# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER:NDA 20-980

## CHEMISTRY REVIEW(S)

~~AUG 4 1998~~ F/H-C

**DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS**
Review of Chemistry, Manufacturing and Controls

JUL 28 1998

**NDA #:** 20-980 **CHEM. REVIEW:** # 1 **REVIEW DATE:** 28-Jul-98

| SUBMISSION/TYPE: | DOCUMENT DATE: | CDER DATE: | ASSIGNED DATE: |
|---|---|---|---|
| NDA 20-980/000 | 27-Mar-98 | 30-Mar-98 | 06-Apr-98 |

**NAME & ADDRESS OF APPLICANT:**

Novartis Consumer Health, Inc.
560 Morris Avenue
Summit, New Jersey 07901-1312
ATTN: Christine Babiuk, Ph.D.
Associate Director, Regulatory Affairs
(908) 598-7816

**DRUG PRODUCT NAME:**

| | |
|---|---|
| Proprietary: | Lamisil |
| NonProprietary/USAN: | terbinafine HCl |
| Code Names / #'s: | 4021030/SF 86-327 ch |
| Chemical Type: | 6S |
| Therapeutic Class: | Anti- fungal (topical) |

**ANDA Suitability Petition/DESI/Patent Status:** NOT APPLICABLE.

**PHARMACOLOGICAL CATEGORY / INDICATION:** Treatment of Tinea Pedis/Interdigital & Plantar-Type S/Tinea Corporis/Cruris caused by Dermatophytes including Trichophyton

| | |
|---|---|
| **DOSAGE FORM:** | Cream |
| **STRENGTHS:** | 1% |
| **ROUTE OF ADMINISTRATION:** | Topical |
| **DISPENSED:** | ___ Rx _X_ OTC |

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT.:**
(E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-napthalenemethanamine hydrochloride

| | | |
|---|---|---|
| **Molecular Formula:** | $C_{21}H_{25}N$ (free base) | |
| | $C_{21}H_{26}NCl$ | (hydrochloride salt) |
| **Molecular Weight:** | 291.44 | (free base) |
| | 327.79 | (hydrochloride salt) |
| **CAS No.:** | 78628-80-5 | |

**SUPPORTING DOCUMENTS:** NDA 20-192

**REMARKS / COMMENTS:**
Novartis Pharmaceuticals Corporation in accordance with 21 CFR 314.50 and in coordination with Novartis Consumer Health, Inc., submitted NDA 20-980 as an RX-TO-OTC SWITCH for their LAMISIL Cream, 1% drug product. This application incorporated by reference NDA 20-192, approved 12/30/92, for chemistry, pharmacology and clinical microbiology which were not submitted in this application. A statement in this NDA provided that no changes had occurred with either the drug substance (DS) specifications, the drug product or its container/closure system.

Therefore, the only CMC issues reviewed for this new efficacy supplement were the EA Categorical Exclusion, the CMC components listed in the new OTC Labeling and the FUR status of the three Novartis manufacturing sites. All are discussed below.

The sponsor applied for an environmental assessment categorical exclusion as per 21 CFR 25.31(b). This submission indicated an Expected Introduction Concentration (EIC) of DS into the aquatic environment of 0.44 ppb. According to the final Environment Assessment, ruling effective 8/28/97, a categorical exclusion can be granted if the EIC at the point of entry into the aquatic environment is < 1.0 ppb per year, or equivalent to ≈ 40,700 kg of terbinafine hydrochloride per year. As noted, the sponsor's EIC easily falls within the categorical exclusion requirement.

The labeling for this OTC Lamisil Cream 1% product remains the same as the previously approved labeling in NDA 20-192 therefore it remains approved.

EER inspection status was conducted for the two DS manufacturers at their Novartis Pharma Inc. site in Basel, Switzerland and their Novartis Ringaskiddy, Ireland production site as well as their drug product manufacturing site at the Sandoz Consumer Pharmaceutical Plant in Lincoln, Nebraska. All manufacturing sites were approved.

**CONCLUSIONS & RECOMMENDATIONS**

NDA 20-980 is RECOMMENDED FOR APPROVAL based upon an acceptable EA categorical exclusion, on unchanged OTC labeling and on positive FUR inspection data.

/S/

James D. Vidra, Ph.D.
Review Chemist, HFD-830/HFD-540

Attachment

cc: NDA 20-980/000
HFD-540/Division File
HFD-540/PrjMgt/Cross
HFD-540/Chm/Vidra
HFD-540/ChmSup/DeCamp WD 7/28/98
HFD-830/DivDir/Chen
filename: N20980.000 9/3 8/4/98

540 CMC

DEC 2 2 1998

# DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

**NDA #:** 20-980 **CHEM. REVIEW :** # 2 **REVIEW DATE:** 21-Dec-98

| SUBMISSION/TYPE: | DOCUMENT DATE: | CDER DATE: | ASSIGNED DATE: |
|---|---|---|---|
| NDA 20-980/000 | 27-Mar-98 | 30-Mar-98 | Review #1 |
| BZ | 15-Jun-98 | 17-Jun-98 | 30-Jun-98 |
| BC | 15-Oct-98 | 16-Oct-98 | 29-Oct-98 |
| BC | 27-Oct-98 | 28-Oct-98 | 04-Nov-98 |

**NAME & ADDRESS OF APPLICANT:**

Novartis Consumer Health, Inc.
560 Morris Avenue
Summit, New Jersey 07901-1312
ATTN: Christine Babiuk, Ph.D.
Associate Director, Regulatory Affairs
Telephone: (908) 598-7816
Fax: (908) 273-2869

**DRUG PRODUCT NAME:**

| | |
|---|---|
| Proprietary: | Lamisil |
| NonProprietary/USAN: | terbinafine HCl |
| Code Names / #'s: | 4021030/SF 86-327 ch |
| Chemical Type: | 6S |
| Therapeutic Class: | Anti- fungal (topical) |

**ANDA Suitability Petition/DESI/Patent Status:** NOT APPLICABLE.

**PHARMACOLOGICAL CATEGORY / INDICATION:** Treatment of Tinea Pedis/Interdigital & Plantar-Type S/Tinea Corporis/Cruris caused by Dermatophytes including Trichophyton

**DOSAGE FORM:** Cream
**STRENGTHS:** 1%
**ROUTE OF ADMINISTRATION:** Topical
**DISPENSED:** ___ Rx _X_ OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT.:**
(E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-napthalenemethanamine hydrochloride

| | | |
|---|---|---|
| **Molecular Formula:** | $C_{21}H_{25}N$ | (free base) |
| | $C_{21}H_{26}NCl$ | (hydrochloride salt) |
| **Molecular Weight:** | 291.44 | (free base) |
| | 327.79 | (hydrochloride salt) |
| **CAS No.:** | 78628-80-5 | |

**SUPPORTING DOCUMENTS:** NDA 20-192
NDA 20-980

**REMARKS / COMMENTS:**

Novartis Pharmaceuticals Corporation in accordance with 21 CFR 314.50 and in coordination with Novartis Consumer Health, Inc., submitted NDA 20-980 as an RX-TO-OTC SWITCH for their LAMISIL Cream, 1% drug product. This application refers to NDA 20-192, approved 12/30/92, for chemistry, pharmacology and clinical microbiology which were not submitted in this application. A statement in this NDA provided that no changes had occurred with either the drug substance (DS) specifications, the drug product or its container/closure system.

This review covers three amendments, e.g. a minor multidisciplinary amendment, BZ, and two minor chemistry amendments, BC dated 10/15/98 and 10/27/98. Each amendment is reviewed individually.

1. Minor Multidisciplinary Amendment NDA 20-980/BZ requested FDA approval for a stability protocol proposal qualifying a new tube sealant. The submitted protocol would perform stability testing on the new tube sealant placed on the four previously approved tubes, i.e. the 2, 7, 15 & 30 gram tubes. These tubes will be placed on stability at: 25°C/60%RH, 30°C/60%RH & 40°C/75%RH for 5, 1 & 0.5 years respectively. All stability-indicating tests were submitted.

2. Minor Chemistry Amendment NDA 20-980/BC dated 10/15/98 requested FDA approval for the OTC preferred trade name of LAMISIL$^{AT}$ Cream. This trade name was submitted to the LNC on 10/18/98 and approved by that committee.

3. Minor Chemistry Amendment NDA 20-980/BC dated 10/27/98 requested FDA approval to market two new OTC drug product packages, i.e. their 12 and 24 gram tubes. These two new packages are qualified by being "bracketed" on the previously approved 7 and 30 gram prescription packages which had been approved for 24 month expiry dating.

**CONCLUSIONS & RECOMMENDATIONS**

Review #1 continues to be Recommended for Approval for NDA 20-980. The CMC review of these three amendments do not change that initial recommendation.

/S/

James D. Vidra, Ph.D.
Review Chemist, HFD-830/HFD-540

Attachment

cc: NDA 20-980/BZ & BC
HFD-540/Division File
HFD-540/PrjMgt/Cross
HFD-540/Chm/Vidra
HFD-540/ChmSup/DeCamp WS 12/22/98
HFD-830/DivDir/Chen
filename: N20980.BZ.BC
HFD-540/DIVDIR/WILKIN
12/31/98

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20-980

## PHARMACOLOGY REVIEW(S)

JUN 3 1998

**REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA**
**Division of Dermatologic and Dental Drug Products, HFD-540**

**NDA 20-980** (Original submission 03-30-1998)
**Drug:** Terbinafine HCl Cream1%

**Sponsor:** Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080
Christine Babiuk
(908) 598-7816

**Number of Volumes:** Five (5)
**Date CDER Received:** 03-30-1998
**Date Assigned:** 04-06-1998
**Date of Review:** 06-03-1998

**Dosage and Route of Administration:** Topical cream
**Category:** Antifungal
**Indication:** Treatment of athletes foot (interdigital tinea pedis), jock itch (tinea cruris), and ringworm (tinea corporis).

**Review Objective:** Rx-to-OTC switch

**Related submissions:**

**INDs**

**NDAs**
20-192; Lamisil Cream 1% (approved, 12-30-1992)
20-539; Lamisil Tablets (approved,05-10-1996)
20-749; Lamisil Solution 1% ( approved,10-17-1997)
20-846; Lamisil DermGel 1% (approved , 04-29-1998)

**Background:** Over the years, a number of applications have been submitted to support the different antifungal formulations of the active ingredient, terbinafine hydrochloride. To support these applications, the sponsor has extensively evaluated the safety of this compound in a wide spectrum of animal and *in vitro* studies. These studies were conducted with the tablet, cream, solution and gel formulations. The animal safety profile for terbinafine hydrochloride has been well established, therefore, there are no non-clinical safety issues involved in Rx-to-OTC switch of this drug. The 1% cream formulation is in the U.S. market since 1992, and is also sold as prescription drug in 82 other countries. No adverse effects of any clinical significance have been reported. The OTC formulation will be identical to the approved cream currently marketed under prescription. However, the label for OTC preparation will be different from the Rx label in terms of number of indications and the reduced duration of treatment. Of the currently approved four indications (athlete's foot; jock itch; ringworm; plantar tinea pedis), only plantar tinea pedis will be maintained under the prescription status. The reduced

duration of treatment to one week from 2-3 weeks will further enhance the clinical safety of the drug product. The OTC label shall be drafted by the OTC reviewer.

**Regulatory Recommendation:** I have no objection to Rx-to-OTC switch for terbinafine Hydrochloride Cream 1%.

/S/ 06/05/98

Kumar D. Mainigi, Ph.D., M.P.H., D.A.B.T.
Toxicologist

CC: NDA 20-980
HFD-82
HFD-540
HFD-560
MO/Vaughan
MO/Aurecchia/HFD-560
Chem/Vidra
Micro/Altaie
Biopharm/Bashaw
Pharm/Mainigi
Pharm/Jacobs
CSO/Cross
CSO/Wright/HFD-560

Concurrence:
A Jacobs, TL,HFD-540 6/3/98
J.Wilkin,Dir,HFD-540 6/9/98