CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-980

ADMINISTRATIVE DOCUMENTS

Terbinafine HCl Cream, 1%

NOVARTIS CERTIFICATION
IN COMPLIANCE WITH THE
GENERIC DRUG ENFORCEMENT ACT OF 1992

NOVARTIS PHARMACEUTICALS CORPORATION certifies that it did not and will not use in any capacity the services of any person debarred under section 306 (a) or 306 (b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

3/27/98
Date

Stephenie Barba
Executive Director
Drug Regulatory Affairs

SECTION 13: PATENT INFORMATION

Terbinafine HCl is covered by US Patent 4,680,291 (issued July 14, 1987 and expires on July 14, 2004) and US Patent 4,755,534 (issued July 5, 1988 and, in view of a 543 day extension, expires on December 30, 2006). Both patents cover terbinafine, pharmaceutical compositions containing the drug, and its use as an antimycotic agent.

EXCLUSIVITY SUMMARY FOR NDA # 20-980

Trade Name Lamisil Cream, 1% Generic Name terbinafine hydrochloride cream, 1%

Applicant Name Novartis Consumer Health, Inc. HFD-540

Approval Date If Known 3/9/09

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety? No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /__/ NO /_X_/

This NDA provides for the Rx to OTC switch of Lamisil (terbinafine hydrochloride cream) Cream, 1%, for the indications of Tinea corporis, Tinea cruris and Tinea pedis.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA 20-192, Lamsil Cream, 1%
NDA 20-539, Lamisil Oral Tablets, 250 mg
NDA 20-749, Lamisil Solution, 1%
NDA 20-846, Lamisil DermGel, 1%

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X_/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 2-1

Investigation #2, Study # 2-2

Investigation #3, Study # 3-1

Investigation #4, Study # 3-2

Investigation #5, Study # 2509-01

Investigation #6, Study # 2509-02

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1, Study # 2-1	YES /_X_/	NO /__/
Investigation #2, Study # 2-2	YES /_X_/	NO /__/
Investigation #3, Study # 3-1	YES /_X_/	NO /__/
Investigation #4, Study # 3-2	YES /_X_/	NO /__/
Investigation #5, Study # 2509-01	YES /_X_/	NO /__/
Investigation #6, Study # 2509-02	YES /_X_/	NO /__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Investigation #1, Study # 2-1	NDA 20-192
Investigation #2, Study # 2-2	NDA 20-192
Investigation #3, Study # 3-1	NDA 20-192
Investigation #4, Study # 3-2	NDA 20-192
Investigation #5, Study # 2509-01	NDA 20-192/SE1-003
Investigation #6, Study # 2509-02	NDA 20-192/SE1-003

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1, Study # 2-1	YES /___/	NO /_X_/
Investigation #2, Study # 2-2	YES /___/	NO /_X_/
Investigation #3, Study # 3-1	YES /___/	NO /_X_/
Investigation #4, Study # 3-2	YES /___/	NO /_X_/
Investigation #5, Study # 2509-01	YES /___/	NO /_X_/
Investigation #6, Study # 2509-02	YES /___/	NO /_X_/

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"): N/A

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1, Study # 2-1 (IND	YES /_X_/	NO /__/
Investigation #2, Study # 2-2 (IND	YES /_X_/	NO /__/
Investigation #3, Study # 3-1 (IND	YES /_X_/	NO /__/
Investigation #4, Study # 3-2 (IND	YES /_X_/	NO /__/
Investigation #5, Study # 2509-01 (IND	YES /_X_/	NO /__/
Investigation #6, Study # 2509-02 (IND	YES /_X_/	NO /__/

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1, Study # 2-1 (IND	YES /_X_/	NO /__/
Investigation #2, Study # 2-2 (IND	YES /_X_/	NO /__/
Investigation #3, Study # 3-1 (IND	YES /_X_/	NO /__/
Investigation #4, Study # 3-2 (IND	YES /_X_/	NO /__/
Investigation #5, Study # 2509-01 (IND	YES /_X_/	NO /__/
Investigation #6, Study # 2509-02 (IND	YES /_X_/	NO /__/

c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

/S/
Signature of Senior Regulatory Management Officer — Date: 2/3/99

/S/
Signature of DDDDP Division Director — Date: 3/9/99

/S/
Signature of DOTCDP Division Director — Date: 03/09/99

Form OGD-011347 Revised 10/13/98
cc: Original NDA 20-980 HFD-540/560 Division Files HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

TE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA 20-980 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade and generic names/dosage form: Lamisil (terbinafine HCl cream) Cream, 1% Action: AP

Applicant Novartis Consumer Health, Inc. Therapeutic Class 6S

Indication(s) previously approved Tinea corporis, Tinea cruris, Interdigital Tinea pedis, Plantar Tinea pedis (moccasin type).
Pediatric information in labeling of approved indication(s) is adequate X inadequate ___
Proposed indication in this application Rx to OTC Switch of Tinea pedis, Tinea corporis, Tinea cruris

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.
IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? X Yes (Continue with questions) ___No (Sign and return the form)
WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
Neonates (Birth-1 month) _Infants (1 month-2yrs) _Children (2-12yrs) X Adolescents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

X 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). See attached explanation.

___3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

c. The applicant has committed to doing such studies as will be required.
(1) Studies are ongoing,
(2) Protocols were submitted and approved.
(3) Protocols were submitted and are under review.
(4) If no protocol has been submitted, attach memo describing status of discussions.

d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical Officer (e.g., medical review, medical officer, team leader)

Signature of Preparer and Title /S/ Date 3/3/99

/S/ 3/7/99

cc: Orig NDA 20-980
HFD-540/Div File
NDA 20-922 Action Package
HFD-540/DIV DIR/Wilkin
HFD-540/DERM TL/Walker
HFD-540/MO/Vaughan 3/5/99
HFD-560/MO/Aurecchia
HFD-540/PM/Cross
HFD-006/KRoberts

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK) (revised 10/20/97)

Pediatric Page Memorandum

2. Attached explanation.

There were too few pediatric patients enrolled in studies submitted under this NDA (Rx to OTC switch) to establish safe use in infants (1 month - 2 yrs) and children (2 - 12 yrs). The prescription drug product, Lamisil Cream, 1% , is approved for use in adolescents (12 - 17 yrs) for treatment of tinea pedis (interdigital and moccasin types) and tinea corporis/cruris. Tinea pedis and tinea cruris rarely occurs in the non-adolescent age groups; however, tinea corporis does occur in the less than 12 year old age groups.

3/7/99

APPEARS THIS WAY
ON ORIGINAL

MEMO

To: Susan Walker, M.D., Medical Team Leader-Dermatology

From: E. Dennis Bashaw, Pharm.D., Pharmacokinetics Team Leader

Date: Tuesday, February 2, 1999

Subject: NDA 20-980 (Lamisil OTC Switch)

This memo is an addendum to the final PK review for this application that was finalized on June 18, 1998. Since the issuance of this review a decision was made to broaden the OTC indication to include all type of tinea pedis in the OTC indication instead of limiting it to interdigital tinea. Specifically this would include the so-called moccasin type of tinea pedis where the entire surface of the foot is involved. A concern was noted as to whether or not this increase in potential surface area would have any pharmacokinetic implications.

It is my opinion as both the reviewing pharmacokineticist and as group leader that this should not be an issue for concern as the increase in absorption (secondary to increased surface area exposure) would not result in markedly higher levels. This is based on a re-examination of the original data contained in the following review files:

NDA 20-192 1% Terbinafine Cream
NDA 20-539 Terbinafine 250 and 500mg tablets
NDA 20-749 1% Terbinafine Spray

A single dose of the 250mg oral tablet of terbinafine in NDA 20-539 gave peak plasma levels of 1,796ng/ml (Study SFP-101). By comparison in a study with the 1% cream formulation (NDA 20-192) patients suffering from T. versicolor had peak plasma levels of 6ng/ml, although the surface area was unstated. These levels compare favorably with the data from the 1% spray product where levels of ~10ng/ml were found after 8 days treatment of an average of 59cm^{2}s of involved skin (T. cruris). While the increased surface area will undoubtedly result in slightly higher plasma levels than those seen here, they would still be markedly inferior to those produced by a single oral tablet and would be within the range of our current experience.

On the basis of these data, there does not appear to be a need for additional pharmacokinetic information for this application nor for any special labeling instructions (beyond those already present in the proposed package insert) for this indication.

CC: NDA 20-980 (ORIG),
HFD-540/DIV File
HFD-540/CSO/Cross
HFD-880(Bashaw)
HFD-880(Lazor)
CDR. ATTN: B. Murphy