CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-958

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880)** **Tracking/Action Sheet for Formal/Informal Consults**			
From: **Abimbola Adebowale Ph.D.**			**To: DOCUMENT ROOM (LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
Letter DATE: **September 29th, 2006**	IND No.: NA Serial No.:	NDA No. **21-958**	DATE OF DOCUMENT **September 29th, 2005**	**Document ID: NA** **Docket #: NA** **Document Type and Sequence No.: New NDA for Rx to OTC Switch**
NAME OF DRUG **Lamisil® (terbinafine) DermGel, 1 %**	PRIORITY CONSIDERATION **Standard**		Date of informal/Formal Consult: **September 29th, 2005**	
NAME OF THE SPONSOR: **Novartis Consumer Health, Inc. Parsippany, NJ 07054-0622**				

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	X OTHER *(SPECIFY BELOW)*: [Summaries of Clinical Pharmacology information from approved terbinafine applications were included]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☐ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others		☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)		[]

REVIEW COMMENT(S)

X **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

Background:

Terbinafine is a synthetic allylamine derivative with a broad spectrum of antifungal activity. Lamisil (terbinafine) DermGel, 1% (NDA 20-846) was approved for prescription use on October 17th, 1997, but has not been marketed in the U.S. This New Drug Application (NDA) represents a partial switch of Lamisil DermGel, 1 %, from prescriptive to OTC status. The indications of interdigital-type tinea pedis (athlete's foot), tinea

cruris (jock itch) and tinea corporis (ringworm) are being sought for OTC. The indication for the treatment of tinea versicolor, approved under NDA 20-846 will remain a prescriptive indication. The doing regimen proposed for OTC is the same as that currently approved for prescription use. Basically, it is intended to be used in adults and children 12 years and older as follows: ***Athlete's Foot:*** Apply between the toes only once a day at bedtime for 1 week or as directed by a doctor; ***Jock Itch and Ringworm:*** Apply once a day (morning or night) for 1 week or as directed by a doctor.

Overview of Clinical Pharmacology (CP) information

The applicant stated that the indication, population, dosing regimen and formulation for OTC are the same as that currently approved for Rx use therefore no new clinical pharmacology information was included in this submission. However, synopses of the CP data that were submitted in the original approved Rx terbinafine gel (NDA 20-846) were included. In addition data comparing plasma concentrations of terbinafine following dermal application of Lamisil Cream (NDA 20-192), Lamisil Solution (NDA 20-749), Lamisil DermGel (NDA 20-846) and Lamisil Oral tablets (NDA 20-539) were summarized from the original NDAs with reference to the appropriate sections in those NDA.

Table 1: Summary of Currently Approved Terbinafine Drug Products

NDA #	Dosage Form	Approval Date
Prescription Products		
20-192	Lamisil ® Cream 1 %	December 30, 1992
20-539	Lamisil ® Tablets	May 10th, 1996
20-749	Lamisil ® Solution 1 %	October 17th, 1997
20-846	Lamisil ® DermGel, 1 %	April 29th, 1998
OTC Products		
20-980	Lamisil ® Cream 1 %	March 9th, 1999
21-124	Lamisil ® Solution and Spray 1 %	March 17th, 2000

Formulation:

The applicant stated that the Lamisil DermGel 1% formulation for OTC marketing is identical to that approved terbinafine gel for prescription (Rx) distribution on April 29th, 1998 under NDA 20-846. In this submission, the applicant did not provide any new formulation information except a reference back to NDA 20-846 for Chemistry, Manufacturing and Controls (CMC) and, new CMC information to support [redacted] ***with chemistry reviewer Dr. J. Chang***).

Human Pharmacokinetics and Bioavailability (Human PK and BA):

Lamisil ® DermGel, 1 % (NDA 20-846) was originally reviewed in Office of Clinical Pharmacology (OCP) by Dr. Veneeta Tandon in 1998. In the original NDA the applicant submitted four human PK and BA studies. The titles of these four studies are listed below:

1. SFW 409-E-00: Determination of plasma concentrations of terbinafine after repeated applications as a Lamisil ® 1 % emulsion gel to the normal skin of healthy volunteers
2. SFW 410-E-00: Determination of plasma concentrations of terbinafine after repeated applications as a Lamisil ® 1 % emulsion gel to the diseased skin in patients with tinea cruris/corporis
3. SFG 205-E-00: A study to investigate the skin pharmacokinetics of Lamisil® (terbinafine) 1 % emulsion gel compared to Lamisil ® 1 % cream in healthy subjects, following a single application on

Recommendations: This application for OTC marketing represents a partial move of the Lamisil ® DermGel from prescription to OTC status. Since the formulation, indication, dosage form, dosing regimen and route of administration are identical to that which was originally studied with the prescription product, and there were no outstanding clinical pharmacology commitments from the Lamisil ®DermGel 1 % approval; the information provided in this submission is acceptable from a clinical pharmacology perspective.

SIGNATURE OF REVIEWER: __Abi Adebowale_____ **SIGNATURE OF TEAM LEADER:** ____ **Dennis Bashaw** _____	Date __04/18/06_____ Date _____
CC.: **HFD #** [ONP]; **TL:** [Dennis Bashaw]; **DD:** [John Hunt]	**Project Manager:** _____Neal Patel_____ **Date** _____

Attachment 1

Table 6-1 Comparative systemic terbinafine concentrations

tudy Number	Dosage Form	# of subjects mg/d applied number of days	Mean AUC ng h/mL	Mean Cmax ng/mL (range)	Systemic exposure over treatment period $C_{average}$ (ng h/mL)
FW 409	DermGel	12 Volunteers – normal skin 67.5 mg/d 7 days OD	62.6	3.82	Not calculated
FW 410	DermGel	12 Tinea cruris patients 35.7 mg/d 7 days OD	40.5	2.48	Not calculated
F2 503-E-00	Cream	8 Volunteers-normal skin 41.25 mg/d 6 days BID	64.8	(0–11.4)	464
F2 503-E-00	Cream	8 Volunteers abraded skin 13.75 mg/d 6 days BID	29.3	(0-5.3)	205
FF 103	Solution	10 Tinea cruris patients 115 mg/d		9.2	1546
FP 101	Oral	8 Volunteers 250 mg/d	$AUC_{(0\text{-}244hr)}$ 10481.0	1796	71,841 (100% per definition)

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/s/

Abi Adebowale
5/16/2006 11:45:49 AM
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Dennis Bashaw
5/17/2006 04:45:52 PM
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