

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204286Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 204286

SUPPL # NA

HFD # NA

Trade Name Naftin Gel, 2%

Generic Name (naftifine hydrochloride) Gel, 2%

Applicant Name Merz Pharmaceuticals, LLC

Approval Date, If Known TBD

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

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

YES  NO

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

NA

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

NA

d) Did the applicant request exclusivity?

YES  NO

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

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

NA

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES  NO

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

Naftin Cream 1% NDA 19-599

Naftin Cream 2%    NDA 19-599/S11  
Naftin Gel 1%      NDA 19-356

2. Combination product.

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

YES       NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III      THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

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

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

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

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

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

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

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

Investigation #1

IND # 105603      YES       NO   
Explain:

Investigation #2

IND # 105603      YES       NO   
Explain:

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

NA

Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

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

YES  NO

If yes, explain:

=====  
Name of person completing form: Strother D. Dixon  
Title: Regulatory Project Manager  
Date: May 8, 2013

Name Division Director signing form: Susan J. Walker, MD, FAAD  
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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STROTHER D DIXON  
05/15/2013

DAVID L KETTL  
05/16/2013

SUSAN J WALKER  
05/17/2013



MERZ PHARMACEUTICALS

Debarment Certification Statement

Merz Pharmaceuticals, LLC hereby certifies that it did not and will not use in any capacity the service of any person debarred under section 306 of the Federal, Food, Drug, and Cosmetic Act in connection with this application.

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Bhushan Hardas, MD, MBA  
Vice President and US Head of R&D

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Joy Willard, RN  
Clinical Project Manager

4215 Tudor Lane  
Greensboro, NC 27410  
Ph: 336.856.2003  
fax: 336.217.2439

www.merzusa.com

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 204286 BLA # NA	NDA Supplement # NA BLA Supplement # NA	If NDA, Efficacy Supplement Type: NA				
Proprietary Name: Naftin Established/Proper Name: (naftifine hydrochloride) Dosage Form: Gel		Applicant: Merz Pharmaceuticals, LLC Agent for Applicant (if applicable):				
RPM: Strother D. Dixon		Division: Division of Dermatology and Dental Products				
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)  Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> </div> <div style="width: 50%;"> <p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> </div> </div>						
<p>❖ <b>Actions</b></p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 70%; padding: 5px;"> <ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>June 30, 2013</u></li> </ul> </td> <td style="width: 30%; padding: 5px; vertical-align: top;"> <input checked="" type="checkbox"/> AP   <input type="checkbox"/> TA   <input type="checkbox"/> CR </td> </tr> <tr> <td style="padding: 5px;"> <ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul> </td> <td style="padding: 5px; vertical-align: top;"> <input checked="" type="checkbox"/> None </td> </tr> </table>			<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>June 30, 2013</u></li> </ul>	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>June 30, 2013</u></li> </ul>	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR					
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>	<input checked="" type="checkbox"/> None					

The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?                  Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics<sup>3</sup></p> <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority                  Chemical classification (new NDAs only): 5</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span></p> <p>Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR <span style="margin-left: 200px;">REMS: <input type="checkbox"/> MedGuide</span>  <input type="checkbox"/> Submitted in response to a PMC <span style="margin-left: 100px;"><input type="checkbox"/> Communication Plan</span>  <input type="checkbox"/> Submitted in response to a Pediatric Written Request <span style="margin-left: 100px;"><input type="checkbox"/> ETASU</span>  <span style="margin-left: 400px;"><input type="checkbox"/> MedGuide w/o REMS</span>  <span style="margin-left: 400px;"><input type="checkbox"/> REMS not required</span></p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>• Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>• Press Office notified of action (by OEP)</li> </ul>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>• Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<p><input checked="" type="checkbox"/> None  <input type="checkbox"/> HHS Press Release  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input type="checkbox"/> Other</p>

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # NA and date exclusivity expires: NA
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # NA and date exclusivity expires: NA
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # NA and date exclusivity expires: NA
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
<b>❖ Patent Information (NDAs only)</b>	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?

Yes       No

(Note: The date that the patent owner received the applicant’s notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If “Yes,” skip to question (4) below. If “No,” continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If “No,” continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes       No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If “No,” the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If “No,” continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

<p>❖ Copy of this Action Package Checklist<sup>4</sup></p>	<p>6/28/13</p>
<b>Officer/Employee List</b>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<b>Action Letters</b>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) 6/26/13</p>
<b>Labeling</b>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	<p>6/26/13</p>
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<p>8/31/12</p>
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	<p>NA</p>

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	NA
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	NA
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	NA
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	6/17/13
<ul style="list-style-type: none"> <li>❖ Proprietary Name                     <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i></li> </ul> </li> </ul>	Letter - 5/7/13 Review - 5/6/13
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 10/29/12 <input checked="" type="checkbox"/> DMEPA 4/2/13 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) 5/29/13 <input checked="" type="checkbox"/> SEALD 5/28/13 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	10/29/12
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> </li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP                     <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)                     <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>5/22/13</u>                              If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Outgoing communications ( <i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	IR - 3/28/13, IR 1/10/13, Filing - 11/05/12, IR - 9/20/12, Ack - 9/6/12,
❖ Internal memoranda, telecons, etc.	2/19/13 Proprietary Name Telecon
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 5/16/12
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/26/13
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/04/13
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 1, 6/18/13
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	NA - See CDTL
• Clinical review(s) ( <i>indicate date for each review</i> )	6/04/13 (review), 10/19/12 (filing)
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	p. 21, Clinical Review 6/04/13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	
• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested 4/29/13 Review, 3/5/13 DSI Letter, 3/5/13 - DSI Letter

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 6/26/13 (addendum to review) 3/15/13 (review), 10/11/12 (filing)
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 5/6/13 (review), 10/19/12 (filing)
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 5/3/13 (review), 10/22/12 (filing)
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 4/9/13 (review), 10/15/12 (filing)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 4/22/13 (review), 10/24/12 (filing)
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None

Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	4/22/13, p. 48 CMC Review
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup></i> )	Date completed: 11/30/12, p. 49-50 CMC Review <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.



NDA 204286

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Merz Pharmaceuticals, LLC  
4215 Tudor Lane  
Greensboro, NC 27410

ATTENTION: Misty M. D'Ottavio, RN  
Senior Manager, Regulatory Affairs

Dear Ms. D'Ottavio:

Please refer to your New Drug Application (NDA) dated August 30, 2012, received August 31, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Naftifine Hydrochloride Gel, 2%.

We also refer to your February 8, 2013, correspondence, received February 8, 2013, requesting review of the proposed proprietary name, Naftin Gel 2%. We also refer you to your February 20, 2013 amendment, received February 20, 2013, revising the proprietary name request to review the proposed proprietary name, Naftin. We have completed our review of the proposed proprietary name Naftin and have concluded that it is acceptable.

The proposed proprietary name will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. If **any** of the proposed product characteristics as stated in your February 8, 2013 and February 20, 2013 submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet L. Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application contact Strother D. Dixon, Regulatory Project Manager in the Office of New Drugs (OND) at (301) 796-1015.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
05/07/2013



NDA 204286

## INFORMATION REQUEST

Merz Pharmaceuticals, LLC  
Attention: Misty M. D'Ottavio, RN  
Senior Regulatory Affairs Manager  
4215 Tudor Lane  
Greensboro, NC 27410

Dear Ms. D'Ottavio:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Naftin (naftifine hydrochloride) Gel, 2%.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by April 10, 2013 in order to continue our evaluation of your NDA.

1. Your proposed acceptance criteria for degradation products are not supported by the registration stability data. Tighten as follows to reflect the stability characteristics of your drug product.
  - a. Specified Unidentified, each: NMT (b)(4)%
  - b. Unspecified each: NMT (b)(4)%
  - c. Total: NMT (b)(4)%
2. Delete the acceptance criterion of "Specified identified, each NMT" from the specification table because you have not structurally identified and specified any degradation product in the drug product.

If you have any questions, call Strother D. Dixon, Regulatory Project Manager, at (301) 796-1015.

Sincerely,

*{See appended electronic signature page}*

Susan J. Walker, M.D., F.A.A.D.  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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SUSAN J WALKER  
03/28/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

**MEMORANDUM**

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

**MEETING DATE:** February 19, 2013  
**TIME:** 1:00 PM  
**LOCATION:** WO 22 Room 5157  
**APPLICATION:** NDA 204286  
**DRUG NAME:** Naftin (naftifine hydrochloride) Gel, 2%  
**TYPE OF MEETING:** Proposed Proprietary Name

**MEETING CHAIR:** Lubna Merchant

**MEETING RECORDER:** Janet Anderson

**FDA ATTENDEES:**

Lubna Merchant, PharmD, MS, Team Leader, DMEPA  
Carlos M Mena-Grillasca, RPh, Safety Evaluator, DMEPA  
Lisa Khosla, PharmD, MHA, Safety Evaluator, DMEPA  
Janet Anderson, PharmD Safety Regulatory Project Manager

**EXTERNAL ATTENDEES:**

Misty D'Ottavio, Sr. Manager, Regulatory Affairs  
David Dobrowski, Director, Regulatory Affairs  
Brandi Woods, Manager, Regulatory Affairs  
Stefan Plaum, Assoc. Medical Director  
Joy Willard, Project Management

**Background**

Merz Pharmaceuticals submitted the proposed primary proprietary name, "Naftin Gel, 2%", for NDA 204286, naftifine hydrochloride gel 2% on February 8, 2012.

DEMPA requested this teleconference to clarify if the dosage form and strengths are actually intended to be part of the proposed name and to inform Merz of DMEPA's concerns with this practice.

### **Product Information**

- Active Ingredient: Naftifine Hydrochloride
- Proposed 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 thin layer once daily to the affected areas plus an approximate ½ inch margin of healthy surrounding skin for 2 weeks.
- How Supplied: 45 grams aluminum tubes
- Storage: Room temperature

### **Meeting Objectives**

This is a courtesy call to seek clarification regarding your proposed proprietary name "Naftin Gel, 2%" for naftifine hydrochloride NDA 204286.

### **DMEPA Discussion**

We acknowledge that you previously responded to an email from Janet Anderson, OSE PM, in which you confirmed that the proposed name for this application is "Naftin Gel, 2%". In fact, your Request for Proprietary Name Review submitted on February 8, 2013 indicates that the proposed proprietary name is "Naftin Gel, 2%" and that the "modifier '2%' represent the percentage of active drug included in the product and will keep it consistent with the currently marketed Naftin products".

However, upon review of the proposed container labels and carton labeling submitted with this application we note that the proprietary name is presented as 'Naftin' and the dosage form and strength are presented as part of the established name. If the intended proprietary name is "Naftin Gel, 2%", as you indicate on the request for review, the container labels and carton labeling would then have to read "Naftin Gel, 2% (naftifine hydrochloride) gel, 2%", so we would like to clarify what your intended proprietary name is.

NDA 204286

**Conclusion**

The Applicant indicated that the intended name for this application is [REDACTED] (b)(4)”. Per DMEPA advice, the Applicant will submit an Amendment to the Proprietary Name Request submitted on February 8, 2013 clarifying that their intended proposed proprietary name is [REDACTED] (b)(4) Naftin Gel, 2%.

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/s/  
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JANET L ANDERSON  
02/20/2013



NDA 204286

**INFORMATION REQUEST**

Merz Pharmaceuticals, LLC  
Attention: Misty M. D'Ottavio, RN  
Senior Regulatory Affairs Manager  
4215 Tudor Lane  
Greensboro, NC 27410

Dear Ms. D'Ottavio:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Naftin (naftifine hydrochloride) Gel, 2%.

We are reviewing the Product Quality and Clinical sections of your submission and have the following comments and information requests. We request a prompt written response by January 18, 2013 in order to continue our evaluation of your NDA.

1. The results of degradation products in the drug product batches at release and during stability testing can not be located in your submission.
  - a. Identify the location or provide the data.
  - b. The data should include peaks that are above the ICH reporting threshold of 0.1%.
2. In regards to trial MRZ 90200/1010/1, there appears to be errors in Table 13 on page 58 of the study report and the associated data source Table 14.2.2.2.
  - a. The fraction excreted in urine appears to be incorrectly high. For example, subject 54032 is listed in Table 14.2.2.2 with a  $Fe\%_{0-24}$  of 3.99. Based on  $Ae_{0-24}$  of 0.164  $\mu\text{g}$  naftifine base (from Table 14.2.3.5) and the mean daily dose of 69540.8  $\mu\text{g}$  naftifine base (i.e., 3.92 g of Natifine Gel, 2% from Table 14.2.4), the  $Fe\%$  should be approximately 0.0002. Clarify how  $Fe\%$  was calculated for these tables and make corrections as needed.
  - b. It appears that the unit for CLr in Tables 13 and 14.2.2.2 is incorrect. For example subject 54032 is listed in Table 14.2.2.2 with a CLr of 3.77 L/h. Based on  $Ae_{0-24}$  of 0.164  $\mu\text{g}$  naftifine base (from Table 14.2.3.5) and AUC of 43.41  $\text{ng}\cdot\text{hr}/\text{mL}$  (from Table 14.2.1.2) the CLr calculated as  $Ae/AUC$  should be approximately 3.77  $\text{mL}/\text{h}$  instead of 3.77 L/h. Clarify how CLr in L/h was calculated and make corrections as needed. It appears that the CLr in  $\text{mL}/\text{min}$  was a unit conversion from L/h and the values would also need to be adjusted accordingly.

If you have any questions, call Strother D. Dixon, Regulatory Project Manager, at (301) 796-1015.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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DAVID L KETTL  
01/10/2013



NDA 204286

## FILING COMMUNICATION

Merz Pharmaceuticals, LLC  
Attention: Misty M. D'Ottavio, RN  
Senior Regulatory Affairs Manager  
4215 Tudor Lane  
Greensboro, NC 27410

Dear Ms. D'Ottavio:

Please refer to your New Drug Application (NDA) dated August 27, 2012, received August 31, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (naftifine hydrochloride) Gel, 2%.

We also refer to your amendments dated September 19, October 5, 16 and 19, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is June 30, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 7, 2013.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information by November 21, 2012:

Submit a low viscosity drug product sample whose viscosity is near the proposed lower limit of the viscosity acceptance criterion [REDACTED] <sup>(b) (4)</sup> for dosage form evaluation.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Make the following changes to the Highlights (HL) Limitation Statement:
  - a. Remove the dosage form and strength.
  - b. Join the two sentences of the Highlights (HL) Limitation Statement into one paragraph: “These highlights do not include all the information needed to use NAFTIN<sup>®</sup> safely and effectively. See full prescribing information for NAFTIN<sup>®</sup>.”
  - c. Bold the HL Limitation Statement.
2. In the Product Title section of the HL, “Gel” should be in lower case.
3. Bold the product title “NAFTIN (naftifine hydrochloride) gel, 2% for topical use”.
4. Bold the initial approval statement “Initial U.S. Approval: 1990” in the HL.
5. Bold the revision date “Revised XX/XXXX” in the HL.
6. In the Table of Contents, bold the heading “FULL PRESCRIBING INFORMATION: CONTENTS\*”
7. Change the font to 8 point for section heading “16 HOW SUPPLIED/ STORAGE AND HANDLING”.

We request that you resubmit labeling that addresses these issues by November 21, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Amundson Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full deferral of pediatric studies in subjects 12 to 17 years of age for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

We acknowledge receipt of your request for a partial waiver of pediatric studies in subjects younger than 12 years of age for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

If you have any questions, call Strother D. Dixon, Regulatory Project Manager, at (301) 796-1015.

Sincerely,

*{See appended electronic signature page}*

Susan J. Walker, M.D., F.A.A.D.  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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STANKA KUKICH

11/05/2012

Signing for Susan Walker, Division Director



NDA 204286

**INFORMATION REQUEST**

Merz Pharmaceuticals, LLC.  
Attention: Misty M. D'Ottavio, RN  
Senior Regulatory Affairs Manager  
4215 Tudor Lane  
Greensboro, NC 27410

Dear Ms. D'Ottavio:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NAFTA-600 (naftifine hydrochloride) Gel, 2%.

We also refer to your August 27, 2012 submission, containing your new NDA.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by September 28, 2012 in order to continue our evaluation of your NDA. Please notify the Project Manager listed below once you have submitted your response.

1. Information provided under Establishment Information in Form 356h is incomplete. Revise Form 356h by providing complete establishment information requested by Form 356h for all facilities involved in the manufacturing/testing of drug substance and/or drug product, including the statement of readiness for inspection for each facility. We request a single, comprehensive list of all involved facilities available in one location in the application, and all facilities should be identified on Form 356h or associated continuation sheet.
2. Clarify whether (b) (4) (DMF (b) (4)) is the sole drug substance supplier for this NDA. Your referenced NDA 19599 has two drug substance suppliers: (b) (4) (DMF (b) (4)) and (b) (4) (DMF (b) (4)).
3. Clarify whether there are any testing laboratories involved in the release and/or stability testing of drug substance lots for this NDA.
4. We recommend that you provide current drug substance information that resides in NDAs 19599 and 19356 for Section 3.2.S.2 through 3.2.S.7 of this NDA, or make a specific reference to a DMF with a letter of authorization for a section if applicable. We recommend that you should not leave these sections blank as they are because the exact location of each critical information (e.g. establishment, manufacturing process, regulatory specification, post approval stability protocol, storage condition and retest date, etc.) would then be unclear and

the critical information could not be identified. Consequently, the NDA in its present form does not permit a substantial review on the drug substance.

5. Provide the proposed drug substance regulatory specification table in Section 3.2.S.4 of this NDA.
6. Provide Master Batch Record for the proposed drug product or indicate its location in the original submission of the NDA.
7. Provide annual production forecast for the next 5 years for all related NDAs and supplements (all dosage forms and strengths), and the calculation of the estimated concentration of the substance at the point of entry into the aquatic environment based on the combined forecast.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Branch Chief, Branch IV  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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MOO JHONG RHEE  
09/20/2012  
Chief, Branch IV



NDA 204286

**NDA ACKNOWLEDGMENT**

Merz Pharmaceuticals, LLC  
Attention: Misty M. D'Ottavio, RN  
Senior Regulatory Affairs Manager  
4215 Tudor Lane  
Greensboro, NC 27410

Dear Ms. D'Ottavio:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

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

Date of Application: August 30, 2012

Date of Receipt: August 31, 2012

Our Reference Number: NDA 204286

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 30, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinformo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 204286** submitted on August 30, 2012, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Dermatology and Dental Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1015.

Sincerely,

*{See appended electronic signature page}*

Strother D. Dixon  
Regulatory Project Manager  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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STROTHER D DIXON  
09/06/2012



IND 105603

**MEETING MINUTES**

Merz Pharmaceuticals, LLC  
Attention: Misty M. D'Ottavio, RN  
Senior Manager, Regulatory Affairs  
4215 Tudor Lane  
Greensboro, NC 27410

Dear Ms. D'Ottavio:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NAFTA-600 (naftifine hydrochloride) Gel, 2%.

We also refer to the teleconference between representatives of your firm and the FDA on May 16, 2012. The purpose of the meeting was to obtain FDA agreement on the content, format, and information to be provided in support of a NDA submission for NAFTA-600.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Barbara Gould, Chief, Project Staff Management, at (301) 796-4224.

Sincerely,

*{See appended electronic signature page}*

Stanka Kukich, M.D.  
Deputy Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** May 16, 2012; 11:00 am  
**Meeting Location:** Teleconference

**Application Number:** IND 105603  
**Product Name:** NAFT-600 (naftifine hydrochloride) Gel, 2%  
**Proposed Indication:** Interdigital [REDACTED]<sup>(b)(4)</sup> Tinea pedis  
**Sponsor/Applicant Name:** Merz Pharmaceuticals, LLC

**Meeting Chair:** Stanka Kukich, M.D.  
**Meeting Recorder:** Barbara Gould, M.B.A.H.C.M.

**FDA ATTENDEES**

Julie Beitz, M.D., Director, ODE III  
Victoria Kusiak, M.D., Deputy Director, ODE III  
Stanka Kukich, M.D., Deputy Director, DDDP  
Gordana Diglicic, M.D., Clinical Team Leader, DDDP  
Melinda McCord, M.D., Clinical Reviewer, DDDP  
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DNDQA II  
Gene Holbert, Ph.D., Product Quality Reviewer, DNDQA II, Branch IV  
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP  
Jerry Wang, Ph.D., Pharmacology Reviewer, DDDP  
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader, DCP3  
Chinmay Shukla, Ph.D., Clinical Pharmacology Reviewer, DCP 3  
Mohamed Alesh, Ph.D., Biostatistics Team Leader, DB III  
Carin Kim, Ph.D., Biostatistics Reviewer, DB III  
Barbara Gould, M.B.A.H.C.M., Chief, Project Management Staff, DDDP  
Strother Dixon, Regulatory Project Manager, DDDP  
Roy A. Blay, Ph.D., Director Regulatory, OC/OSI

**SPONSOR ATTENDEES**

Bhushan Hardas, MD, MBA, Vice President and Head, US Research and Development  
David Dobrowski, Director, Regulatory Affairs  
Misty D'Ottavio, RN, Senior Manager, Regulatory Affairs  
Stefan Plaum, MD, Associate Medical Director  
Joy Willard, RN, BSN, Clinical Project Manager  
Babajide Olayinka, MSc, Biostatistician

**Purpose of the Meeting:**

The purpose of this meeting is to obtain FDA agreement on the content, format, and information to be provided in support of a NDA submission for NAFT-600.

**Regulatory Correspondence History**

We have had the following meeting(s)/teleconference(s) with you:

- 04/14/10 – Guidance Meeting
- 07/24/09 – Advice/Information Request (Minutes)

We have sent the following correspondences:

- 11/10/11 – Advice/Information Request
- 10/14/11 – Advice/Information Request
- 05/03/11 – Advice/Information Request
- 04/07/11 – Advice/Information Request
- 03/28/11 – Advice/Information Request
- 02/15/11 – Advice/Information Request
- 07/20/10 – Advice/Information Request
- 05/15/10 – Meeting Minutes
- 11/13/09 – Advice/Information Request

**Regulatory**

**Question [11]:**

Merz intends to submit the NAFT-600 NDA in eCTD format. Merz proposes to cross reference all of Module 4 documents within NDA 019599/S-011 application (NAFT-500), by providing a detailed listing (Appendix 8) of all Module 4 reports and document location from NDA 019599/S-011, in Section 1.4.4 of the eCTD XML. Is this acceptable to the Agency?

**Response:**

Yes, this approach is acceptable.

**Question [12]:**

Does the Agency agree that a deferral can be submitted for an assessment under the Pediatric Research Equity Act (PREA) for subjects ages 12 to 17 with tinea pedis?

**Response:**

Your proposal appears reasonable. The Agency would consider a deferral of pediatric studies with the submission of scientific rationale for deferring the assessments, a description of the planned studies, and evidence that the studies will be conducted with due diligence and at the earliest possible time.

You should submit a partial waiver request that includes evidence that the request meets the statutory reason(s) for waiver of pediatric assessment requirements. Whether or not the waiver will be granted will be a review issue.

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

**Meeting Discussion:**

Based on the proposal to modify the study design with additional treatment arms, the sponsor anticipates a delay in the finalization of the study protocol.

**Chemistry, Manufacturing and Controls (CMC)**

**Question [8]:**

Does the Agency agree that Merz may submit batch records and stability data from Lots ADU, CFS, and DFU to satisfy the requirements for the Executed Batch Records as part of the NDA?

**Response:**

Yes. Also include a blank Master Batch Records for the commercial scale in the initial submission of the proposed NDA.

**Question [9]:**

Does the Agency agree that the approach described above is acceptable (including submission of 24 month data for batch CFS during the review period)?

**Response:**

The proposed stability update to 24 months during NDA review is reasonable, provided that the update will be received by the Agency before Month 5 of the NDA review. Update the stability data for all registration stability batches.

Also see the Agency's comment regarding number of batches in the response to Question 10.

**Question [10]:**

Will the proposed stability data provide adequate information for the evaluation of expiration dating for the drug product packaged in 45g coated aluminum tubes and in 2g coated aluminum tubes (Appendix 6 and Appendix 7)?

**Response:**

No, the data presented in Appendices 6 and 7 are not adequate for the evaluation of expiration dating. Stability data for related substances and package integrity are missing. The number of batches for the 45 g and the 2 g size may not be adequate either. Provide data from three batches for each fill size as recommended by ICH Q1A (R2).

**Additional CMC Comments**

1. Confirm the to-be-marketed formulation is the originally developed formulation and not the reformulated one.
2. Provide information for the proposed commercial-scale batch size and manufacturing site. If the proposed commercial site is different from the Phase 3 site, bridging studies may be needed. Examples of the bridging studies can be found in SUPAC-SS.
3. Provide representative sample for dosage form evaluation.

**Meeting Discussion:**

The sponsor stated they will manufacture one additional 45 gram stability batch and two additional 2 gram stability batches, and provide stability data 5 months after submission of the NDA. The Agency advised that the stability data should be received no later than 30 days after receipt of the NDA.

**Pharmacology/Toxicology**

**Question [7]:**

During the Guidance meeting for IND 105,603 held April 14, 2010, the Agency noted that a Phase 4 carcinogenicity study could be performed for either NAFT- 500 (Naftin Cream 2%) or NAFT- 600 (Naftin Gel 2%) to address concerns for carcinogenic potential of naftifine HCL. Merz and the Agency agreed for conduction of this study using NAFT-500. This study protocol will be submitted December 2012, as required per Merz's post-marketing commitment for NAFT-500. Does the Agency agree this study will satisfy the requirements for both NAFT-500 and NAFT- 600?

**Response:**

The Agency requests only one of the two products (NAFT-500 or NAFT-600) be tested for carcinogenicity to address the concern for carcinogenic potential of naftifine HCL. It is acceptable to conduct the 2-year dermal rat carcinogenicity study with the naftifine HCL cream formulation (i.e., NAFT-500).

You are referred to the meeting minutes that were relayed to you on 05/14/2010 (IND 105603), 05/14/2010 (IND 77530), and 01/26/2011 (IND 77530) for more information. We reiterate that a second carcinogenicity study may be needed, if the systemic exposure to the drug substance or its metabolites under maximal use conditions in humans is significantly high, or if data from the first carcinogenicity study indicate cause for concern (e.g., increased incidence of tumors or preneoplastic lesions).

**Clinical/Biostatistics/Clinical Pharmacology**

**Question [1]:**

Does the Agency concur that the design and scope of the clinical development program as presented in Table 1 is adequate for NDA submission, filing, and to provide a substantive review of the application in the proposed indication?

**Response:**

The two Phase 3 clinical trials (double-blinded, vehicle controlled with what appears to be an adequate number of subjects with appropriate efficacy endpoints), Dermal safety trials, Thorough QT/QTc trial and Maximal Use Pharmacokinetic trial described in the briefing package appear to support the filing of the NDA.

However, we are concerned that the PK trial (MRZ 90200/1010/1) may not have been conducted under maximal use conditions because the inclusion criteria did not require bilateral disease. On page 0025 of the meeting package, you stated that one of the main inclusion criteria for the phase 1 pharmacokinetic (PK) trial MRZ 90200/1010/1 was “*had tinea pedis on one or both feet*”. We acknowledge that the treatment was applied to both feet even if the subject had tinea pedis on only one foot based on your definition of maximal use condition. Clarify how many subjects had tinea pedis on both feet and how many subjects had tinea pedis on only one foot in your PK trial. In addition, confirm that the PK trial MRZ 90200/1010/1 was conducted with the to-be-marketed formulation.

On page 0026 of the meeting package, you provided study results (*section 12.2.15*) of the PK trial MRZ 90200/1010/1. We noticed that the reported values and their CV% for many PK parameters are identical to those shown on the current Prescribing Information for Naftin Cream 2%. Clarify whether your PK study results provided in the meeting package were for NAFT-600 Gel 2%.

**Meeting Discussion:**

The sponsor clarified that all 32 subjects had tinea pedis on both feet and that the PK trial was conducted with the to-be-marketed formulation.

**Question [2]:**

The SAP for the ISE has been included as Appendix 1 to this briefing package. Does the Agency agree with the ISE and data presentation plans?

**Response:**

You plan to conduct meta-analyses by pooling the two pivotal Phase 3 trials with one Phase 1 maximal use study for the Integrated Summary of Effectiveness (ISE).

It should be noted that the Integrated Summary of Effectiveness section is an *integrated analysis of data across studies* that should comprehensively examine the effectiveness of the drug as assessed in all studies with data relevant to drug efficacy. Therefore, rather than pooling the data to provide a summary of results, the sponsor should provide an integrated discussion of the results *across studies*, and include discussions of consistency and replication of study findings

and discuss important statistical issues, if any, that may affect the results. Furthermore, as discussed in the Guidance, the sponsor should “provide comprehensive, detailed, in-depth analysis of the efficacy results in aggregate, with a clear rationale for the methods used in the analysis”. All studies, including a tabular listing of all studies with data relevant to drug efficacy should be included in the Integrated Summary of Effectiveness (ISE) as well as in the Integrated Summary of Safety (ISS).

Furthermore, it should be noted that establishing an efficacy claim would be based on efficacy data from individual Phase 3 studies along with replication of study findings. The sponsor might conduct the pooled analysis as an exploratory analysis.

You should provide the Agency with SAS transport files in electronic form. The sponsor might refer to the Analysis Data model (ADaM) Examples in Commonly Used Statistical Analysis Methods for guidance:

[http://www.cdisc.org/stuff/contentmgr/files/0/5aee16f59e8d6bd2083dbb5c1639f224/misc/adam\\_examples\\_final.pdf](http://www.cdisc.org/stuff/contentmgr/files/0/5aee16f59e8d6bd2083dbb5c1639f224/misc/adam_examples_final.pdf).

The submission should include adequate documentation for the data sets including definitions of each variable in the data set, formulas for derived variables and decodes for any factor variables so that all categories are well-defined in the documentation. The documentation should indicate which variables are derived.

In addition to the electronic data sets, the submission should include the following items for the Phase 3 studies:

1. Study protocols including the statistical analysis plan, protocol amendments and their dates, and an annotated copy of the Case Report Form.
2. The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.
3. For the analysis dataset, the sponsor should include the treatment assignments, outcomes for each scheduled visits along with variables that indicate the original study site as well as the analysis study site.

The FDA prefers that the sponsor arrange a test submission, prior to actual submission. Please refer to the Submit a Sample eCTD or Standardized Data Sample to the FDA Website (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>) for guidance on sending a test submission. You may request dataset(s) analysis for CDISC specifications compliance as part of the test submission. For additional information, contact the Electronic Submission Support Team at [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov), or for standardized data submission questions, contact [edata@fda.hhs.gov](mailto:edata@fda.hhs.gov).

**Question [3]:**

Does the Agency agree the proposed safety database provided in Appendix 2 is adequate for a substantive review of the safety data in the application?

**Response:**

The proposed safety database appears to be acceptable. However, the adequacy of that data is a review issue.

For chronic conditions which may require repeated intermittent treatment for greater than 6 months, the safety data needs articulated in ICH E1A should be addressed. The duration of drug exposure and its relationship to both time and magnitude of occurrence of adverse events are important considerations in determining the size of the data base necessary to characterize and quantify the safety profile. You are referred to the *Guideline for Industry: The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions*

**Question [4]:**

The SAP for the ISS has been included as Appendix 3 to this briefing package. Does the Agency agree with the ISS presentation plans?

**Response:**

In general, we agree with your approach to the presentation of the ISS.

ISS should be submitted to the FDA in accordance with the regulations for NDA submissions.

- For information regarding the location of ISS in the CTD, the sponsor is referred to the Agency Guidance: *Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* at the FDA website (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>)

**Question [5]:**

For both Phase 3 studies, the Missing Value Treated as Treatment Failure (MVTF) was used as the “Missing Value Treated as Treatment Failure (MVTF) as the primary missing value imputation method for the primary (Complete Cure) and the most important secondary efficacy variables (Treatment Effect & Mycological Cure). Other less and more conservative imputation methods (Last Observation Carried Forward & Worst Case Scenario, respectively) will be used as additional imputation methods for sensitivity analyses. The Phase 3 SAPs have been included as Appendix 4 and Appendix 5.

Does the Agency agree with the use of the MVTF as the imputation method for the primary and important secondary endpoints?

**Response:**

As the study is already completed, the Agency would not concur with a specific approach for handling missing data. Whether the proposed method of imputing missing value treated as failure (MVTF) is reasonable for handling missing data depends on the proportion of dropouts in each treatment arm. In addition to the primary method of handling missing data, the Agency

recommends sensitivity analyses with different assumptions than those of the primary imputation method.

**Question [6]:**

Merz proposes Case Report Forms (CRFs) will be submitted for:

- all Serious AEs
- all Severe AEs
- all patients who discontinued for whatever reason (not just do to an AE) after confirmation of a positive baseline culture.

Does the Agency find this acceptable?

**Response:**

Your approach is acceptable.

In addition, you should provide the following:

- Subject narratives for all deaths, all serious adverse events (AEs), and AEs resulting in discontinuation from the trials conducted with your product.
- The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.
- Case report forms (CRFs)
  - for all serious AEs, all severe AEs, and for all subjects who discontinued from the studies for any reason. A study's CRFs should be placed in a CRF folder under the applicable study with a file tag of "case-report-forms." Also provide the following:
    - Electronic links for:
      - a. all serious AEs
      - b. all severe AEs
      - c. all patients discontinued regardless of reason
      - d. all deaths
    - CRFs should be referenced under the study in which it belongs and tagged as "casereport-forms" in that study's stf.xml file.
    - CRFs that are not submitted should be readily available upon request.
- Adverse reaction tables (adverse reactions defined as those AEs with possible or probable causality)  $\geq 1\%$ .
- Adverse event tables  $\geq 1\%$  regardless of causality
- Line listings for all safety data
- Group means for irritancy safety study results.

- Frequency tables for sensitivity safety study results. Define and justify the threshold for calling a score positive (or negative) for sensitization.

Additional comments:

- Submit clinical photographs obtained at baseline and Week 6 during the Phase 3 trials (MRZ 90200/3015/1 and MRZ 90200/3016/1).

**Meeting Discussion:**

The sponsor clarified that no photographs were obtained in the Phase 3 trials (MRZ 90200/3015/1 and MRZ 90200/3016/1).

**Administrative Comments**

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or NDA might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21 CFR 54 and 21CFR 314.50(k).
3. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.
4. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

**PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm>

[084159.htm](#). We encourage you to review the information at this website and use it as you draft prescribing information for your application.

**Post Meeting Addendum:**  
OSI PreNDA Request

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/s/  
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STANKA KUKICH  
06/01/2012