

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-071**

**CHEMISTRY REVIEW(S)**

**Memorandum**

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

**Date:** June 29, 2007

**From:** Yichun Sun, Ph.D.  
Review Chemist, ONDQA

**To:** NDA 22-071, CMC Review #1

**Subject:** Mock-up Labels for Container and Cartons of NDA 22-071

At the time of the CMC review was written, the final mock-up labels for container and cartons of NDA 22-071 was pending. On July 2, 2007, the sponsor submitted the mock-up labels for container and cartons. The sponsor accepted all the changes recommended by the FDA. Therefore, the labels for the container and carton of NDA 22-071 are acceptable. This memorandum closes all pending issues for this NDA from the CMC perspective. Thus, this application is recommended for approval from the perspective of Chemistry, Manufacturing, and Controls. The mock-up labels for container and cartons of NDA 22-071 are shown as follows:

Unit-dose label

**Label for 125 mg packet**

NDC 0078-0499-62	Rx only	Lot & Exp. Area
<b>LAMISIL®</b>		
(terbinafine hydrochloride)		
<b>Oral Granules</b>		
<b>125 mg</b>		
terbinafine base equivalent per packet		
Mfd by: Novartis Pharma Stein AG ©Novartis		
Stein, Switzerland	XXXXXX	

**Front**

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Open here		FSS Bar Code Area
	Refer to Patient instructions on back of carton prior to use.	

**Back**

**Label for 187.5 mg packet**

NDC 0078-0500-62	Rx only
<b>LAMISIL®</b> (terbinafine hydrochloride)	Lot & Exp. Area
<b>Oral Granules</b>	
<b>187.5mg</b>	
terbinafine base equivalent per packet.	
Mfd by: Novartis Pharma Stein AG ©Novartis Stein, Switzerland XXXXXXX	

**Front**

Open here		RSS Bar Code Area
	Refer to Patient instructions on back of carton prior to use.	

**Back**

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       Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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/s/

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Yichun Sun  
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Addendum to CMC Review #1

Moo-Jhong Rhee  
7/2/2007 03:41:27 PM  
CHEMIST  
Chief, Branch III

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**NDA 22-071**

**Lamisil<sup>®</sup> (terbinafine hydrochloride) Oral  
Granules (125 mg/packet and 187.5 mg/packet)**

**Novartis Pharmaceuticals Corporation**

**Yichun Sun Ph.D.**

**Review Chemist**

**Branch III, Division of Pre-Marketing Assessment II  
Office of New Drug Quality Assessment**

**CMC REVIEW OF NDA 22-071  
For the Division of Dermatology and Dental Products  
(HFD-540)**



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## CHEMISTRY REVIEW



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# Chemistry Review Data Sheet

1. NDA: #22-071
2. REVIEW #: 1
3. REVIEW DATE: 13-June-2007
4. REVIEWER: Yichun Sun, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 57,093	09-October-1998
EOP 2 meeting Memorandum (IND 57093)	13-November-2000
IND _____	10-May-2002
IND Letter (Special Protocol Letters)	12-September-2005
IND Letter (Pre-NDA Meeting Minutes)	22-November-2005

b(4)

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	08-September-2006
Amendment (BC)	08-November-2006
Amendment (BC)	22-January-2007
Amendment (BC)	05-February-2007
Amendment (BL)	09-March-2007
Amendment (BL)	30-March-2007
Amendment (BC)	08-May-2007

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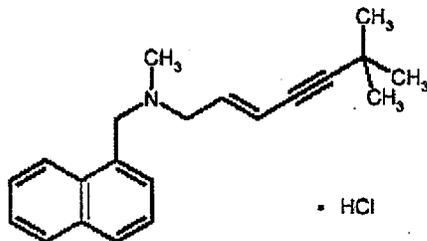
# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

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

(E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine hydrochloride



Empirical formula:  $C_{21}H_{25}N \cdot HCl$   
Molecular weight: 327.90

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
					Adequate	24-April-2007	Y. Sun
					Adequate	31-May-2007	Y. Sun

<sup>1</sup> 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")

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

b(4)



# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-539	Reference for the approved drug substance

### 18. STATUS:

#### ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	ACCEPTABLE	16-Nov-2006	S. Adams (HFD-322)
Pharm/Tox	N/A	----	----
Biopharm	N/A	----	----
LNC	Oral Granules	22-Mar-2007	Yana Mille/Rik Lostritto
Methods Validation	To be validated per ONDQA Policy	----	----
DMET/DDMAC	N/A	----	----
EA	Categorical Exclusion Acceptable	See Review Date Above	Y. Sun
Microbiology	N/A	----	----

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# The Chemistry Review for NDA 22-071

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This application is recommended for approval from the perspective of Chemistry, Manufacturing, and Controls, pending final labels for cartons and container.

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

The sponsor agreed to reassess the in-process control acceptance criteria for \_\_\_\_\_ and \_\_\_\_\_ of granules in the post approval commitments. The sponsor also agreed to conduct a transportation study on the finished drug products to evaluate the effect of \_\_\_\_\_ drug products.

b(4)

### II. Summary of Chemistry Assessments

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

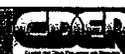
##### Drug Substance

The drug substance, terbinafine hydrochloride, used in the drug products of this NDA is the same drug substance used in the following marketed products: Lamisil<sup>®</sup> Tablets (NDA # 20-539), Cream (NDA # 20-980) and Solution (NDA # 20-749). Details of CMC information for the drug substance are referenced to NDA # 20-539, which was approved on May 10, 1996. The drug substance is chemically and physically stable. Particle size of the drug substance is controlled to maintain processibility for manufacturing drug products and performance of the finished drug products.

##### Drug Product

The drug product, Lamisil<sup>®</sup> (terbinafine hydrochloride) Oral Granules, is immediate-release, film-coated "mini-tablets" ("**mini-tablets**" has been changed to "**Oral Granules**" in the label and labelings according to CDER NLC's recommendation) packaged in an laminated aluminum packet corresponding to strengths of 125 mg (approximately 30 film coated "mini-tablets") and 187.5 mg (approximately 45 film coated "mini-tablets") of terbinafine base, respectively. The mini-tablets are off-white to yellowish, round, and biconvex. They have a diameter of approximately 2.1 mm and contain 4.6875 mg of terbinafine hydrochloride in each mini-tablet (corresponding to 4.167 mg of terbinafine base). The mini-tablets are manufactured by \_\_\_\_\_

b(4)



## Chemistry Assessment Section

\_\_\_\_\_ The drug is released  
from the mini-tablets after dissolution

b(4)

b(4)

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

Lamisil<sup>®</sup> (terbinafine hydrochloride) Oral Granules 125 mg/packet and 187.5 mg/packet are indicated for the treatment of tinea capitis. \_\_\_\_\_ The entire content of each packet is to be taken orally with a spoonful of a soft food (non-acid) such as pudding without chewing.

b(4)

**C. Basis for Approvability or Not-Approval Recommendation**

This application is recommended for approval from the perspective of Chemistry, Manufacturing, and Controls based on the following basis:

- The drug substance, terbinafine hydrochloride, is the same drug substance used in the following marketed products: Lamisil<sup>®</sup> Tablets (NDA # 20-539), Cream (NDA # 20-980), and Solution (NDA # 20-749). Details of CMC information for the drug substance are referenced to NDA # 20-539, which was approved on May 10, 1996.
- The sponsor provided adequate information for composition of the drug products. The drug substance and excipients are controlled to ensure the quality and performance of the drug product.
- The sponsor provided adequate information for the manufacturing processes of the drug products.
- The sponsor provided adequate in-process controls to ensure the quality of the drug products.
- The test methods used for identification and quantitation of the drug product and its impurities were validated.
- The proposed specifications provided by the sponsor are adequate for ensuring the quality of the drug products.
- The packaging materials chosen is safe and adequate to hold and protect the products.
- A 24 months expiration period for film coated mini-tablets in packets can be obtained based on the results of 12 month stability studies conducted.

b(4)



## CHEMISTRY REVIEW TEMPLATE



### Chemistry Assessment Section

- The manufacturing sites have been found acceptable with the Office of Compliance. The EER has an "Acceptable" overall recommendation (16-Nov-2006).

### III. Administrative

#### A. Reviewer's Signature

/s/ Y. Sun, Ph.D.

#### B. Endorsement Block

Yichun Sun Ph.D.  
Reviewer

\_\_\_\_\_  
Date

Shulin Ding Ph.D.  
Pharmaceutical Assessment lead

\_\_\_\_\_  
Date

Moo-Jhong Rhee Ph.D.  
Branch Chief

\_\_\_\_\_  
Date

Linda Athey  
Project Manager

\_\_\_\_\_  
Date

ChemistName/Date: Same date as draft review  
ChemistryTeamLeaderName/Date  
ProjectManagerName/Date

#### C. CC Block

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Chief, Branch III

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Initial Quality Assessment  
Branch III  
Pre-Marketing Assessment Division II

**OND Division:** Division of Dermatology and Dental Products  
**NDA:** 22-071  
**Applicant:** Novartis Pharms  
**Stamp Date:** Sep. 8, 2006  
**PDUFA Date:** July 8, 2007  
**Trademark:** Lamisil  
**Established Name:** Terbinafine hydrochloride  
**Dosage Form:** Under Review  
**Route of Administration:** Oral  
**Indication:** Treatment of tinea capitis in children

**PAL:** Shulin Ding

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

**Summary and Critical Issues:**

A. Summary

The drug substance, terbinafine hydrochloride, is the same drug substance used in marketed Lamisil Tablets (NDA 20-539), Cream (NDA 20-980), and Solution (NDA 20-749). Details of CMC information for the drug substance are referenced to NDA 20-539, which was approved on May 10, 1996.

The drug product, Lamisil (terbinafine hydrochloride) tablets, are immediate-release, film-coated "minitablets" packaged in laminated aluminum \_\_\_\_\_ pouches. The product is for the use of children at \_\_\_\_\_. The entire content of \_\_\_\_\_ is to be poured onto a spoonful of a soft food, and children swallow the combination of food and mini-tablets without chewing. b(4)

The tablets are off-white to yellowish, round, and biconvex. They have a diameter of approximately 2.1 mm and contain 4.6875 mg of terbinafine hydrochloride in each tablet (corresponding to 4.167 mg of terbinafine base). Two fill sizes are proposed: 30 and 45 minitablets per \_\_\_\_\_ corresponding to 125 mg and 187.5 mg of terbinafine base, respectively. Each \_\_\_\_\_ is intended for a single dose. b(4)

The to-be-marketed formulation is the same formulation used in the pivotal clinical studies and registration stability batches. The formulation contains the following excipients: sodium starch glycolate, NF; microcrystalline cellulose, NF; hypromellose \_\_\_\_\_ USP; colloidal silicon dioxide, NF; magnesium stearate, NF; \_\_\_\_\_, polyethylene glycol, NF; basic butylated methacrylate copolymer, dibutyl sebacate, NF; and sodium lauryl sulfate, NF. All are compendial excipients except basic butylated methacrylate copolymer \_\_\_\_\_ b(4)

b(4)

\_\_\_\_\_ has been used in FDA approved drug products; it is, therefore, not a novel excipient. A reference is made by the applicant to \_\_\_\_\_ for \_\_\_\_\_

b(4)

The tablets are manufactured using \_\_\_\_\_

b(4)

\_\_\_\_\_ The proposed commercial manufacturing scale is \_\_\_\_\_  
All registration stability batches were manufactured at the full production scale for bulk tablets. The \_\_\_\_\_ operation of the registration stability batches was conducted at a pilot scale equivalent to \_\_\_\_\_ of the full production scale.

Stability data provided in the initial submission to support an expiry period of 24 months at 25°C (excursions permitted to 15-30°C) include 6 months of data at 25°C/60% RH, 30°C/70% RH, and 40°C/75% RH from three batches for each packaging size. Additional supporting stability data include 12 months of data at 25°C/60% RH and 30°C/70% RH, and 6 month at 40°C/75% RH from three batches of bulk tablets.

b(4)

## B. Critical issues for review

### Established Name and Dosage Form Nomenclature

- The proposed drug product established name, Lamisil (terbinafine hydrochloride) mini-tablets is not consistent with CDER Data Standards Manual. "Mini-tablet" is not a CDER recognized dosage form terminology.

The analytical approach taken by the applicant for this product is atypical for tablets. The applicant's approach is more in line with pellets, granules or powders. The following are some examples:

The dissolution test is done on a composite of tablets instead of on a single tablet.

Tablet weight variation is done on a composite of tablets instead of on a single tablet.

Content uniformity is tested for pouches not for tablets.

The analytical approach is acceptable when considering how the drug product is administered. However, would it be more appropriate to name this product with a non-tablet dosage form name?

### Control of Drug Product

- Although a specification is proposed for bulk tablets in the section on Control of Drug Product, it is not sure if the applicant commits to test the bulk tablets for every batch. In the sections on drug product in-process controls and manufacturing process, testing on bulk tablets is not indicated. In the section on drug product batch analysis, no results are provided for bulk tablets.

Testing on bulk tablets should be routinely conducted when considering the fact that packaging site of minitables is different from the manufacturing site. The

extent of testing may be negotiable. It is noted that the Agency told the applicant in a letter dated Sep. 12, 2005 that minitables would be considered as the final dosage form not an intermediate.

b(4)

In-Process Control for \_\_\_\_\_

- The applicant proposes two methods to be used alternatively for the control of \_\_\_\_\_ weight \_\_\_\_\_ and \_\_\_\_\_ count \_\_\_\_\_ depending on \_\_\_\_\_ size). The proposed acceptance criteria for \_\_\_\_\_ weight and \_\_\_\_\_ count are too broad to ensure that the final product will meet the proposed drug product specification \_\_\_\_\_ for pouches.

b(4)

b(4)

Composite Sample Size

- The assay method for bulk tablets calls for \_\_\_\_\_ per determination. This number is too large to allow a meaningful evaluation of tablet quality. The composite sample size should be more in line with the tablet count per pouch \_\_\_\_\_

b(4)

Control over \_\_\_\_\_ Process of \_\_\_\_\_

- 

b(4)

b(4)

b(4)

Control Over Tablet Breakage

- The proposed drug product \_\_\_\_\_ when one tablet in the pouch is broken. The applicant proposes \_\_\_\_\_ to prevent tablet breakage. The effectiveness of \_\_\_\_\_ in breakage prevention needs to be evaluated, and the \_\_\_\_\_ processed should be validated.

b(4)

Drug Substance Establishment

- The establishment information for drug substance is missing.

Foreign Inspection

- The manufacturing and testing facilities are located in Switzerland and Germany.

### **C. Comments for 74-Day Letter**

Issues:

- The proposed drug product established name, Lamisil (terbinafine hydrochloride) mini-tablets, is not acceptable. "Mini-tablet" is not a CDER recognized dosage form terminology.
- The establishment information for drug substance is missing.

To resolve the issues the applicant should:

- Provide drug product samples (6 units for each packaging size) for evaluation. The appropriate dosage form name for the proposed product is under review.
- Provide drug substance establishment information for all facilities involved in the manufacturing and testing of drug substance.

### **D. Comments/Recommendation:**

There are no filing issues. All facilities are located in the Europe. GMP inspection requests will be submitted shortly after the NDA is filed.

The application is fileable from the CMC and quality perspective. The major review issues include dosage form nomenclature, control over the \_\_\_\_\_ process of the \_\_\_\_\_ and control over tablet breakage.

**b(4)**

Shulin Ding  
Pharmaceutical Assessment Lead

Moo Jhong Rhee  
Chief, Branch III

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## Filing Checklists

### A. Administrative Checklists

YES	NO		Comments
x		On its face, is the section organized adequately?	
	x	Is the section indexed and paginated adequately?	
x		On its face, is the section legible?	
	x	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	*See the footnote below.
x		Has an environmental assessment report or categorical exclusion been provided?	

\*The establishment list is provided for the drug product but not for the drug substance. The drug substance information is referenced to NDA 20-539. It is necessary for the applicant to provide the drug substance establishment list for this NDA because some of facilities approved for NDA 20-539 may not be involved for this NDA.

### B. Technical Checklists

#### 1. Drug Substance Referenced to NDA 20-539.

		Does the section contain synthetic scheme with in-process parameters?	Not applicable.
		Does the section contain structural elucidation data?	Not applicable.
		Does the section contain specifications?	Not applicable.
		Does the section contain information on impurities?	Not applicable.
		Does the section contain validation data for analytical methods?	Not applicable.
		Does the section contain container and closure information?	Not applicable.
		Does the section contain stability data?	Not applicable.

#### 2. Drug Product

x		Does the section contain manufacturing process with in-process controls?	
x		Does the section contain quality controls of excipients?	
x		Does the section contain information on composition?	
x		Does the section contain specifications?	
x		Does the section contain information on degradation products?	
x		Does the section contain validation data for analytical methods?	
x		Does the section contain information on container and closure systems?	
x		Does the section contain stability data with a proposed expiration date?	
x		Does the section contain information on labels of container and cartons?	
x		Does the section contain tradename and established name?	

### C. Review Issues

x		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	
	x	Is a team review recommended?	
x		Are DMFs adequately referenced?	

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/s/  
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Chief, Branch III

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