

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204286Orig1s000

OTHER REVIEW(S)

The maximal use PK study conducted in adults indicated that following topical administration of Naftine Gel 2%, naftifine hydrochloride was quantifiable in plasma in all 30 subjects (Cmax on Day 14 was 3.7 ng/mL).

Since the PK information provided to support the adolescent population was found inadequate to conclude similarity in systemic exposure between the adolescent population and the adult population, a confirmatory maximal use PK study in adolescents is needed.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study would be an open label, multiple dose PK study of Naftin Gel 2% under maximal clinical use conditions in subjects aged 12 years to 17 years 11 months, with a minimum of 18 evaluable subjects with tinea pedis toward the upper end of disease severity in the patient population. Safety evaluation would be included in the study design for both local and systemic safety.

The primary pharmacokinetic analysis of naftifine hydrochloride is to include a determination of the following parameters: steady state AUC, C_{max} and T_{max}.

It should be noted that there is an existing post marketing requirement (PMR) attached to the approval of Naftin Cream 2% (PMR #1857 for PK/Safety/Tolerability study under maximal use conditions in subjects ages 12 years to 17 years 11 months). In July 2012, the applicant submitted the study protocol to address this PMR. In proposed PK/safety study under maximal use Naftin Gel 2% arm is included. This appears to be adequate to address the safety needs for the adolescent population from age 12-17 years 11 months for Naftin Gel 2%.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

MEMORANDUM

Date: May 29, 2013

To: Strother D. Dixon
Regulatory Health Project Manager,
Division of Dermatology and Dental Products (DDDP)

CC: Milena Lolic, MD
Medical Officer, ODE III, DDDP

David Kettl, MD
Clinical Team Leader, ODE III, DDDP

From: Celestina Arowosegbe, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 204286
NAFTIN (naftifine hydrochloride) Gel, 2% for topical use
Package Insert (PI)

As requested in your consult dated October 1, 2012, OPDP has reviewed the draft PI for NAFTIN (naftifine hydrochloride) Gel, 2% for topical use. OPDP's comments are based on the proposed substantially complete, marked-up version of the PI received on May 21, 2013. OPDP's comments on the PI are provided directly on the attached copy of the labeling.

If you have any questions about OPDP's comments, please contact Celestina Arowosegbe at 301-796-4661 or at Celestina.Arowosegbe@fda.hhs.gov

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CELESTINA O AROWOSEGBE
05/29/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

| | |
|--|--|
| Product Title | NAFTIN (naftifine hydrochloride) Gel, 2% for topical use |
| Applicant | Merz Pharmaceuticals LLC |
| Application/Supplement Number | NDA 204286 |
| Type of Application | Original Submission |
| Indication(s) | For the treatment of interdigital type tinea pedis (b) (4) caused by the organisms <i>Trichophyton rubrum</i> , <i>Trichophyton mentagrophytes</i> , and <i>Epidermophyton floccosum</i> in patients 18 years of age and older |
| Established Pharmacologic Class ¹ | allylamine antifungal |
| Office/Division | ODE III/DDDP |
| Division Project Manager | Strother Dixon |
| Date FDA Received Application | August 31, 2012 |
| Goal Date | June 30, 2013 |
| Date PI Received by SEALD | May 28, 2013 |
| SEALD Review Date | May 28, 2013 |
| SEALD Labeling Reviewer | Jeanne M. Delasko |
| SEALD Division Director | Laurie Burke |

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

| Section | Required/Optional |
|--|---|
| • Highlights Heading | Required |
| • Highlights Limitation Statement | Required |
| • Product Title | Required |
| • Initial U.S. Approval | Required |
| • Boxed Warning | Required if a Boxed Warning is in the FPI |
| • Recent Major Changes | Required for only certain changes to PI* |

Selected Requirements of Prescribing Information

| | |
|---|---|
| • Indications and Usage | Required |
| • Dosage and Administration | Required |
| • Dosage Forms and Strengths | Required |
| • Contraindications | Required (if no contraindications must state “None.”) |
| • Warnings and Precautions | Not required by regulation, but should be present |
| • Adverse Reactions | Required |
| • Drug Interactions | Optional |
| • Use in Specific Populations | Optional |
| • Patient Counseling Information Statement | Required |
| • Revision Date | Required |

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

NO

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment: *The two statements (see above) must appear as a paragraph and not as two separate statements in HL with spacing inbetween. Also, do not include the product strength (i.e., 2%) in the HL Limitation Statement. Only include the name of drug product.*

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

Selected Requirements of Prescribing Information

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *Revision date must read 06/2013, not “XX/XXXX.”*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

Selected Requirements of Prescribing Information

- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:
-

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

| |
|--------------------------------------|
| Boxed Warning |
| 1 INDICATIONS AND USAGE |
| 2 DOSAGE AND ADMINISTRATION |
| 3 DOSAGE FORMS AND STRENGTHS |
| 4 CONTRAINDICATIONS |
| 5 WARNINGS AND PRECAUTIONS |
| 6 ADVERSE REACTIONS |
| 7 DRUG INTERACTIONS |
| 8 USE IN SPECIFIC POPULATIONS |
| 8.1 Pregnancy |
| 8.2 Labor and Delivery |
| 8.3 Nursing Mothers |
| 8.4 Pediatric Use |
| 8.5 Geriatric Use |
| 9 DRUG ABUSE AND DEPENDENCE |
| 9.1 Controlled Substance |
| 9.2 Abuse |
| 9.3 Dependence |
| 10 OVERDOSAGE |
| 11 DESCRIPTION |
| 12 CLINICAL PHARMACOLOGY |

Selected Requirements of Prescribing Information

| |
|---|
| 12.1 Mechanism of Action |
| 12.2 Pharmacodynamics |
| 12.3 Pharmacokinetics |
| 12.4 Microbiology (by guidance) |
| 12.5 Pharmacogenomics (by guidance) |
| 13 NONCLINICAL TOXICOLOGY |
| 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility |
| 13.2 Animal Toxicology and/or Pharmacology |
| 14 CLINICAL STUDIES |
| 15 REFERENCES |
| 16 HOW SUPPLIED/STORAGE AND HANDLING |
| 17 PATIENT COUNSELING INFORMATION |

Comment:

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

Comment: For subsection 12.1, the cross reference should read [see Clinical Pharmacology (12.4)], not [see Microbiology (12.4)]. Also, the cross reference should appear in italics.

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

YES

Selected Requirements of Prescribing Information

46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

YES

47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

N/A

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

JEANNE M DELASKO
05/28/2013

LAURIE B BURKE
05/28/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: April 29, 2013

TO: Milena Lolic, M.D., Medical Officer
David Kettl, M.D., Clinical Team Leader
Strother D. Dixon, Regulatory Health Project Manager
Division of Dermatology and Dental Products (DDDP)

FROM: Janice Pohlman, M.D., M.P.H.
Medical Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204286

APPLICANT: Merz Pharmaceuticals

DRUG: naftifine hydrochloride (Naftin[®] Topical Gel 2%)
NME: No
THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: Treatment of interdigital (b) (4) tinea pedis

CONSULTATION REQUEST DATE: October 17, 2012

INSPECTION SUMMARY GOAL DATE: May 7, 2013

DIVISION ACTION GOAL DATE: June 17, 2013

PDUFA DATE: June 30, 2013

I. BACKGROUND:

Naftin[®] Gel 2% is a formulation of naftifine hydrochloride in a gel base. It is a topical antifungal agent. Naftin[®] Cream 1% and 2% and Naftin[®] Gel 1% are commercially available and approved for use in the treatment of tinea pedis.

The Applicant submitted two studies of similar design, Protocol MRZ 90200/3015/1 and MRZ 90200/3016/1 in support of the application, NDA 204286. The DDDP chose to audit one clinical investigator (CI) site for each of the two studies.

MRZ 90200/3015/1 and MRZ 90200/3016/1

Each study was a multicenter, double-blind, randomized, parallel group, placebo-controlled study. The primary objective of the studies was to evaluate the safety and effectiveness of Naftin[®] 2% Gel applied topically once a day for two weeks in the treatment of subjects with interdigital (b)(4) tinea pedis. Subjects were randomized in a 2:1 ratio to treatment with Naftin[®] Gel 2% versus placebo. The primary efficacy endpoint was complete clinical cure at the Week 6 follow-up visit. A complete clinical cure was defined as mycological cure (i.e. negative dermatophyte culture and negative KOH) and clinical cure (i.e. absence of erythema, scaling, and pruritus).

II. RESULTS (by Site): One CI was inspected for each study. The basis for choosing the CI sites was the large number of subjects enrolled and relatively large treatment effect.

| Name of CI Location | Protocol #, Site #, and # of Subjects | Inspection Date | Final Classification |
|---|---|----------------------|----------------------|
| John H. Tu, M.D. Skin Search of Rochester, Inc. 100 White Spruce Blvd. Rochester, NY 14623 | MRZ 90200/3015/1 Site #001-027 50 enrolled subjects | December 12-20, 2012 | NAI |
| Robert Dunne, M.D. 2717 Wickham Rd., Suite 4 Melbourne, FL 32935 | MRZ 90200/3016/1 Site #001-052 60 enrolled subjects | December 17-21, 2012 | NAI |

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. John H. Tu, M.D.
Skin Search of Rochester, Inc.
100 White Spruce Blvd.
Rochester, NY 14623

- a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811 from December 12-20, 2012. At this site, 52 subjects were screened, 50 subjects were enrolled, and 44 subjects completed the study.

An audit of 21 subjects' records was conducted. The audit evaluated informed consent documents (or assent forms if applicable), source records, study drug accountability, Form, FDA 1572s, financial disclosures, site training, and IRB and sponsor/monitoring correspondence.

- b. General observations/commentary:

Data listings submitted to the NDA were verified against source documents for demographics, adverse events, signs and symptoms of disease severity, KOH analysis, dermatophyte culture, concomitant medications, visit dates, discontinuations, and protocol deviations. There was no under-reporting of adverse events.

The study was conducted in accordance with good clinical practices and no Form FDA 483 was issued.

- c. Assessment of data integrity:

The study appears to have been conducted adequately. The data generated by this site appear acceptable in support of the indication sought.

2. Robert Dunne, M.D.
2717 Wickham Rd., Suite 4
Melbourne, FL 32935

- a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811 from December 17-21, 2012. At this site, 60 subjects were screened, 60 subjects were enrolled, and 50 subjects completed the study.

An audit of 35 subjects' records was conducted. The audit included review of inclusion/exclusion criteria, study procedures, concomitant medications, protocol deviations, adverse events, study drug accountability logs, laboratory requisitions and results.

- b. General observations/commentary:

Data listings submitted to the NDA were verified with electronic case report forms and related source documents. The primary efficacy endpoint data was verifiable. There was no

under-reporting of adverse events.

Overall, the study was conducted in accordance with good clinical practices and no Form FDA 483, Inspectional Observations was issued.

c. Assessment of data integrity:

The study appears to have been conducted adequately. The data generated by this site appear acceptable in support of the indication sought.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

A single clinical investigator site was audited for each of two studies submitted in support of NDA 204286 for treatment of interdigital (b) (4) tinea pedis. The final inspection classification for Dr. Tu's site for Protocol MRZ 90200/3015/1 was NAI (No Action Indicated). The final inspection classification for Dr. Dunne's site for Protocol MRZ 90200/3016/1 was NAI.

Based upon the review of inspectional findings for these clinical investigator sites, the study data collected appears reliable in support of the requested indication.

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H., Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

JANICE K POHLMAN
04/29/2013

SUSAN D THOMPSON
04/29/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: April 2, 2013

Reviewer: Carlos M Mena-Grillasca, RPh, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, MS, PharmD
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Naftin (Naftifine Hydrochloride) Gel, 2%

Application Type/Number: NDA 204286

Applicant/sponsor: Merz Pharmaceuticals, LLC

OSE RCM #: 2012-2869

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Naftin NDA 204141 for areas of vulnerability that could lead to medication errors. The Applicant is proposing a new strength for the gel formulation to the Naftin product line.

1.1 REGULATORY HISTORY

Naftin Gel, 2% (NDA 204286) is currently under review. The proposed proprietary name Naftin is been evaluated separately under OSE review 2013-459. In addition, the Naftin (Naftifine Hydrochloride) product line includes the following products:

| NDA Num. | Product | Approval Date |
|----------|------------------|-----------------|
| 019599 | Naftin Cream, 1% | June 1, 1998 |
| 019356 | Naftin Gel, 1% | October 1, 1990 |
| 019599 | Naftin Cream, 2% | March 1, 2012 |

1.2 PRODUCT INFORMATION

The following product information is provided in the Naftin (Naftifine Hydrochloride) Gel, 2% submission.

- Active Ingredient: Naftifine Hydrochloride
- Indication of Use: Treatment of interdigital (b)(4) tinea pedis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* in patients (b)(4) years of age and older.
- Route of Administration: Topical
- Dosage Form: Gel
- Strength: 2%
- Dose and Frequency: Apply a thin film to the affected skin areas once daily for 2 weeks.
- How Supplied: 2 gram physician sample tubes; 45 gram tubes
- Storage: 25 °C (77 °F); excursions permitted 15 °-30 °C (59 °-86 °F).
- Container and Closure System: Aluminum tubes with (b)(4) caps.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Naftin medication error reports. We also reviewed the Naftin container labels, carton and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1.

| Table 1: AERS Search Strategy | |
|--------------------------------------|--|
| Date | February 22, 2013 |
| Drug Names | Active ingredient: Naftifine and Naftifine Hydrochloride Product Name: Naftin |
| MedDRA Search Strategy | Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT |
| Time Limitation | None |

The FAERS database search identified 1 case (5098547v1). After individual review, the case was not included in the final analysis because the case describes an adverse event not related to a medication error.

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels and Carton Labeling submitted August 30, 2012 (Appendix B and C)
- Insert Labeling submitted August 30, 2012
- Currently approved labels/labeling for the other Naftin products (Appendix D)

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

The Applicant is proposing a new 2 % strength for the gel formulation. The proposed 2% gel formulation and the currently marketed 2% cream formulation share the same dose and frequency (i.e. thin layer to affected area once daily for 2 weeks). However, there are differences in indication and dosages among all the Naftin formulations currently marketed and the proposed 2% gel as presented in the following table:

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

| Product | Indication | Dosage | How Supplied |
|-----------------|---|---|--|
| Naftin Cream 1% | Topical treatment of tinea pedis, tinea cruris and tinea corporis caused by the organisms <i>Trichophyton rubrum</i> , <i>Trichophyton mentagrophytes</i> , and <i>Epidermophyton floccosum</i> | Apply a sufficient quantity into the affected areas once a day for 4 weeks | Tubes: 15 g, 30 g, 60 g, 90 g Pump: 30 g, 90 g |
| Naftin Cream 2% | Topical treatment of interdigital tinea pedis, tinea cruris and tinea corporis caused by the organism <i>Trichophyton rubrum</i> in patients 18 years of age and older | Apply a thin layer once daily to the affected area for 2 weeks | Tubes: 30 g, 45 g, 60 g |
| Naftin Gel 1% | Topical treatment of tinea pedis, tinea cruris and tinea corporis caused by the organisms <i>Trichophyton rubrum</i> , <i>Trichophyton mentagrophytes</i> , <i>Trichophyton tonsurans</i> , and <i>Epidermophyton floccosum</i> | Apply a sufficient quantity into the affected areas twice a day for 4 weeks | Tubes: 40 g, 60 g, 90 g |
| Naftin Gel 2% | Topical treatment of interdigital ^{(b) (4)} tinea pedis caused by the organisms <i>Trichophyton rubrum</i> , <i>Trichophyton mentagrophytes</i> , and <i>Epidermophyton floccosum</i> in patients ^{(b) (4)} years of age and older. | Apply a thin layer to the affected once daily for 2 weeks. | Tubes: 45 g |

We note that all the currently marketed Naftin products as well as the proposed Naftin Gel 2% have separate Prescribing Information (PI). Considering that the FAERS search did not retrieve any medication errors, we do not have any recommendations regarding separate PI's at this time.

We note that the currently marketed Naftin products are available in multiple package sizes, which seems adequate since the surface area to be treated for the approved indications (i.e. tinea pedis, tinea cruris, and tinea corporis) may vary. Since the proposed 2% gel formulation will only be indicated for tinea pedis, having one package size (i.e. 45 g) seems adequate.

We reviewed the container labels and carton labeling and noted that the presentation of the established name seems to be less than ½ the size of the proprietary name. In addition, we found that the blue round graphic preceding the product name interferes with the readability of the name. Finally, we evaluated if the container labels and carton labeling of the proposed 2% gel formulation was well differentiated from the currently marketed Naftin products and found it adequate.

Lastly, DMEPA had recently reviewed the container labels and carton labeling for the Naftin Cream 2% formulation (OSE RCM # 2011-524, dates September 11, 2011 and January 11, 2012). DMEPA provided recommendations to the Applicant that were addressed and the labels and labeling found acceptable. We note that for the proposed Naftin Gel 2% formulation the Applicant has implemented DMEPA's previous recommendations.

4 CONCLUSIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label and to mitigate any confusion to promote the safe use of the product.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this Application:

5.1 COMMENTS TO THE APPLICANT

A. Proposed Container Labels and Carton Labeling (all package sizes)

1. Revise the presentation of the established name to ensure that it is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).
2. Delete the blue and white round graphic preceding the product name or reduce the size and relocate the graphic away from the proprietary name, established name, and strength statement. As currently presented the graphic interferes with the readability of the product name and could be considered more prominent than more relevant information such as the proprietary name, established name, dosage form, strength, and route of administration.

If you have further questions or need clarifications, please contact Janet Anderson, project manager, at 301-796-0675.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid trade names or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CARLOS M MENA-GRILLASCA
04/02/2013

LUBNA A MERCHANT
04/02/2013

SCOTT M DALLAS
04/02/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 204286

Application Type: New NDA

Name of Drug: Naftin (naftifine hydrochloride) Gel, 2%

Applicant: Merz Pharmaceuticals

Submission Date: August 27, 2012

Receipt Date: August 31, 2012

1.0 Regulatory History and Applicant's Main Proposals

NDA 204286 NAFT-600 (naftifine hydrochloride) Gel, 2% was received on August 31, 2012 for the treatment of interdigital (b) (4) tinea pedis. The associated IND is IND 105603 (naftifine hydrochloride) Gel, 2%. The sponsor had a Pre-NDA Meeting on May 16, 2012.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by November 21, 2012. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

YES 6. Section headings are presented in the following order in HL:

| Section | Required/Optional |
|---|---|
| • Highlights Heading | Required |
| • Highlights Limitation Statement | Required |
| • Product Title | Required |
| • Initial U.S. Approval | Required |
| • Boxed Warning | Required if a Boxed Warning is in the FPI |
| • Recent Major Changes | Required for only certain changes to PI* |
| • Indications and Usage | Required |
| • Dosage and Administration | Required |
| • Dosage Forms and Strengths | Required |
| • Contraindications | Required (if no contraindications must state “None.”) |
| • Warnings and Precautions | Not required by regulation, but should be present |
| • Adverse Reactions | Required |
| • Drug Interactions | Optional |
| • Use in Specific Populations | Optional |
| • Patient Counseling Information Statement | Required |
| • Revision Date | Required |

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment: *The HL Limitation Statement is not bolded. The sentence “See full prescribing information...” is a separate paragraph and should be added to the same paragraph.*

Product Title

NO 10. Product title in HL must be **bolded**.

Comment: *Bold the product title.*

Initial U.S. Approval

NO 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *The text is not bolded.*

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

- N/A 12. All text must be **bolded**.
Comment:
- N/A 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
Comment:
- N/A 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.
Comment:
- N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)
Comment:
- N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).
Comment:

Recent Major Changes (RMC)

- N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
Comment:
- N/A 18. Must be listed in the same order in HL as they appear in FPI.
Comment:
- N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.
Comment:
- N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Indications and Usage

- YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”
Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *Bold the revision date*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- NO** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment: *Bold "Full Prescribing Information: Contents*"*

YES

Selected Requirements of Prescribing Information (SRPI)

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- NO 37. All section and subsection headings and numbers must be **bolded**.
Comment: *The font should be 8 point throughout. Section 16 is 10 point.*
- YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

| |
|--------------------------------------|
| Boxed Warning |
| 1 INDICATIONS AND USAGE |
| 2 DOSAGE AND ADMINISTRATION |
| 3 DOSAGE FORMS AND STRENGTHS |
| 4 CONTRAINDICATIONS |
| 5 WARNINGS AND PRECAUTIONS |
| 6 ADVERSE REACTIONS |
| 7 DRUG INTERACTIONS |
| 8 USE IN SPECIFIC POPULATIONS |
| 8.1 Pregnancy |
| 8.2 Labor and Delivery |
| 8.3 Nursing Mothers |
| 8.4 Pediatric Use |
| 8.5 Geriatric Use |

Selected Requirements of Prescribing Information (SRPI)

| |
|--|
| 9 DRUG ABUSE AND DEPENDENCE |
| 9.1 Controlled Substance |
| 9.2 Abuse |
| 9.3 Dependence |
| 10 OVERDOSAGE |
| 11 DESCRIPTION |
| 12 CLINICAL PHARMACOLOGY |
| 12.1 Mechanism of Action |
| 12.2 Pharmacodynamics |
| 12.3 Pharmacokinetics |
| 12.4 Microbiology (by guidance) |
| 12.5 Pharmacogenomics (by guidance) |
| 13 NONCLINICAL TOXICOLOGY |
| 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility |
| 13.2 Animal Toxicology and/or Pharmacology |
| 14 CLINICAL STUDIES |
| 15 REFERENCES |
| 16 HOW SUPPLIED/STORAGE AND HANDLING |
| 17 PATIENT COUNSELING INFORMATION |

Comment:

- N/A 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: *Medication Guide, Patient Information, or Instructions for Use are not included in the labeling.*

- N/A 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A 42. All text is **bolded**.

Comment:

- N/A 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

Selected Requirements of Prescribing Information (SRPI)

YES 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

YES 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

N/A Patient Counseling Information

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: *Sponsor did not reference nor include a Med Guide, Instructions for Use or Patient Information*

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/s/

STROTHER D DIXON
10/29/2012

CRISTINA Petruccelli Attinello
10/29/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

| Application Information | |
|--|---|
| NDA # 204286 | |
| Proprietary Name: Naftin Established/Proper Name: (naftifine hydrochloride) Dosage Form: Gel Strengths: 2% | |
| Applicant: Merz Pharmaceuticals, LLC Agent for Applicant (if applicable): Misty D'Ottavio | |
| Date of Application: August 27, 2012 Date of Receipt: August 31, 2012 Date clock started after UN: NA | |
| PDUFA Goal Date: June 30, 2013 | Action Goal Date (if different): |
| Filing Date: October 30, 2012 | Date of Filing Meeting: October 15, 2012 |
| Chemical Classification: (1,2,3 etc.) (original NDAs only) 5 | |
| Proposed indication(s)/Proposed change(s): For the treatment of interdigital (b) (4) tinea pedis | |
| Type of Original NDA: AND (if applicable) Type of NDA Supplement: | <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) |
| <i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i> | |
| Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i> | <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted |
| Resubmission after withdrawal? <input type="checkbox"/> | Resubmission after refuse to file? <input type="checkbox"/> |
| Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i> | <input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product) |

| | | | | |
|---|--|-----------|-----------|----------------|
| <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: | <input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) | | | |
| Collaborative Review Division (if OTC product): NA | | | | |
| List referenced IND Number(s): 105603 | | | | |
| Goal Dates/Product Names/Classification Properties | YES | NO | NA | Comment |
| PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i> | X | | | |
| Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i> | X | | | |
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i> | X | | | |
| Application Integrity Policy | YES | NO | NA | Comment |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> | | X | | |
| If yes, explain in comment column. | | | X | |
| If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified: | | | X | |
| User Fees | YES | NO | NA | Comment |
| Is Form 3397 (User Fee Cover Sheet) included with authorized signature? | X | | | |

| <p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p> | <p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p> | | | | | | | | | | | | | | | | | | | |
|--|--|------------------|------------------------|------------------------|--|--|--|--|--|--|--|--|--|--|--|--|--|--|----------|--|
| <p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p> | <p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p> | | | | | | | | | | | | | | | | | | | |
| <p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p> | <p>YES</p> | <p>NO</p> | <p>NA</p> | <p>Comment</p> | | | | | | | | | | | | | | | | |
| <p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> | | | <p>X</p> | | | | | | | | | | | | | | | | | |
| <p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p> | | | <p>X</p> | | | | | | | | | | | | | | | | | |
| <p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p> | | | <p>X</p> | | | | | | | | | | | | | | | | | |
| <p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1449 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table> | Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | | | | | <p>X</p> | |
| Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | | | | | | | |
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| <p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p> | | | | | | | | | | | | | | | | | | | | |
| <p>Exclusivity</p> | <p>YES</p> | <p>NO</p> | <p>NA</p> | <p>Comment</p> | | | | | | | | | | | | | | | | |
| <p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p> | | <p>X</p> | | | | | | | | | | | | | | | | | | |

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| <p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p> | | | X | |
| <p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 3</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> | X | | | |
| <p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p> | | X | | |
| <p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p> | | | X | |

| Format and Content | | | | |
|--|--|----|----|---------|
| <p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> | <input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD) | | | |
| <p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p> | | | | |
| Overall Format/Content | YES | NO | NA | Comment |
| <p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p> | X | | | |
| <p>Index: Does the submission contain an accurate comprehensive index?</p> | X | | | |
| <p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p> | X | | | |

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

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| <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) | | | | |
| If no, explain. | | | | |
| BLAs only: Companion application received if a shared or divided manufacturing arrangement? | | | X | |
| If yes, BLA # | | | | |
| Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs) | YES | NO | NA | Comment |
| Was there an agreement for any minor application components to be submitted within 30 days after the original submission? | | | X | |
| <ul style="list-style-type: none"> If yes, were all of them submitted on time? | | | X | |
| Is a comprehensive and readily located list of all clinical sites included or referenced in the application? | | | X | |
| Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? | | | X | |
| Forms and Certifications | | | | |
| <i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i> | | | | |
| Application Form | YES | NO | NA | Comment |
| Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? | X | | | |
| <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i> | | | | |
| Are all establishments and their registration numbers listed on the form/attached to the form? | | X | | Registration numbers are not on the form |
| Patent Information (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)? | | X | | |
| Financial Disclosure | YES | NO | NA | Comment |
| Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? | X | | | |

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| <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> | | | | |
| <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i> | | | | |
| Clinical Trials Database | YES | NO | NA | Comment |
| Is form FDA 3674 included with authorized signature? | X | | | |
| <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> | | | | |
| <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i> | | | | |
| Debarment Certification | YES | NO | NA | Comment |
| Is a correctly worded Debarment Certification included with authorized signature? | X | | | |
| <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> | | | | |
| <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i> | | | | |
| Field Copy Certification (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? | | | X | |
| <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> | | | | |
| <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i> | | | | |
| Controlled Substance/Product with Abuse Potential | YES | NO | NA | Comment |
| <u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? | | | X | |
| <i>If yes, date consult sent to the Controlled Substance Staff:</i> | | | | |
| <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i> | | | | |
| Pediatrics | YES | NO | NA | Comment |

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|--|--|-----------|-----------|--------------------------|
| <u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i> | X | | | New formulation/strength |
| If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included? | | X | | |
| If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i> | X | | | |
| If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i> | | X | | |
| <u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i> | | X | | |
| Proprietary Name | YES | NO | NA | Comment |
| Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i> | | X | | |
| REMS | YES | NO | NA | Comment |
| Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i> | | X | | |
| Prescription Labeling | <input type="checkbox"/> Not applicable | | | |
| Check all types of labeling submitted. | <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels | | | |

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

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| | <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify) | | | |
| | YES | NO | NA | Comment |
| Is Electronic Content of Labeling (COL) submitted in SPL format? | X | | | |
| <i>If no, request applicant to submit SPL before the filing date.</i> | | | | |
| Is the PI submitted in PLR format? ⁴ | X | | | |
| If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? | | | X | |
| <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i> | | | | |
| All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP? | X | | | |
| MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available) | X | | | |
| Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)? | X | | | |
| OTC Labeling | <input type="checkbox"/> Not Applicable | | | |
| Check all types of labeling submitted. | <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify) | | | |
| | YES | NO | NA | Comment |
| Is electronic content of labeling (COL) submitted? | | | X | |
| <i>If no, request in 74-day letter.</i> | | | | |
| Are annotated specifications submitted for all stock keeping units (SKUs)? | | | X | |
| <i>If no, request in 74-day letter.</i> | | | | |
| If representative labeling is submitted, are all represented SKUs defined? | | | X | |
| <i>If no, request in 74-day letter.</i> | | | | |

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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| All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA? | | | X | |
| Other Consults | YES | NO | NA | Comment |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i> OSI - October 18, 2012 Clinical Microbiology – October 2, 2012 | X | | | |
| Meeting Minutes/SPAs | YES | NO | NA | Comment |
| End-of Phase 2 meeting(s)? Date(s): | | X | | |
| <i>If yes, distribute minutes before filing meeting</i> | | | | |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): May 16, 2012 | X | | | |
| <i>If yes, distribute minutes before filing meeting</i> | | | | |
| Any Special Protocol Assessments (SPAs)? Date(s): | | X | | |
| <i>If yes, distribute letter and/or relevant minutes before filing meeting</i> | | | | |

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 15, 2012

NDA #: 204286

PROPRIETARY NAME: Naftin

ESTABLISHED/PROPER NAME: naftifine hydrochloride

DOSAGE FORM/STRENGTH: Topical Gel, 2%

APPLICANT: Merz Pharmaceuticals, LLC

PROPOSED INDICATION(S): Treatment of interdigital (b) (4) tinea pedis

BACKGROUND: NDA 204286 NAFT-600 (naftifine hydrochloride) Gel, 2% was received on August 31, 2012 for the treatment of interdigital (b) (4) tinea pedis. The associated IND is IND 105603 (naftifine hydrochloride) Gel, 2%. The sponsor had a Pre-NDA Meeting on May 16, 2012.

REVIEW TEAM:

| Discipline/Organization | Names | | Present at filing meeting? (Y or N) |
|---|-------------|----------------------|-------------------------------------|
| Regulatory Project Management | RPM: | Strother D. Dixon | Y |
| | CPMS/TL: | Barbara Gould | N |
| Cross-Discipline Team Leader (CDTL) | David Kettl | | Y |
| Clinical | Reviewer: | Milena Lolic, MD | Y |
| | TL: | David Kettl, MD | Y |
| Social Scientist Review (<i>for OTC products</i>) | Reviewer: | NA | NA |
| | TL: | NA | NA |
| OTC Labeling Review (<i>for OTC products</i>) | Reviewer: | NA | NA |
| | TL: | NA | NA |
| Clinical Microbiology (<i>for antimicrobial products</i>) | Reviewer: | Simone Shurland, PhD | Y |
| | TL: | Peter Coderre, PhD | Y |

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| | | | |
| Clinical Pharmacology | Reviewer: | Doanh Tran, PhD | Y |
| | TL: | Edward D. Bashaw, PhD | Y |
| Biostatistics | Reviewer: | Kim Carin, PhD | NA |
| | TL: | Mohammed Alosch, PhD | Y |
| Nonclinical (Pharmacology/Toxicology) | Reviewer: | Jinayong Wang, PhD | Y |
| | TL: | Barbara Hill, PhD | Y |
| Statistics (carcinogenicity) | Reviewer: | NA | NA |
| | TL: | NA | NA |
| Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>) | Reviewer: | NA | NA |
| | TL: | NA | NA |
| Product Quality (CMC) | Reviewer: | Rajiv Agarwal, PhD | Y |
| | TL: | Shulin Ding, PhD | N |
| Quality Microbiology (<i>for sterile products</i>) | Reviewer: | NA | NA |
| | TL: | NA | NA |
| CMC Labeling Review | Reviewer: | NA | NA |
| | TL: | NA | NA |
| Facility Review/Inspection | Reviewer: | NA | NA |
| | TL: | NA | NA |
| OSE/DMEPA (proprietary name) | Reviewer: | TBD | NA |
| | TL: | TBD | NA |
| OSE/DRISK (REMS) | Reviewer: | NA | NA |
| | TL: | NA | NA |
| OC/OSI/DSC/PMSB (REMS) | Reviewer: | NA | NA |
| | TL: | NA | NA |

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| Bioresearch Monitoring (OSI) | Reviewer: | Menfo Imoisili | N |
| | TL: | Janice Pohlman, M.D., M.P.H. | N |
| Controlled Substance Staff (CSS) | Reviewer: | NA | NA |
| | TL: | NA | NA |
| Other reviewers | Lynn Panholzer, OPDP | | N |
| Other attendees | Susan Walker, MD, Division Director, DDDP | | Y |
| | Kathleen Fritch, PhD, Biostatistics Reviewer, DB III | | Y |
| | Cristina Attinello, M.P.H., Regulatory Project Manager, DDDP | | Y |

FILING MEETING DISCUSSION:

| | |
|---|--|
| GENERAL | |
| <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p> | <input checked="" type="checkbox"/> Not Applicable |
| CLINICAL | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> | <input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined |

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| <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> | Reason: |
| <ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| <p>BIOSTATISTICS</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |

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| Comments: | |
| IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments: | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| PRODUCT QUALITY (CMC) Comments: | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter |
| <u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="margin-left: 40px;">If no, was a complete EA submitted?</p> <p style="margin-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> Comments: | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments: | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <u>Facility Inspection</u> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments: | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |

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|---|---|
| <p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p> | <p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p> |
| <p><u>CMC Labeling Review</u></p> <p>Comments:</p> | <p><input type="checkbox"/> Review issues for 74-day letter</p> |
| REGULATORY PROJECT MANAGEMENT | |
| <p>Signatory Authority: Susan Walker, MD</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p> | |
| REGULATORY CONCLUSIONS/DEFICIENCIES | |
| <input type="checkbox"/> | The application is unsuitable for filing. Explain why: |
| <input checked="" type="checkbox"/> | <p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p> |
| ACTIONS ITEMS | |
| <input type="checkbox"/> | Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug). |
| <input type="checkbox"/> | If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER). |
| <input type="checkbox"/> | If filed, and the application is under AIP, prepare a letter either granting (for signature by |

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|--------------------------|--|
| | Center Director) or denying (for signature by ODE Director) an exception for review. |
| <input type="checkbox"/> | BLA/BLA supplements: If filed, send 60-day filing letter |
| <input type="checkbox"/> | If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier) |
| <input type="checkbox"/> | Send review issues/no review issues by day 74 |
| <input type="checkbox"/> | Conduct a PLR format labeling review and include labeling issues in the 74-day letter |
| <input type="checkbox"/> | Update the PDUFA V DARRTS page (for NME NDAs in “the Program”) |
| <input type="checkbox"/> | BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f] |
| <input type="checkbox"/> | Other |

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STROTHER D DIXON
10/29/2012

CRISTINA Petruccelli Attinello
10/29/2012