

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204286Orig1s000

CHEMISTRY REVIEW(S)

NDA 204286

Naftin (Naftifine Hydrochloride) Gel 2%

Merz Pharmaceuticals, LLC

Rajiv Agarwal, Ph.D

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV**

**CMC REVIEW OF NDA 204286
For the Division of Dermatology and Dental Products (HFD-540)**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 204286
2. REVIEW #: 1
3. REVIEW DATE: 16-APR-2013
4. REVIEWER: Rajiv Agarwal, Ph.D
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	31-AUG-2012
Amendment	17-OCT-2012
Amendment	14-NOV-2012
Amendment	18-JAN-2013
Amendment	09-APR-2013
Amendment	15-APR-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Merz Pharmaceuticals, LLC
Address: 4215 Tudor Lane
Representative: Misty M.D' Ottavio
Telephone: 336-217-2419

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Naftin
b) Non-Proprietary Name: (naftifine hydrochloride)
c) Code Name/# (ONDQA only): NAFT-600
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

CMC Review Data Sheet

10. PHARMACOL. CATEGORY: For the treatment of interdigital ^{(b) (4)}
 tinea pedis

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 2%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC

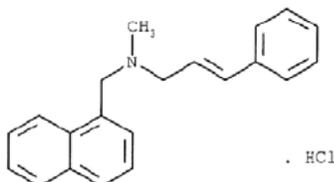
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(E)-*N*-Cinnamyl-*N*-methyl-1-naphthalenemethylamine hydrochloride



Molecular formula: C₂₁H₂₁N.HCl

Molecular weight: 323.86

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Naftifine	1,4	Adequate	15-JAN-2013	Dr. Allan

CMC Review Data Sheet

(b) (4)	(b) (4)				Fenselau for 19356 and 19599	
	(b) (4)	III	1	Adequate	30-MAY-2008	Dr. Bogdon Kurtya for NDA 21228
	(b) (4)	III	1	Adequate	8-MAY-1995	See cross referenced DMF review in DMF review by Ernest Pappas for NDA 50218

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	105603	Active
NDA	19599 (cream) and 19356 (gel)	Approved

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	30-NOV-2012	Office of Compliance
Methods Validation	N/A, according to the current ONDQA policy	16-APR-2013	Dr. Rajiv Agarwal
EA	Categorical exclusion is requested, and granted (see review)	16-APR-2013	Dr. Rajiv Agarwal

Executive Summary Section

The CMC Review for NDA 204286

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has made an "Acceptable" recommendation for the facilities involved in this application.

The proposed labels and labeling (Description and How Supplied sections) have required information.

Therefore, from the ONDQA perspective, this NDA is recommended for approval with an expiration dating period of 24 months

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The CMC information related to the naftifine hydrochloride drug substances was evaluated in NDAs (approved NDA 19599 and 19356) and is also presented in the cross referenced (b) (4) DMF (b) (4). The information was reviewed by Dr. Allan Fenselau on 15-JAN-2013, in conjunction with the cross referenced NDAs. The open part of the DMF is also provided in the current NDA and is reviewed herein. The Chemistry, Manufacturing, and Controls information pertaining to the drug substance is adequate.

The final recommendation from the Office of Compliance on the compliance to the cGMP involving all facilities pertaining to the drug substance manufacturing and testing operations is Acceptable (Attachment).

Executive Summary Section

(2) Drug Product

The drug product, a topical gel, is packaged in two different configurations, depending on whether it is the presentation for commercial distribution (45 g) or the physician samples (2 g).

Naftin Gel, 2% will be packaged in the 45g aluminum (b)(4) tubes with (b)(4) and white (b)(4) caps supplied by (b)(4). The same container closure systems (2 g and 45 g sizes) are used to package the marketed Naftin, Cream, 2% product (NDA 19599). The DMF (b)(4) contains the quality information pertaining to the some tube components is reviewed by Dr. Bogdon Kurtya on 30-MAY-2008. (b)(4), a drug contact surface was reviewed in 8-MAY-1995 and is deemed adequate (b)(4).

Naftin Gel, 2% was developed to provide a higher strength of the currently marketed Naftin Gel, 1% (NDA 19356), which contains 1% w/w naftifine hydrochloride. One critical aspect of the formulation is vulnerability to microbial growth. Benzyl alcohol is used as the (b)(4) in the (b)(4) formulation.

The justification of these changes are provided in the submission and are related to improve the feel, reduce the irritation.

All excipients used in the manufacture of the drug product are listed in the FDA's Inactive Ingredient Guide (IIG) at or below the levels outlined for topical gel formulations

Adequate in-process tests and critical parameters and their acceptance criterion are in place to ensure the purity, quality and strength of the gel drug product can be maintained during the manufacturing process. The benzyl alcohol results from the stability lots were within specification. The results ranged from (b)(4)

Executive Summary Section

(b) (4)

This testing was however, conducted on the packaged registration stability tube batches. All results were well within specification of (b) (4) of label claim. This testing (head, middle and crimp) will be performed on the registration stability batches through the completion of the stability protocol time points. Since the results are all well within specification and based on the historical batch analysis, the homogeneity testing will not be performed on future commercial drug product packaged in the container closure system. The drug product is packaged in aluminum tube, therefore, loss of solvents was not observed for the stability lots.

The applicant did not provide the data for degradation products at release or during stability and did not provide any justification for not performing the test. However, the applicant requests a generous acceptance criteria of specified and unspecified degradation products in specifications. The applicant provided the data to justify the acceptance criterion for degradation product. Based on the ICH 3QB (R2) and the dose, it is determined that that the acceptance criteria for degradation products are too generous and needs to be tightened unless justified. This deficiency was communicated to the applicant on 10-JAN-2013; responses were provided on 18-JAN-2013. The acceptance criteria for degradation products were tightened as recommended by the Agency on 15-APR-2013.

The applicant requests a 24-month expiration dating period at 25°C/60% RH (controlled room temperature), a 24-month of expiration dating period is granted.

The final recommendation from the Office of Compliance on the compliance to the cGMP involving all facilities pertaining to the drug product manufacturing and testing operations is Acceptable (See Attachment).

B. Description of How the Drug Product is Intended to be Used

Apply a thin layer of NAFTIN (naftifine hydrochloride) Gel, 2% once daily to the affected areas plus an approximate ½ inch margin of healthy surrounding skin for 2 weeks. For interdigital tinea pedis, treat all interdigital areas. (b) (4)

Executive Summary Section

C. Basis for Approvability Recommendation

The raw materials including the active ingredient are well controlled and the manufacturing processes are also satisfactorily controlled with adequate control parameters. The specifications for the active ingredient and the drug products are deemed satisfactory to ensure the identity, strength, purity, and quality of the drug product. Submitted stability data are sufficient to support the proposed expiration dating period of 24 months. Container/closure system is adequate to protect the drug product during the storage.

All manufacturing facilities are in compliance with cGMP per the Office of Compliance (see the **Attachment**).

Labels have the required information, and **Description** and **How Supplied sections** of PI have adequate information as required.

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

B. Endorsement Block:

Rajiv Agarwal, Ph.D

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D, Branch Chief, Branch IV, DNDQA II, ONDQA

C. CC Block: entered electronically in DARRTS

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

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

/s/

RAJIV AGARWAL
04/22/2013

MOO JHONG RHEE
04/22/2013
Chief, Branch IV



CMC Assessment Section

IV. Attachment:

EES Report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 204288000 Sponsor: MERZ PHARMS
Org. Code: 540 4215 TUDOR LANE
Priority: 5 GREENSBORO, NC 27410
Stamp Date: 31-AUG-2012 Brand Name: (nalfine hydrochloride) Gel, 2%
PDUFA Date: 30-JUN-2013 Estab. Name:
Action Goal: Generic Name: (nalfine hydrochloride) Gel, 2%
District Goal: 01-MAY-2013 Product Number; Dosage Form; Ingredient; Strengths
001; GEL; NAFTIFINE HYDROCHLORIDE; 2%
FDA Contacts: C. TRAN-ZWANETZ Project Manager (HFD-800) 3017863877
R. AGARWAL Review Chemist 3017861322
S. DING Team Leader 3017861349

Overall Recommendation: ACCEPTABLE on 30-NOV-2012 by R. SAFAAI-JAZI () 3017864483
PENDING on 24-OCT-2012 by EES_PROD

Establishment: CFN: (b) (4) FEI: (b) (4)
DMF No:
Responsibilities: FINISHED DOSAGE OTHER TESTER AADA:
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-OCT-2012
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
DMF No:
Responsibilities: FINISHED DOSAGE MANUFACTURER AADA:
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: (b) (4) OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-NOV-2012
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION



CMC Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-OCT-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-OCT-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Initial Quality Assessment
Branch IV
Division of New Drug Quality Assessment II

OND Division: Division of Dermatology and Dental Products
NDA: 204286
Applicant: Merz Pharmaceuticals, LLC
Stamp Date: Aug. 31, 2012
PDUFA Date: July 1, 2013
Trademark: Naftin[®]
Established Name: Naftifine hydrochloride
Dosage Form: Gel
Route of Administration: Topical
Indication: Treatment of interdigital (b)(4) tinea pedis

CMC Lead: Shulin Ding

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Summary and Critical Issues:

A. Summary

Merz Pharmaceuticals has submitted a 505(b)(1) New Drug Application (NDA) for the prescription use of Naftin[®] (naftifine hydrochloride) gel, 2% for the topical treatment of interdigital (b)(4) tinea pedis. The proposed product is double strength of the currently marketed Naftin (naftifine hydrochloride) gel, 1% (NDA 19356) but with a different formulation and dosing regimen. The proposed regimen for the 2% gel is once a day for two weeks whereas that of the currently marketed 1% gel is twice a day for four weeks of treatment.

The applicant references DMF (b)(4) held by (b)(4) for the CMC information of the proposed drug substance. A letter of authorization from (b)(4) has been provided. The proposed drug substance manufacturing site is located at (b)(4). The last CMC review on the DMF was filed on 2/27/2004, and the DMF was deemed deficient. Submissions to the DMF subsequent to the last CMC review have not been reviewed.

The proposed drug product is a clear to slightly hazy, colorless to yellow gel packaged in (b)(4) aluminum tubes equipped with (b)(4) caps. The proposed trade size is 45 g. The physician sample size is 2 g. In addition to the active ingredient, the formulation also contains the following excipients: propylene glycol, USP; polysorbate 20, NF; alcohol (b)(4), USP; hydroxyethyl cellulose, NF; benzyl alcohol, NF; trolamine, NF; EDTA, USP; and (b)(4), USP. All excipients are compendial, and none originate from human/animal source.

The to-be-marketed formulation is the same formulation used in Phase 3 clinical trials and registration stability batches. The formulation is prepared (b)(4)

(b) (4)

Registration stability data provided in the initial submission for the trade size (45 g) to support the proposed expiration dating period of 24 months at 20°-25°C (excursions permitted to 15°-30°C) include 9-18 months of long term and 6 months of accelerated stability data from two pilot batches (b) (4). As to the sample size (2 g), only 9 months of long term and 6 months of accelerated stability data from one pilot batch (b) (4) are provided in the initial submission to support the proposed expiration dating period of 24 month at 20°-25°C (excursions permitted to 15°-30°C). (b) (4)

(b) (4) A freeze/thaw special study was also performed to support the storage/handling of the drug product.

B. Critical issues for review

1. Environmental Assessment

The applicant cites 21CFR 25.31(b) to support its categorical exclusion claim from the preparation of Environmental Assessment. Although the calculation of estimated concentration of the substance at the point of entry into the aquatic environment was provided in the 10/5/12 amendment, it is unclear whether the calculation included all naftifine NDAs and sNDAs held by Merz. A clarification needs to be sought.

2. Establishment Information and Drug Product Master Batch Record

An IR letter was sent on Sep. 20, 2012 to request clarification for some facilities, statement of readiness for inspection, and drug product Master Batch Records. The applicant's response (amendment received on Oct. 5, 2012) is deemed adequate for NDA filing. Drug Product Master Batch Record and the statement of readiness for inspection for each facility were included in the 10/5/12 amendment.

3. Drug Substance Information

There is no information submitted in the initial submission for Section 3.2.S except name, structure and general properties of naftifine HCl. Upon request, the applicant clarified that (b) (4) (DMF (b) (4)) is the sole drug substance supplier for this NDA, and provided the open part of DMF (b) (4) to the NDA in the 10/5/12 amendment. The response is deemed adequate for filing.

4. Drug Product Related Substances

(b) (4)

D. Comments/Recommendation:

The application is acceptable for filing from CMC perspective. The major CMC review issues with this NDA are related substances, dosage form, viscosity acceptance criterion, and drug product container/closure qualification.

Drug substance manufacturing site is located in (b) (4) Drug product manufacturing site is located in the U.S. GMP inspection requests have been submitted.

Shulin Ding, Ph.D.
CMC Lead

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV

NDA Number: 204286 **Supplement Number and Type:** 0000 **Established/Proper Name:** Naftifine hydrochloride, 2%
Applicant: Merz **Letter Date:** Aug. 27, 2012 **Stamp Date:** Aug. 31, 2012

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		In the amendment dated Oct. 5, 2012.
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			n/a

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		Provided in the 10/5/12 amendment.

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x		Categorically exclusion is claimed.

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	x		Also referenced to DMF (b) (4) for details.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	Referenced to DMF (b) (4).
14.	Does the section contain information regarding the characterization of the DS?	x		Also referenced to DMF (b) (4) for details.
15.	Does the section contain controls for the DS?	x		Also referenced to DMF (b) (4) for details.
16.	Has stability data and analysis been provided for the drug substance?	x		Also referenced to DMF (b) (4) for details.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	n/a
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	n/a

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	n/a
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	n/a
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	n/a

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		Provided in 10/17/12 amendment.

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		x	This is not a sterile product.

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Naftifine HCl	3/5/2012	
(b) (4)	III	(b) (4)	(b) (4)	3/26/12	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			n/a
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	x		See pages 2 and 3.

{See appended electronic signature page}

Shulin Ding, Ph.D.
 CMC Lead
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
 Branch Chief
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

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

/s/

SHULIN DING
10/24/2012

MOO JHONG RHEE
10/24/2012
Chief, Branch IV