported Pregnancies

MedDRA Preferred Term	n
Drug exposure during pregnancy	17
Breast feeding	5
Normal newborn	2
Application site reaction	1
Blister	1
Burns first degree	1
Cellulitis	1
Epidermolysis	1
Hypoglycemia neonatal	1
Skin burning sensation	1
Small for dates baby	1

[Source: NDA 21-958, Vol. 8, pp. 68, Table 8-25.]

Of note, there was a case, a 41 year old woman treated with topical Lamisil cream followed by tablets for onychomycosis during the first two weeks of pregnancy (PHBS1996GB01272). The subject subsequently miscarried. Concomitant medication included dydrogesterone. Follow-up information indicated that the patient had become pregnant inadvertently and had a history of miscarriages.

According to the sponsor, the review of Periodic Safety Update Reports (PSUR) numbers 6 and 7 and Addendum to PSUR No. 7 (current through 15 February 2005) revealed no new information regarding pregnancy risk associated with the use of topical terbinafine. Examination of cases reported to the Novartis Worldwide Safety Database and the FDA SRS and AERS databases regarding AEs associated with the use of topical Lamisil during pregnancy revealed no new information concerning pregnancy risk.

7.1.14 Assessment of Effect on Growth

The sponsor provided no new information on the subject.

7.1.15 Overdose Experience

Albeit no information is available on overdose in humans with Lamisil DermGel, 1 %, the sponsor provided the following statement. "Acute overdose as a result of topical application of the product is extremely unlikely since the entire content of the largest proposed tube is — which would contain — of terbinafine. Although the bioavailability of Lamisil DermGel, 1 %, is not known with precision, it appears to produce plasma levels comparable to or lower than other topical terbinafine formulations. Assuming comparable bioavailability, namely 5% or less, topical application of an entire tube of Lamisil DermGel might result in systemic exposure to — of terbinafine. By comparison, the standard 250-mg terbinafine tablet has an estimated bioavailability of 40% resulting in a systemic exposure of approximately 100 mg from a single dose. The tablet is currently approved for up to 12 weeks of once daily therapy for toenail onychomycosis. With respect to oral ingestion of the 1 % topical

Clinical Review

Juan Carlos Pelayo, M.D.

NDA 21-958

Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

formulations, ingestion of the entire contents of the largest tube of gel (_____g) would deliver at most _____g of active drug. Assuming 40% bioavailability, this would result in a systemic exposure of _____g. Clinical overdose experience with other formulations of terbinafine is limited. Five grams of terbinafine in the tablet form (equivalent to the terbinafine content of approximately 15, 30 gram tubes of Lamisil DermGel formulation) have been taken without severe adverse reactions. The overdose symptoms included nausea, vomiting, abdominal pain, dizziness, rash, frequent urination and headache [Lamisil® tablet package insert, January 2004]. The risk of terbinafine overdose from Lamisil DermGel, 1 %, is extremely low; however the alcohol content (11.3%) of the formulation may need to be taken into account in the evaluation of any overdose with Lamisil DermGel.”

7.1.16 Postmarketing Experience

The sponsor queried two sources of post-marketing drug safety data for topical terbinafine, the safety database maintained by Novartis and the one maintained by the FDA.

The Novartis Worldwide Safety database (ARGUS) was queried for all case reports related to topical treatment of terbinafine including the use of Lamisil Cream, Solution, and DermGel as well as cases without an explicit recorded route of administration.

The safety data from the FDA represents information from both the Spontaneous Reporting System (SRS), which was closed in October 1997, and its successor, the Adverse Event Reporting System (AERS).¹⁰

Results

Table ISS-15 summarizes the total number of case reports and adverse events with topical terbinafine from the Novartis Worldwide Safety database. The searches identified a total of 13 Lamisil DermGel, 1%, reports involving 29 adverse event terms, Lamisil Cream 2,642 reports involving 4,133 adverse event terms, 723 Lamisil Solution reports involving 1,180 adverse event terms, and 1,395 Lamisil of unknown route of administration reports involving 2,047 adverse event term.

The exclusive topical use of the drug, regardless of formulation type, was reported in 3,207 cases. Concomitant or sequential oral and topical use was reported in 206 cases and 1,395 reports didn't provide route of administration data.

¹⁰ The sponsor used the following approaches to query the safety databases: using wildcard searching, a composite list of trade names and the generic names for Lamisil (or terbinafine) were extracted from each of the databases, then the drug master file from each of the two databases (SRS and AERS) was queried for all case reports for which topical terbinafine was recorded as a suspect agent (SRS database) or the primary, secondary suspect or interfering agent (AERS database). This report does not include cases where topical terbinafine was recorded as a concomitant medication nor does it include approximately 30 reports for which both oral and topical terbinafine were used in combination.

Clinical Review

Juan Carlos Pelayo, M.D.

NDA 21-958

Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

case of toxic epidermal necrolysis associated with use of topical terbinafine is recorded in the AERS database (ISR 3843612). The case was not fatal and was reported by both a health professional and a consumer. It involved a 41 year old female with systemic lupus erythematosus, cellulitis and exfoliative dermatitis. She was reported to be taking a calcium supplement, Enbrel, Lamotrigine, Lorazepam, Warfarin, Furosemide, Hydroxychloroquine, and Propranolol HCl in addition to topical terbinafine. The patient was hospitalized and the case was, therefore, categorized as serious.

Report of death erroneously identifying topical terbinafine as a suspect agent:

Three cases of death recorded in the AERS database erroneously identified topical terbinafine as a suspect agent. Two cases involve oral terbinafine and the third case is from a blinded trial in which the patient was subsequently found to have been treated with vehicle. Two deaths in the AERS database identify terbinafine cream, 1 % as a suspect agent and were obtained from a literature report.¹¹ These were actually cases in which oral terbinafine was used with other systemic antifungals in an unsuccessful attempt to treat chronic granulomatous disease. They are designated as FDA ISR 3226908 and FDA ISR 3226910. The current Novartis Case Nos. are: PHBS1999DZ01073 and PHBS1999DZ01075; the old Novartis Case Nos. are: LIT/99/00053/LAS and LIT/99/00054/LAS. These cases have not been included by the sponsor in the tabulations for FDA databases in this document. These literature cases have been assessed as due to oral terbinafine in the context of apparent futile long-term administration of multiple anti-fungal regimens in resistant chronic granulomatous dermatophytosis.

The third reported death FDA ISR 3670255, current Novartis Case No. PHEH2000US08629; old Novartis Case No. 0320463A was from a blinded clinical trial of terbinafine cream versus vehicle for tinea pedis prophylaxis. At the time of the initial reporting, the case had not been unblinded, but the AERS database recorded the suspect agent as topical Lamisil. Subsequently, the patient was found to have been treated with vehicle only. The death was identified through routine follow-up as part of the trial. A relative of the patient informed the study coordinator of the death. The death certificate attributed the cause of death to hypertensive cardiovascular disease.

Report of death for topical and oral terbinafine combined:

FDA ISR 3488210. Novartis Case No. PHEH2000US00279 (old Novartis Case No. USA/00/00062/LAS). A 71 year old man died in _____ of lung cancer with metastasis to his liver. He had been treated with oral Lamisil for 3 months for onychomycosis from September to December 1998 and with Lamisil Spray for recurrent onychomycosis beginning 20 July 1999. At the time he started Lamisil Spray, his liver functions were abnormal (AST 117 u/L and ALT 194 u/L). The patient's death was judged to be unrelated to his treatment with Lamisil by the prescribing podiatrist.

Report of death for terbinafine without route of administration data:

There are 4 additional deaths in the AERS database which identify terbinafine as a suspect agent but which have no route of administration data. One case was a direct report to the FDA and the

¹¹ Boudghene-Stambouli O, Merad-Boudia A. Failure of griseofulvin, of ketoconazole, of itraconazole and of terbinafine in the chronic granulomatous dermatophytosis. Australasian Journal of Dermatology 1997; 38: 83.

Clinical Review
Juan Carlos Pelayo, M.D.
NDA 21-958
Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

other 3 were in both the FDA and Novartis databases. All are described in the following paragraphs.

FDA ISR 3645508.

This was the single direct report made to the FDA. The case was that of a 93 year old woman reported on January 10, 2001, but the "Event date" was recorded as April 4, 1989, which antedates the approval of any topical formulation of terbinafine. The initial approval of Lamisil Cream was granted in Great Britain on October 3, 1990. The reason for the almost 12-year lag in reporting is unclear and it appears likely the event date is incorrect. The patient's medications were hydralazine (10 mg and 20 mg; no route of administration (ROA) data were given), identified as the primary suspect agent, and Lamisil (without dose or ROA data), identified as a secondary suspect medication. The single AE term associated with the case was "Death" and the outcomes recorded were "Life-threatening" and "Death". No report source was recorded in the database. No other information on the case is available.

FDA ISR: 3446418

Novartis Case No. PHBS2000GB00065 (old Novartis Case No. GB/00/00023/LAS).

This was a case of a child (gender unknown) born with Trisomy 13 in _____ to a 40 year old mother who "had taken Lamisil" during the first month of her pregnancy. The child died at age 8 months. The case was reported from Great Britain. No other information is recorded.

FDA ISR 3889908 and ISR 3889905

Novartis Case No. PHNU2001DE02515 (previously also PHNU2001DE02706).

A 69 year old man developed an "allergic exanthema" five days after starting Lamisil for "nail tinea". The Lamisil was then discontinued. Two days later the physician noted an acute deterioration of his general condition and the onset of depression. The patient was hospitalized and subsequently transferred to a psychiatric hospital due to suicidal ideation. From there he was transferred some time later to another hospital because of black tarry stools and a tachyarrhythmia with atrial fibrillation. Gastroscopy showed an atypical duodenitis. He subsequently developed purpura not attributable to thrombocytopenia and a skin biopsy suggested a small vessel vasculitis and a tentative diagnosis of Henoch-Schoenlein purpura was made. Steroids were begun. His course was complicated by persistent proteinuria (6 g/day) and deteriorating renal function. Renal biopsy showed glomerulonephritis with focal segmental necrosis. The patient then developed massive and persistent gastrointestinal hemorrhage requiring over 100 units of blood products over several days but, despite the volume of blood loss, the site of the bleeding could not be identified. He subsequently required respiratory support, developed candida and klebsiella sepsis and multi-organ failure. He died 2 ½ months after first being hospitalized. No autopsy was performed. His Novartis case report records 50 AE terms. The AERS database records 28 terms.

FDA ISR 3989692

Novartis Case No. PHBS2002ES11587

An 80 year old female patient was reported to have died of a cerebrovascular accident. The report was made from Spain in September 2002 in what is described on the MedWatch form as an observational post-marketing study report. No other information is available.

Clinical Review
Juan Carlos Pelayo, M.D.
NDA 21-958
Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

Other Serious AEs

ARGUS Database

Of interest serious cases only accounted for 2% of all topical cases and, 19.4% of all topical + oral cases and 6.9% of all the cases of unknown formulation. The latter incidence rate perhaps reflects the combining of topical cases with cases with probable oral exposure.

There were only two serious reports with six associated MedDRA terms for Lamisil DermGel without oral exposure. The terms reported included: pain, bullous dermatitis, exfoliative dermatitis, eczema, rash erythematous and skin discoloration.¹²

In the serious reports for Lamisil cream without oral exposure, there were 52 serious reports with 144 associated MedDRA terms. The most commonly reported terms included: erythema (7/4.9%), contact dermatitis (4/2.7%), pruritus (4/2.7%), rash (4/2.7%), abdominal pain (3/2.0%), application site reaction (3/2.0%), peripheral edema (3/2.0%), skin ulcer (3/2.0%), urticaria (3/2.0%), and surgery (3/2.0%).¹³

The review of serious reports for Lamisil solution without oral exposure revealed nine serious reports associated with 45 MedDRA terms. The most commonly reported terms included: pain (3/6.7%), erythema (3/6.7%), peripheral edema (2/4.4%), cellulitis (2/4.4%), and rash (2/4.4%).¹⁴

FDA Database

Other serious AEs from the SRS and AERS databases are presented below in Table ISS-16. In the aggregate, the results for serious AEs for topical terbinafine (regardless formulation) from the FDA database are in keeping with the corresponding safety data from the Novartis Worldwide database.

Table ISS-16 FDA Databases – Serious AEs Reports for Topical Terbinafine

MedDRA Preferred Term	Serious N (%)
Total terms (col %)	137 (100)
Total cases (row %)	36 (3.0)
Ageusia	5 (3.6)
Dermatitis	4 (2.9)
Pruritus	4 (2.9)
Rash erythematous	4 (2.9)
Dermatitis exfoliative	4 (2.9)
Condition Aggravated	3 (2.2)
Pain	3 (2.2)
Dermatitis contact	3 (2.2)
Application site reaction	2 (1.5)
Dermatitis bullous	2 (1.5)
Pyrexia	2 (1.5)

¹² NDA 21-958, Vol. 8, Appendix 9a.

¹³ NDA 21-958, Vol. 8, Appendix 9b.

¹⁴ NDA 21-958, Vol. 8, Appendix 9c.

Clinical Review
 Juan Carlos Pelayo, M.D.
 NDA 21-958
 Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

Cellulitis	2 (1.5)
Abdominal pain	2 (1.5)
Chills	2 (1.5)
Erythema	2 (1.5)
Edema	1 (0.7)
Rash	1 (0.7)
Skin discoloration	1 (0.7)
Skin disorder	1 (0.7)
Blister	1 (0.7)
Eye pain	1 (0.7)
Edema peripheral	1 (0.7)

[Source: NDA 21-958, Vol. 8, pp. 87, Table 8-31.]

Adverse Events

ARGUS Database

Herein, to avoid the confounding effect of AEs resulting from oral terbinafine to the interpretation of the safety profile of topical terbinafine, just AEs reported in subjects who received topical treatment without oral exposure, are presented.

In the Lamisil DermGel without oral exposure cohort (n=10) a total of 25 AEs were reported. The most frequent AEs included application site erythema (8.0%, 2/25), irritation (8.0%, 2/25), pruritus (8.0%, 2/25), vesicles (8.0%, 2/25), and drug ineffective (8.0%, 2/25). There was one report of skin ulcer (4.0%, 1/25).

The most common AEs reported in the Lamisil cream without oral exposure group were therapeutic response decreased (16.1%, 602/3732), drug ineffective (12.6%, 471/3732), condition aggravated (9.3%, 348/3732), application site reaction (6.7%, 250/3732), pruritus (4.1%, 156/3732), and rash (3.6%, 137/3732). Of note dysgeusia, an uncommon adverse event for topical products was reported with an incidence rate of 0.5% (17/3732). This adverse event has been reported with the use of oral terbinafine.

A total of 1180 AEs were reported for patients in the Lamisil solution without oral exposure group. As was the case for the other formulations the most commonly reported terms in this group were application site reaction (13.0%, 153/1180), condition aggravated (10.2%, 120/1180), drug ineffective (9.0%, 106/1180), and therapeutic response decreased (8.9%, 105/1180). Dysgeusia was reported four times (0.3%, 4/1180).

FDA's SRS and AERS Databases¹⁵

There were a total of 1387 case reports with 2200 AE terms for topical terbinafine (regardless formulation) or terbinafine without route of administration information in the two databases. The vast majority of case reports (86.4%, 1199/1387) and AE terms (74.9%, 1647/2200) were cases with a recognized topical route of administration.

¹⁵ The sponsor did not include cases where topical terbinafine was recorded as a concomitant medication nor did it include reports for which both oral and topical terbinafine were used in combination. AE data from each of the databases have been merged and are presented in combined listing.

Clinical Review

Juan Carlos Pelayo, M.D.

NDA 21-958

Lamisil^{AT}® AdvancedTM / Terbinafine Gel 1%

For topical terbinafine, 92.9% (1114/1199) of the case reports were not serious, 3.0% (36/1199) were judged serious and 4.0% (48/1199) had no outcome data and thus could not be categorized for seriousness.

Table ISS-17 presents the most frequently reported AEs for the case reports of topical terbinafine in descending order of frequency based on the not serious data.

Table ISS-17 FDA Databases – Most Frequent Adverse Events Reports for Topical Terbinafine

MedDRA Preferred Term	No Outcome Data N (%)	Not Serious N (%)
Drug effect decreased	2 (2.9)	464 (32.2)
Condition Aggravated		259 (18.0)
Application site reaction	10 (14.7)	223 (15.5)
Dermatitis	1 (1.5)	61 (4.2)
Pruritus	3 (4.4)	26 (1.8)
Paraesthesia	4 (5.9)	23 (1.6)
Edema	1 (1.5)	23 (1.6)
Pain	5 (7.4)	16 (1.1)
Rash	7 (10.3)	14 (1.0)
Rash erythematous	2 (2.9)	15 (1.0)
Skin discoloration	1 (1.5)	17 (1.2)
Dermatitis exfoliative		13 (0.9)
Skin disorder	3 (4.4)	10 (0.7)
Drug ineffective	6 (8.8)	7 (0.5)
Hypersensitivity	2 (2.9)	10 (0.7)
Nail disorder		11 (0.8)
Urticaria	1 (1.5)	10 (0.7)
Contact dermatitis	1 (1.5)	6 (0.4)
Dry skin		10 (0.7)
Headache		10 (0.7)
Tinea pedis		8 (0.6)
Blister		6 (0.4)
Dermatitis bullous		5 (0.3)
Dizziness		7 (0.5)
Dysgeusia		7 (0.5)
Eye pain		6 (0.4)
Edema peripheral	1 (1.5)	5 (0.3)
Pyrexia		5 (0.3)
Rx response decreased		7 (0.5)
Ageusia		1 (0.1)
Cellulitis	1 (1.5)	3 (0.2)
Nausea	1 (1.5)	5 (0.3)
Abdominal pain		3 (0.2)

Clinical Review
Juan Carlos Pelayo, M.D.
NDA 21-958
Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

Chills		3 (0.2)
Erythema		3 (0.2)
Fatigue		5 (0.3)
Myalgia		5 (0.3)
Total terms (col %)	68 (100)	1441 (100)
Total cases (row %)	48 (4.0)	1114 (92.9)

[Source: NDA 21-958, Vol. 8, pp. 87, Table 8-31.]

By and large the postmarketing information on AEs presented is in accordance with the safety profile already identified for topical terbinafine.

7.1.17 Additional Submissions, Including Safety Update

On April 20, 2006, the sponsor submitted to the FDA's Office of Nonprescription Products and the Division of Nonprescription Clinical Evaluation the 4 Month Safety Update for NDA 21-958.

For the 4 Month Safety Update the sponsor queried the Novartis Worldwide Safety Database for all case reports received from August 01, 2005 to February 28, 2006 related to topical terbinafine. These included cases involving the use of Lamisil Cream, Solution, and DermGel as well as cases without an explicit recorded route of administration. Of note cases that involved both the topical formulations and oral terbinafine were identified and analyzed separately.

Results

The search of the aforementioned database identified a total of 8 Lamisil DermGel reports involving 13 AE terms, Lamisil Cream 327 reports involving 556 AE terms, 14 Lamisil Solution reports involving 20 AE terms, and 176 Lamisil of unknown route of administration reports involving 270 AE terms. Exclusively topical use of the drug was reported in 333 cases and combined or sequential oral and topical use was reported in 16 cases.

Consumers reported 88% of the topical cases and 60% of the topical plus oral and unknown formulation cases, the remaining cases were reported by Health Care Professionals.

Deaths

Of note there were no reports of death during this review period.

Serious adverse events

During this time period there were no serious reports for Lamisil Solution (with or without oral exposure) or with Lamisil DermGel (with or without oral exposure). And the absolute number of reports for Lamisil cream without oral exposure was not large enough to make meaningful conclusions. There were 4 serious case reports with 16 associated MedDRA AE terms. With the exception of application site irritation (12.5%), each of the remaining 16 terms was singly reported with an incidence rate of 6.2% including disease progression, face edema, lower extremity mass, edema peripheral, contusion, angioneurotic edema, ecchymosis, erythema, and discoloration, nodule, lesion, ulcer of the skin, and wound debridement.

Clinical Review
Juan Carlos Pelayo, M.D.
NDA 21-958
Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

Among the serious Lamisil cases of unknown formulation most of the events were singly reported with 43% (13/30) in the skin and subcutaneous tissue disorders.

Most frequent AEs

The limited number of reports for Lamisil DermGel precludes a meaningful evaluation of AEs, overall the most commonly reported AEs were drug ineffective (30.8%; 4/13) and erythema (15.8%; 2/13). Similarly, in the Lamisil Solution without oral terbinafine exposure only 2 events were reported for two patients.

For the Lamisil Cream a total of 511 events were reported for 313 patients as follows: drug ineffective (32.3%; 165/511), condition aggravated (4.3%; 22/511), erythema (4.1%; 21/511), pruritus (4.1%; 21/511), accidental exposure (3.1%; 16/511) and application site erythema (2.9%; 15/511).

For the Lamisil unknown formulation category a total of 270 AEs were reported corresponding to 176 cases, the most frequently reported events were drug ineffective (18.5%; 50/270), Ageusia and dysgeusia (13.3%; 36/270), rash (3.3; 9/270), alopecia (3.0; 8/270), and pruritus (2.6%; 7/270).

Overall the information on AEs presented in this update is consistent with the safety profile already identified for topical terbinafine.

7.1.18 Explorations for Predictive Factors

7.1.18.1 Explorations for dose dependency for adverse findings

No consistent relationship of AEs to the dose, frequency, duration of use or total number of exposures can be recognized for topical terbinafine. The relationship of AE frequency to drug exposure was examined in detail at the time of the original NDA for terbinafine HCl cream, 1%, and is summarized in Table HA (page 08-00446) of NDA 20-192. The conclusions from that analysis were corroborated by a similar absence of a dose-response effect for Lamisil DermGel (NDA 20-846, Volume 49, page 10-4594) and terbinafine, 1%, solution (NDA 20-749, Volume 78, page 8-24603) as described in their respective NDAs.

Since percutaneous absorption studies conducted for the original cream NDA demonstrated low systemic absorption of the drug (NDA 20-192, Section 8.C.2), it is not surprising that an AE dose-response is not observed.

7.1.18.2 Explorations for time dependency for adverse findings

Percutaneous absorption studies with terbinafine 1% topical formulations in normal or diseased skin demonstrate that a low proportion of the topically applied terbinafine reaches the systemic circulation, resulting in very low plasma concentrations (see Section 8.C.2 of the original 1% cream NDA 20-192, Section 8.C.1 of NDA 20-749 for the 1% solution and Section 8.C.1 of NDA 20-846, for the 1 % Lamisil DermGel). At a maximum, these concentrations are a small

Clinical Review
Juan Carlos Pelayo, M.D.
NDA 21-958
Lamisil^{AT}® AdvancedTM / Terbinafine Gel 1%

fraction of the plasma concentration obtained after oral administration of terbinafine 250 mg tablets. Consequently, AEs due to systemic exposure and long-term adverse effects are unlikely to occur.

There are no long-term (six months or longer) studies for Lamisil DermGel, 1%, or other topical formulations. Post-marketing experience with topical terbinafine now encompasses an estimated _____ patient exposures and no evidence of long-term AEs has emerged. The proposed consumer labeling recommends treating tinea pedis or corporis/cruris for one week only. The prescription labeling sanctioned treatment for up to four weeks. Treatment durations of up to six weeks were evaluated for the original cream NDA 20-192 and the AE rates observed in the longer studies were not markedly different from those seen in shorter treatment durations (one to four weeks).

Long-term use of the product is discouraged and market research has indicated that consumers usually treat cutaneous fungal infections with topical medication for a maximum of six to seven days.

No delayed onset adverse effects have been reported. In fact, continued clinical and symptomatic improvement following cessation of therapy is common. The improvement may be due to a combination of the persistence of measurable drug in the stratum corneum following cessation of treatment and the time required for healthy, uninfected skin to regenerate.

7.1.18.3 Explorations for drug-demographic interactions

No data have emerged from the clinical testing with any of the topical formulations suggesting a clinically important safety issue dependent on age (above 12 years old), gender or ethnicity.

Since the drug under consideration is intended for consumers over the age of 12, and is a topical formulation with therapeutic effects local to the site of application, no dose adjustments for weight would be required.

7.1.18.4 Explorations for drug-disease interactions

There are no relevant findings from pharmacokinetic or pharmacodynamic studies on this subject. Furthermore the low systemic absorption of terbinafine from topical use makes this an unlikely possibility.

7.1.18.5 Explorations for drug-drug interactions

There are no recognized clinically significant interactions of topical terbinafine with other drugs. Specifically, no interaction with the cytochrome P-450 system has been identified and topical terbinafine is not known to have any important effect on the metabolism of any other drugs. Also topical terbinafine has not been recognized to interact with other topical preparations despite extensive worldwide use.¹⁶

¹⁶ According to the sponsor since its initial approval in Great Britain in 1990, it is estimated that there have been

Clinical Review

Juan Carlos Pelayo, M.D.

NDA 21-958

Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

Nevertheless, the records from the Novartis Worldwide Safety Database for Lamisil Cream and Solution show five cases of reported possible drug interaction with topical drug. Two of these were reported previously with NDA 21-124 for OTC solution terbinafine. A sixth case of a decreased International Normalized Ratio (INR) in a patient on phenprocoumon is reported in the database but no dose or route of administration information is recorded and the narrative of the case describes the "intake of Lamisil". The case is presumed to involve oral terbinafine and will not be described here.

- One report (FDA SRS Control No. C01904693; Old Novartis Case No. USA/96/01671/LAS; New Novartis Case No. PHEH1996US10340) is that of a man using topical Lamisil and Noroxin who developed difficulty urinating. He was switched from Noroxin to Macrochantin with relief, Lamisil therapy continued. No additional details are available. Urinary retention is not a labeled AE for either Noroxin or Lamisil. The case was not categorized as serious.
- The second case (FDA SRS Control No. C01904722; Old Novartis Case No. USA/96/02576/LAS; New Novartis Case No. PHEH1996US01700) was that of a patient using both topical Lamisil and Bactroban who developed a "full body rash." No other details are available. Both drugs can produce rashes. The case was not categorized as serious.
- The third case (FDA AERS ISR No. 3850298; Novartis Case No. PHRM2001FR02881) from France involved a 54 year old woman taking both Lamisil tablets (250 mg/day), Lamisil Cream and thioridazine (7 drops/day) and clonazepam for delusions. Two months after initiating Lamisil she experienced two episodes of paroxysmal tachycardia. The patient had a history of vascular facial neuralgia, dysthymic disorder, personality disorder and abnormal repetitive facial movements. Her thioridazine was discontinued also. No further information was available. The AE is recorded as serious in the Novartis Safety database but does not have an outcome which would label it as serious in the AERS database.
- A fourth case (PHFR2002GB03008) was reported from a health authority. The report describes a patient with a history of epilepsy well controlled on carbamazepine who suffered a seizure one week after starting topical terbinafine. The patient recovered. The reporter questioned whether terbinafine and carbamazepine could interact to reduce carbamazepine levels.
- A fifth report (PHEH2005US01355) came from a physician who reported that while using Lamisil^{AT} Cream and Lipitor (atorvastatin) he experienced muscle spasms in both legs. He felt this was the result of an interaction between the drugs and discontinued both. No further information is available.

The AERS database records 6 cases of drug interaction in which terbinafine was one of the patient's drugs. One is the case described in the preceding paragraph. The other five were

over _____ patient exposures worldwide.

Clinical Review
Juan Carlos Pelayo, M.D.
NDA 21-958
Lamisil^{AT}® AdvancedTM / Terbinafine Gel 1%

reported by different manufacturers and none gives dose or route of administration information for terbinafine and none lists terbinafine as the primary suspect agent. Terbinafine is listed as a secondary suspect agent in each of the cases. Based on the recorded AE terms apart from "Drug Interaction NOS" the cases appear to involve: 1. jaundice with increased ALT and AST; 2. hepatic failure and aplastic anemia; 3. myalgia; 4. prolonged QT interval; 5. urinary frequency and incontinence; and 6. paroxysmal tachycardia and drug withdrawal. The first two of these cases were serious based on the recorded outcomes and involved Lipitor (primary suspect) and Lamisil" (secondary suspect) in the first case and Lipitor (primary suspect), Lamisil (secondary suspect), Atenolol, Zestril, Cardura and Coumadin in the second case.

7.1.19 Causality Determination

The paucity of information on all these cases, in addition to the lack of information on de-challenge and re-challenge makes difficult to ascribe causality to terbinafine. The small number of possible drug interactions, particularly for documented use of topical terbinafine, compared to the over 230 million worldwide exposures makes it reasonable to conclude that drug interactions may not be a clinically important issue with topical terbinafine.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Once daily / one week duration / topical application.

8.2 Drug-Drug Interactions

Drug-drug interactions have been extensively examined for the oral formulation of terbinafine and the data have been presented in the NDA for oral terbinafine (NDA 20-539). Because those analyses failed to provide significant information, no formal program to evaluate drug-drug, drug-disease or drug-demographic interactions has been undertaken by the sponsor for the topical formulations of terbinafine. With respect to drug-demographic interactions, no data have emerged from the clinical testing with any of the topical formulations suggesting a clinically important safety issue dependent on age (above 12 years old), gender or ethnicity.

Given the low concentration of topical drug (1%) and therefore the small skin exposure to active material (20 mg of terbinafine for 2 grams of topical formulation) and the limited systemic bioavailability (no more than 0.6% of that observed with 250 mg tablet) and the relatively short course of topical exposure (1 week) recommended for tinea pedis and tinea cruris, the risk of drug-drug interactions with the topical formulations of terbinafine should be judged to be very unlikely and of no clinical significance.

8.3 Special Populations

The sponsor didn't submit results from studies performed on special populations.

Clinical Review

Juan Carlos Pelayo, M.D.

NDA 21-958

Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

Furthermore, the small number of AEs and the even smaller number of drug-related AEs in the pivotal safety studies precluded any meaningful subgroup analyses to assess differences in the safety profile of terbinafine 1% gel based on gender, age and race.

8.4 Pediatrics

The Pediatric Research Equity Act requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

Novartis Consumer Health, Inc. intends to label the product for adults and children 12 and above. According to the sponsor the above intent is "in agreement with the FDA's Acting Director, Division of Pediatric Drug Development that the product should be left prescription in children under the age of 12 who could benefit from a learned intermediary especially for the proper diagnosis and treatment of ringworm."

In a letter from the FDA to Novartis Pharmaceuticals Corporation on July 14, 2003, in response to a Written Request for pediatric studies for terbinafine hydrochloride in children under 12 years with ringworm, the Agency stated that "Since application of this product to a small lesion would not result in a significant systemic exposure to patients, further studies of topical terbinafine in children were considered of limited benefit."

For the aforementioned reasons, Novartis Consumer Health, Inc. is requesting a waiver for pediatric studies for NDA 21-958.

8.5 Advisory Committee Meeting

This application has not been specifically discussed at an Advisory Committee Meeting.

8.6 Literature Review

The sponsor conducted a review of the medical literature for citations pertinent to the safety of topical terbinafine using the National Library of Medicine's MEDLINE database covering the period from 1966 to mid-July 2005.¹⁷ According to the sponsor this searches identified only 2 citations reporting deaths, both were in liver transplants recipients with Aspergillus infections.

1. In one case reported in 2001, the patient seven weeks after liver transplantation had hemorrhagic, eroded plaques develop on his arms. The results of routine histology, immunoperoxide staining for CMV antibody, and fungal culture revealed coexistent cutaneous aspergillus flavus and CMV infections. The patient was treated with

¹⁷ The following terms were used to identify the references: Terbinafine AND (cream OR solution OR gel OR topical) AND adverse event, death, overdose, drug interaction.

Clinical Review

Juan Carlos Pelayo, M.D.

NDA 21-958

Lamisil^{ATM} AdvancedTM / Terbinafine Gel 1%

ganciclovir, amphotericin B, and topical terbinafine cream; however, 2 weeks after the development of the cutaneous lesions, the patient died.¹⁸

2. In the other case reported in 1994, the patient a liver transplant recipient with end-stage hepatitis C-induced cirrhosis, who was receiving the experimental immunosuppressive drug FK-506 developed primary cutaneous aspergillosis caused by aspergillus ustus. Of note, this species seldom infects human beings. Trauma to the skin of the right arm from tape and from an arm board holding intravenous and intra-arterial catheters in place and to the left leg from an occlusive knee brace may have contributed to this unusual mycosis. The patient's cutaneous aspergillosis responded to a combination of intravenous amphotericin B and topical terbinafine cream. Although the patient died shortly thereafter from hepatic failure, there was no evidence of systemic aspergillosis.¹⁹

Finally, a search for all MEDLINE articles from 1966 to mid-July 2005 using only "terbinafine" as a search term was conducted in stages and all the citations with abstracts and their applied Medical Subject Heading (MeSH) terms were downloaded into a series of files. The sponsor then searched the files for the term "death". No pertinent citations were identified. The files were then searched for the term "adverse" and all the citations identified in this manner (approximately 300) were then scanned manually for relevance to topical terbinafine. Sixteen of the citations for which the title and abstract did not distinguish between oral and topical terbinafine were obtained for review. None of them dealt with topical terbinafine. In sum, according to the sponsor no new information pertinent to the safety of topical terbinafine for the indications being sought was identified by a search of the MEDLINE database.

8.7 Other Relevant Materials

There are not other relevant materials regarding the safety profile of terbinafine gel, 1% that need to be addressed in this medical review.

8.8 Labeling Review

There are no safety issues that need to be addressed in the labeling for Lamisil DermGel, 1%.

8.9 Comments to Applicant

From a safety standpoint there are no comments to be conveyed to the sponsor.

9 APPENDICES

None

¹⁸ J AM ACAD DERMATOL. 2001 FEB; 44 (2 SUPPL):370-2.

¹⁹ J AM ACAD DERMATOL. 1994 AUG; 31 (2 PT 2):344-7

Clinical Review
Juan Carlos Pelayo, M.D.
NDA 21-958
Lamisil^{AT} AdvancedTM / Terbinafine Gel 1%

9.1 Review of Individual Study Reports

Because the number of subjects evaluated in each clinical study is small, the safety results from the individual clinical studies were combined, and they are presented in the Integrated Review of Safety.

9.2 Line-by-Line Labeling Review

There are no safety issues that need to be incorporated in the nonprescription labeling for terbinafine gel, 1%.

REFERENCES

Pertinent references have been incorporated into the document as footnotes.

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CLINICAL REVIEW

Application Type NDA
Submission Number 21-958
Submission Code 000

Letter Date September 29, 2005
Stamp Date September 30, 2005
PDUFA Goal Date July 31, 2006

Reviewer Name Phyllis A. Huene, M.D.
Review Completion Date February 13, 2006

Established Name Terbinafine
(Proposed) Trade Name Lamisil Derm Gel
Therapeutic Class Antimycotic agent
Applicant Novartis

Priority Designation S

Formulation Terbinafine 1% topical gel
Dosing Regimen Once daily for 7 days
Indication Tinea pedis, tinea cruris,
tinea corporis
Intended Population Adults and children 12 years of
age and older

Table of Contents

EXECUTIVE SUMMARY	4
RECOMMENDATION ON REGULATORY ACTION	4
RECOMMENDATION ON POSTMARKETING ACTION	4
Risk management activity	4
Required Phase 4 commitments	5
Other Phase 4 requests	5
SUMMARY OF CLINICAL FINDINGS	5
Brief overview of clinical program	5
Efficacy	6
Safety	7
Dosage and administration	7
Drug interactions and special populations	7
INTRODUCTION AND BCKGROUND	7
PRODUCT INFORMATION	7
CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS	8
AVAILABILITY OF ACTIVE INGREDIENT IN THE UNITED STATES	8
IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS	8
PRESUBMISSION REGULATORY ACTIVITY	8
OTHER RELEVANT BACKGROUND INFORMATION	8
SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES	8
DATA SOURCES	8
Sources of clinical data	8
CLINICAL PHARMACOLOGY	8
INTEGRATED REVIEW OF EFFICACY	8
INDICATION	8
Methods	8
General discussion of endpoints	9
Study design	9
Efficacy findings	10
Efficacy conclusions	14

Clinical review
Phyllis A. Huene, M.D.
NDA 21-958/N000
Lamisil (terbinafine) DermGel 1%

INTEGRATED REVIEW OF SAFETY	14
ADDITIONAL CLINICAL ISSUES	14
OVERALL ASSESSMENT	14
CONCLUSIONS	14
RECOMMENDATION ON REGULATORY ACTION	14
RECOMMENDATION ON POSTMARKETING ACTIONS	14

APPEARS THIS WAY ON ORIGINAL

EXECUTIVE SUMMARY

Recommendations on regulatory action: It is recommended that from an efficacy standpoint, the application be approved for the OTC treatment of tinea pedis, tinea cruris, and tinea corporis.

This clinical review is a review of efficacy only, and is based on a previous medical officer's review of NDA 20-846 for Lamisil DermGel 1% for prescription use for the same indications, which was submitted in 1997. NDA 20-846 was approved for tinea pedis and tinea corporis. It was not approved for tinea cruris, although the clinical review found it to be efficacious for this condition, because of safety concerns, as were expressed by the team leader. (The safety concerns were not defined at the time, but presumably these consisted of potentially enhanced irritation, sensitization, and absorption, due to application to inflamed intertriginous areas.) Lamisil DermGel has never been marketed in the US.

The clinical review of NDA 20-846 would clearly not meet current standards. The number of evaluable patients in each study was small and probably insufficiently representative of individual causative organisms, a substantial percentage of patients were unaccounted for in two of the studies, the results of mycological cultures are not described, and the results for tinea corporis were not separated from those of tinea cruris.

However, since the product has been approved for prescription use for tinea pedis and tinea corporis, and it is just as efficacious for these conditions on a non-prescription basis as on a prescription basis, then the product is approvable for these indications. Of the dermatophytoses, tinea pedis is the most difficult to treat, and therefore efficacy demonstrated for tinea pedis may be extrapolated to include tinea cruris, to allow the conclusion that efficacy for tinea cruris has also been adequately shown.

Recommendations on Postmarketing Actions

- 1) Risk management activity: This review concerns only the effectiveness of the product for the proposed indications. The safety of the product for OTC use is being reviewed by the Office of Non-Prescription Drug Products.

Clinical review
Phyllis A. Huene, M.D.
NDA 21-958/N000
Lamisil (terbinafine) DermGel 1%

5

- 2) Required Phase 4 commitments: No Phase 4 commitments are recommended by this reviewer.
- 3) Other Phase 4 requests: None.

Summary of clinical findings

- 1) Brief Overview of Clinical Program.

The formulation of Lamisil DermGel in the current NDA 21-958 is the same as that in NDA 20-846, which was submitted in 1997 by Novartis Pharmaceutical Corp for the prescription use of Lamisil (terbinafine) DermGel 1% for tinea versicolor, tinea pedis, and tinea corporis. The clinical studies provided in NDA 21-958 are those originally provided in NDA 20-846; no new clinical studies on efficacy are provided in NDA 21-958.

NDA 20-846 was reviewed by Ella Toombs, M.D., and the application was approved in April 1998 for the following indications:

"Tinea (pityriasis) versicolor due to *Malassezia furfur* (formerly *Pityrosporum ovale*), tinea pedis (athlete's foot) or tinea corporis (ringworm) due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, or *Epidermophyton floccosum*."

This review is based on Dr. Toombs' review of the efficacy data in NDA 20-846.

The current application requests approval of Lamisil DermGel for the indications tinea pedis, tinea cruris, and tinea corporis. (Tinea cruris was not approved as a prescription indication, while the approved indication tinea versicolor is not being sought as an OTC indication.)

APPEARS THIS WAY ON ORIGINAL

The following studies were provided in support of these indications.

Indication	Study	Country	Treatment	# patients enrolled
Tinea pedis	SFG 102	UK	QD x 5 days	85
	SFG 202	Finland, Belgium	QD x 1 week	101
Tinea corporis/cruris	SFG 201	South Africa	QD x 1 week	83

These were multicenter, double blind, vehicle controlled studies with similar inclusion and exclusion criteria, efficacy parameters, and primary efficacy variables.

2) Efficacy.

The primary efficacy variable was 'Effective Treatment', defined as a negative mycology (KOH exam and culture), and a total score for erythema, desquamation and pruritus of 1 or less, when each was scored on a scale of 0=absent, 1=mild, 2=moderate, and 3=severe.

Tinea pedis: The rates of Effective Treatment in the Lamisil and vehicle groups were as follows.

Effective Treatment Study 102	
Lamisil	25/29 (85%)
Vehicle	3/27 (10%)
p value	0.001

Effective Treatment Study 202	
Lamisil	25/39 (64%)
Vehicle	5/31 (26%)
p value	0.001

Tinea cruris/corporis: The rates of Effective Treatment in the Lamisil and vehicle groups were as follows.

Effective Treatment Study 201	
Lamisil	24/29 (83%)
Vehicle	7/33 (21%)
p value	<0.001

While only one study was performed in tinea cruris/corporis, and the efficacy results were not reported separately for the two loci of infection, it is recognized that tinea pedis is much more difficult to treat than tinea corporis or tinea cruris, and therefore the results for tinea pedis may be extrapolated to conclude that efficacy has also been demonstrated for tinea cruris and tinea corporis.

- 3) Safety: This is being reviewed by the Office of Non-Prescription Drug Products.
- 4) Dosage and administration: Applications are to be made once daily for one week.
- 5) Drug-drug interactions and special populations: Any concerns in this regard are being evaluated by the Office of Non-Prescription Drug Products.

INTRODUCTION AND BACKGROUND

- 1) Product information: Lamisil (terbinafine hydrochloride) 250 mg tablets have been marketed for onychomycosis for over ten years,

and topical Lamisil formulations for dermatophytoses have been marketed for ten or more years.

- 2) Currently available treatment for indication: There are numerous prescription and OTC topical products marketed for tinea pedis and corporis/cruris.
- 3) Availability of the proposed active ingredient: Terbinafine is widely available in topical formulations in the US.
- 4) Other issues (e.g. pharmacologically related products, presubmission regulatory activity, other background information): These are being addressed by the Office of Non-Prescription Drug Products.

SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

These are being addressed by the Office of Non-Prescription Drug Products.

DATA SOURCES

This review of efficacy is based on the review by Dr. Ella Toombs of NDA 20-846 for the prescription use of Lamisil DermGel 1% for tinea pedis and tinea cruris/corporis.

CLINICAL PHARMACOLOGY

This is being addressed by the Office of Non-Prescription Drug Products.

INTEGRATED REVIEW OF EFFICACY

1) Methods

Studies SFG 102 and SFG 202 have been reviewed for a determination of effectiveness in tinea pedis; Study SFG 201 has been reviewed for a determination of effectiveness in tinea cruris/corporis.

2) General discussion of endpoints

The endpoint in all three studies was the percentage of patients with an Effective Treatment, defined as negative mycology (KOH exam and culture), and total scores for erythema, desquamation, and pruritus of 1 or less, using a scale of 0=absent, 1=mild, 2=moderate, and 3=severe.

3) Study design

The study design in regard to inclusion criteria, exclusion criteria, and primary endpoint was the same for all three studies.

The following criteria were used for entry into the studies.

- a. A clinical diagnosis of moderately severe tinea pedis or tinea corporis/cruris, confirmed by microscopy and mycological culture.
- b. Males and females of at least 12 years of age.
- c. Females of childbearing potential had to use reliable contraception throughout the study.

Patients with the following conditions were excluded from the studies.

- a. Drug abuse, pregnancy, lactation, immunodeficiency, or other dermatophytic infections.
- b. Immunosuppressive therapy during or 2 weeks preceding study entry; topical antifungals within 4 weeks of baseline, oral antifungals within 6 weeks of baseline, or other investigational therapy within 8 weeks of baseline.
- c. History of drug hypersensitivity.

Applications were made once daily for 5 days in Study SFG 102 (tinea pedis), and once daily for 7 days in the other studies.

4) Efficacy findings

A. Study 102: Tinea pedis

Fifty-seven patients were enrolled into 14 centers, of which 29 patients in the Lamisil group and 27 patients in the vehicle group were evaluable for efficacy.

The demographic characteristics of the ITT population were as follows.

Demographic characteristics		
	Lamisil	Vehicle
<u>Gender</u>		
Male	21	18
Female	8	9
<u>Age (mean)</u>	41	39
<u>Race</u>		
White	29	22
Black	0	0
Asian	0	0
Other	0	5

The disposition of the patients was as follows.

Patient disposition		
	Lamisil	Vehicle
Patients enrolled	30	27
ITT population	29	27
<u>Discontinuations</u>		
Lost to followup	3	1
Treatment failure	0	2

The percentages of patients with an Effective Treatment at the end of the study were as follows.

Effective Treatment Study 102	
Lamisil	25/29 (85%)
Vehicle	3/27 (10%)
p value	0.001

B. Study 202: Tinea pedis

One hundred and one patients were enrolled into 6 centers, of which 39 patients in the Lamisil group and 31 patients in the vehicle group were evaluable for efficacy.

The demographic characteristics of the ITT population were as follows.

Demographic characteristics		
	Lamisil	Vehicle
<u>Gender</u>		
Male	27	16
Female	12	15
<u>Age (mean)</u>	41	45

The disposition of the patients was as follows.

APPEARS THIS WAY ON ORIGINAL

Patient disposition		
	Lamisil	Vehicle
Patients enrolled	51	50
ITT population	51	49
<u>Discontinuations</u>		
Lost to followup	2	3
Treatment failure	0	5
Other	1	4

The percentages of patients with an Effective Treatment at the end of the study were as follows.

Effective Treatment Study 202	
Lamisil	25/39 (64%)
Vehicle	5/31 (26%)
p value	0.001

C. Study 201: Tinea corporis/cruris

Eighty-three patients were enrolled into 6 centers, of which 29 patients in the Lamisil group and 33 patients in the vehicle group were evaluable for efficacy.

The demographic characteristics of the ITT population were as follows.

APPEARS THIS WAY ON ORIGINAL

Demographic characteristics		
	Lamisil	Vehicle
<u>Gender</u>		
Male	23	25
Female	6	8
<u>Age (mean)</u>	42	36
<u>Race</u>		
White	21	26
Black	0	1
Asian	2	0
Other	6	6

The disposition of the patients was as follows.

Patient disposition		
	Lamisil	Vehicle
Patients enrolled	40	43
ITT population	39	43
<u>Discontinuations</u>		
Lost to followup	2	0
Treatment failure	0	0
Other	2	4

The percentages of patients with an Effective Treatment at the end of the study were as follows.

Effective Treatment Study 201	
Lamisil	24/29 (83%)
Vehicle	7/33 (21%)
p value	<0.001

5) Efficacy conclusions

From an efficacy standpoint, this application for Lamisil DermGel 1% is approvable for the indications tinea pedis and tinea cruris/corporis. Reference is made to the Executive Summary for further discussion of the results.

INTEGRATED REVIEW OF SAFETY

The safety of the product for the OTC treatment of the proposed indications is being reviewed by the Office of Non-Prescription Drug Products.

ADDITIONAL CLINICAL ISSUES

Any additional clinical issues are being addressed by the Office of Non-Prescription Drug Products.

OVERALL ASSESSMENT

- 1) Conclusions: From an efficacy standpoint, this application for Lamisil DermGel 1% is approvable for the indications tinea pedis and tinea cruris/corporis.
- 2) Recommendations on regulatory action: From an efficacy standpoint, the application is approvable.
- 3) Recommendation on Postmarketing Actions: No recommendations for postmarketing actions are made.

APPEARS THIS WAY ON ORIGINAL

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this page is the manifestation of the electronic signature.**

/s/

Phyllis Huene
3/1/2006 11:43:48 AM
MEDICAL OFFICER

Markham Luke
3/1/2006 04:47:58 PM
MEDICAL OFFICER

A subsequent 1999 approval granted indication for tinea cruris.
No efficacy concerns regarding Rx to OTC switch.
Non-prescription review division to evaluate safety for switch
by agreement. Derm review is for efficacy only.

Stanka Kukich
3/7/2006 11:31:20 AM
MEDICAL OFFICER