CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-071

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
22-071

NAME OF APPLICANT / NDA HOLDER
Novartis Pharmaceuticals Corporation

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Lamisil

ACTIVE INGREDIENT(S)	STRENGTH(S)
Terbinafine	EQ 250 mg Base

DOSAGE FORM
Tablets (minitablets)

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

A will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

or each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the formation described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6005001	12/21/1999	5/18/2012

d. Name of Patent Owner
Novartis AG (successor to Sandoz Ltd.)

Address *(of Patent Owner)*
Lichstrasse 35

City/State
Basel 4002 Switzerland

ZIP Code	FAX Number *(if available)*

Telephone Number	E-Mail Address *(if available)*
(161)324-32007	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

General Counsel
Novartis Pharmaceuticals Corporation

Address *(of agent or representative named in 1.e.)*
Novartis Corp., East Hanover Office, One Health Plaza

City/State
East Hanover, New Jersey

ZIP Code	FAX Number *(if available)*
NJ-07936-1080	

Telephone Number	E-Mail Address *(if available)*
(862) 778 8300	

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of ... that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

... this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), ...ug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in ...he manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Gregory C. Houghton	7/28/2006

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Gregory C. Houghton	
Address One Health Plaza	City/State East Hanover, NJ
ZIP Code 07936	Telephone Number (862) 778-2614
FAX Number *(if available)*	E-Mail Address *(if available)*

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
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First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

PSC Media Arts (301) 443-1090 EF

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

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ACTIVE INGREDIENT(S)	STRENGTH(S)
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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6121314	9/19/2000	5/18/2012

d. Name of Patent Owner
Novartis AG (successor to Sandoz Ltd.)

Address *(of Patent Owner)*
Lichstrasse 35

City/State
Basel 4002 Switzerland

ZIP Code	FAX Number *(if available)*

Telephone Number	E-Mail Address *(if available)*
(161) 324-3207	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

General Counsel
Novartis Pharmaceuticals Corporation

Address *(of agent or representative named in 1.e.)*
Novartis Corp., East Hanover Office, One Health Plaza

City/State
East Hanover, New Jersey

ZIP Code	FAX Number *(if available)*
NJ-07936-1080	

Telephone Number	E-Mail Address *(if available)*
(862) 778 8300	

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), g product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in e manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Gregory C. Houghton	7/28/2006

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Gregory C. Houghton	
Address One Health Plaza	City/State East Hanover, NJ
ZIP Code 07936	Telephone Number (862) 778-2614
FAX Number *(if available)*	E-Mail Address *(if available)*

PSC Media Arts (301) 443-1090 EF

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

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- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
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- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 22-071 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: September 8, 2006 Action Date: September 26, 2007

HFD 540 Trade and generic names/dosage form:

Applicant: Novartis Pharmaceuticals Corporation Therapeutic Class: 3S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: For the treatment of Tinea Capitis in patients 4 years of age and older

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.

X No: Please check all that apply: ___Partial Waiver ___Deferred ___X Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

ion A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: _____

udies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min 4 years of age kg_____ mo._____ yr._____ Tanner Stage_____
Max 12 years of age kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

tion D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
1-594-7337

Debarment Certification

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

Sheila A. Mathias, PhD, Senior Associate Director
Drug Regulatory Affairs

Aug 4, 2006
Date

EXCLUSIVITY SUMMARY for NDA # 22-071 SUPPL #

Trade Name Lamisil (terbunafine hydrochloride) oral granules Generic Name
Applicant Name Novaritis HFD-540

Approval Date September 26, 207

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/_X__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /___/

   If yes, what type(SE1, SE2, etc.)?

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

   YES /___X/ NO /___/

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

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

d) Did the applicant request exclusivity?

YES /_X__/NO /___/

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

3 years

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

YES /_x__/ NO /___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /__/ NO /___/

If yes, NDA # __Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /__X_/ NO /___/

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

NDA # NDA 20-539 (terbinafine hydrochloride)

NDA #

NDA #

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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

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

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

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

YES /__x_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

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

YES /__X_/ NO /___/

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

YES /___/ NO /___X/

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 /_X__/

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:

Investigation #1, Study # ___C2301

Investigation #2, Study # _____C2302

Investigation #3, Study #

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 /_x__/

Investigation #2 YES /___/ NO /__X_/

Investigation #3 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:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(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 /_X__/

Investigation #2 YES /___/ NO /__X_/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(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"):

Investigation #__, Study # _____C2301

Investigation #__, Study # _____C2302

Investigation #__, Study #

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 # 57 093 YES /_X__/ ! NO /___/ Explain:

Investigation #2

IND # 50,061 YES /_X__/ ! 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?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ 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 /_X__/

If yes, explain: _____

_____

_____

Kalyani Bhatt

Signature of Preparer Date 6/19/07

Title: Project Manager

Signature of Office or Division Director Date

cc:
Archival NDA 22-071
HFD-540/Division File
HFD-540/RPM Kalyani Bhatt
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347

MEMORANDUM OF TELECON

TELECONFERENCE DATE: May 24, 2007 and June 8, 2007

APPLICATION NUMBER: NDA 22-071
Lamisil (terbinafine hydrochloride)

BETWEEN:

Sponsor:	Novartis
Phone:	866-866-5114
Name:	Stefan Hirsch Ph.D., TRD Project Leader
	Peter Pietzonka Ph.D., Project Leader in Pharmaceutical Development
	Vincent Faivre-Pierret Pharm.D., Process Expert
	Brigitte Edith Thomi Matthes, Principal Scientist, Analytical Department
	Marie Bernasconi Ph.D., Project Management
	Agata Czajgucka Ph.D., Team Leader - Regulatory CMC
	Paula Rinaldi, Regulatory Affairs

AND

Name:	Office of New Drug Quality Assessment/DPA II
	Shulin Ding, Ph.D., Pharmaceutical Assessment Lead
	Yichun Sun, Ph.D., Chemist
	Linda Athey, Regulatory Health Project Manager for Quality
	Division of Dermatology and Dental Products
	Jill Lindstrom, M.D., Lead Medical Officer
	Office of Pharmaceutical Sciences
	Yana Mille, R.Ph., Director, Regulatory

SUBJECT: Outstanding CMC issues

FDA requested a Teleconference with Novartis to discuss outstanding CMC issues. An e-mail was sent to Novartis on May 16, 2007, with a list of issues to be discussed in the Teleconference. On May 23, 2007, FDA received via fax Novartis' response to the items listed in the e-mail. On June 7, 2007, Novartis e-mailed to the FDA updated responses, and another Teleconference was held on June 8, 2007, to discuss the remaining outstanding issues. Below are the questions sent in the May 16, 2007, e-mail, Novartis' response in italics to each item, the discussion at the May 24, 2007, Teleconference, Novartis' updated responses in italics, followed by the discussion in the Follow-up Teleconference.

12 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Question 4:
Packaging Labels:
Besides the recommended changes for the dosage form nomenclature and strength expression, please add "lot Number" and "Expiration Date" to the unit dose label, carton and pack labeling. Additionally, please confirm the "code" on carton and pack is referred to "Bar Code".

Novartis Response to Question 4:
The dosage form nomenclature, strength expression, and "lot Number" and "Expiration Date" will be added to one panel of the unit dose label, carton and pack labeling.

We confirm that "Code" on the carton and pack labeling refers to "Bar Code",

Discussion on Question 4, May 24, 2007:
No further discussion.

{See appended electronic signature page}

Shulin Ding, Ph.D.
Pharmaceutical Assessment Lead

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

/s/

Linda D Mullins-Athey
7/12/2007 01:12:07 PM
PROJECT MANAGER FOR QUALITY

Shulin Ding
7/12/2007 01:34:46 PM
CHEMIST

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: July 7, 2007

To: Paula Rinaldi Regulatory Affairs	From: Kalyani Bhatt, Regulatory Project Manager
Company: Novartis Pharmaceutical Corp	Division of Dermatologic and Dental Products
Fax number: (973)-781-2565	Fax number: 301-796-9894
Phone number: (862)-778-7712	Phone number: 301-796-2110

Subject: NDA 22-071/ Lamisil (terbinafine hydrochloride)

Total no. of pages including cover: 2

Comments:

Please see the following Ophthalmology Information Request

Document to be mailed: ☐ YES ☐ NO

Please see the following information request:

- Please submit the case report forms for the Ophthalmologic Tests for all U.S. patients

- First Priority are US patients that are exposed to Lamisil.

To: Lindstrom, Jill; Brown, Patricia C (ODEIII); Sun, Yichun; Hill, Barbara A; Soukup, Mat; Toyer, Denise P
Cc: Bhatt, Kalyani; Brown, Paul C; Ding, Shulin; Alosh, Mohamed A; Lee, Sue Chih H; Holquist, Carol A
Subject: RE: Lamisil Oral Granules - NDA 22-071 - Revised Draft Labeling (PI)
Jill,

The applicant's changes to Section 7.1 is acceptable based on the justification provided below. I have the following additional comments:

I just noticed a typo in the highlights under Drug Interactions that should be corrected as follows (deletions as strikethroughs and additions in red):

[redacted] b(4)

Also the following statement does not need to be underlined:

[redacted] b(4)

Thanks-you,
Abi

From: Lindstrom, Jill
Sent: Friday, June 15, 2007 12:46 PM
To: Brown, Patricia C (ODEIII); Sun, Yichun; Hill, Barbara A; Soukup, Mat; Adebowale, Abimbola O; Toyer, Denise P
Cc: Bhatt, Kalyani; Brown, Paul C; Ding, Shulin; Alosh, Mohamed A; Lee, Sue Chih H; Holquist, Carol A; Lindstrom, Jill
Subject: FW: Lamisil Oral Granules - NDA 22-071 - Revised Draft Labeling (PI)

Hi team,

See applicant's revised label, strikeout and clean, attached (carton and container will follow). Changes appear to primarily affect CMC, clinpharm, DMETS, and clinical, but I welcome comments from all. Because of the lateness of the hour, please have any comments to Kalyani (cc me) by noon on Monday if possible. If you cannot meet this timeframe, please provide your expected response time. For your planning, we would like to take an action on Wednesday, 20 June.

We're in the home stretch! Thanks to all for your continued hard work!!!

Jill

From: paula.rinaldi@novartis.com [mailto:paula.rinaldi@novartis.com]
Sent: Friday, June 15, 2007 12:17 PM
To: Lindstrom, Jill; Brown, Patricia C (ODEIII); Bhatt, Kalyani; Athey, Linda
Subject: Lamisil Oral Granules - NDA 22-071 - Revised Draft Labeling (PI)

Dear Dr. Bhatt,

Attached is the June 15 Novartis version of the draft Lamisil Oral Granules labeling. Please note the following:

- As discussed, we accepted the FDA changes and then used "track changes" to note all changes from the June 12 FDA version
- We are sending two attachments, one "marked-up" and one "clean" version
- We are also providing a justification for our changes to section 7.1
- The carton and container labeling will be sent by separate email today
- Novartis still proposes the name Lamisil [redacted] As noted previously, we believe that the addition of a modifier will aid in differentiating the oral granules from the currently marketed tablet. There is a significant difference between the currently approved indication, indicated population, and dose. We believe there is potential for confusion by health care professionals and patients, with written prescriptions and dispensing, if Lamisil is used without a modifier for the new formulation. We believe that patient harm is minimized by the addition of a modifier such as [redacted] to the existing brand name Lamisil.

b(4)

b(4)

Novartis Comment regarding section 7.1 and this statement: "Based on this finding, it is likely, that other inhibitors of both CYP2C9 and CYP3A4 (e.g. ketoconazole, amiodarone) may also lead to a substantial increase in the systemic exposure (Cmax and AUC) of terbinafine."

Terbinafine is metabolized by several enzymes. CYP2C9 and CYP3A4 are major contributing enzymes. The interaction of fluconazole with terbinafine is likely to be due to the fact that fluconazole is an inhibitor of both CYP2C9 and CYP3A4, and thus can inhibit terbinafine metabolism to a relevant degree. Similar interactions also are likely with other drugs that are inhibitors of both enzymes. However, there are neither study data to refute nor to prove this hypothesis. A general hypothesis on drug interactions with inhibitors of CYP2C9 and with inhibitors of CYP3A4 is not appropriate. We therefore feel that the wording should be cautious regarding a generalized drug interaction potential, and as specific as possible regarding the type of enzyme inhibitors. It may be appropriate to provide examples of drugs, e.g. ketoconazole and amiodarone, which, like fluconazole, are inhibitors of both enzymes, CYP2C9 and CYP3A4 [Becquemont L et al 2007] [Brown HS et al 2006] [Krishnaiah YS et al 1994] [Niwa T et al 2005] [Ohyama K et al 2000] [Venkatakrishnan K et al 2000] [Zhang W et al 2002].

REFERENCES

Becquemont L, Neuvonen M, Verstuyft C, et al. Amiodarone interacts with simvastatin but not with pravastatin disposition kinetics. Clin Pharmacol Ther 81:679-84 (2007).

Brown HS, Galetin A, Hallifax D, et al. Prediction of in vivo drug-drug interactions from in vitro data. Clin Pharmacokinet 45:1035-50 (2006)

Krishnaiah YS, Satyanarayana S, Visweswaram D. Interaction between tolbutamide and ketoconazole in healthy subjects. Br J Clin Pharmacol 37:205-7 (1994)

Niwa T, Shiraga T, Takagi A. Effect of antifungal drugs on cytochrome P450 (CYP) 2C9, CYP2C19, and CYP 3A4 activities in human liver microsomes. Biol Pharm Bull 28:1805-8 (2005).

Ohyama K, Nakajima M, Suzuki M, et al. Inhibitory effects of amiodarone and its N-deethylated metabolite on human cytochrome P450 activities: Prediction of in vivo drug interactions. Br J Clin Pharmacol 49:244-53 (2000).

Venkatakrishnan K, von Moltke LL, Greenblatt DJ. Effects of the antifungal agents on oxidative drug metabolism. Clin Pharmacokinet 38:111-80 (2000).

Zhang W, Ramamoorthy Y, Kilicarslan T, et al. Inhibition of cytochromes P450 by antifungal imidazole derivatives. Drug Metab Dispos 30:314-8 (2002).

Please let me know if you have any comments or questions. If you cannot reach me, you can contact Arlene McLeer at 862-778-6050.

Paula Rinaldi
Regulatory Affairs
Novartis Pharmaceuticals Corporation
862-778-7712

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

/s/

Abi Adebowale
6/20/2007 11:06:43 AM
BIOPHARMACEUTICS

Tapash Ghosh
6/20/2007 11:50:40 AM
BIOPHARMACEUTICS

MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology WO 22, Mailstop 4447, HFD-420 Center for Drug Evaluation and Research

To: Susan Walker, MD
Director, Division of Dermatologic and Dental Products

Through: Todd Bridges, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Kimberly Pedersen, RPh, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: June 1, 2007

Date of Document: September 8, 2006

Subject:

OSE Review	2007-1156
Proprietary Names:	Lamisil (Terbinafine Hydrochloride Oral Granules) 125 mg and 187.5 mg
Sponsor:	Novartis Pharmaceuticals Corporation
NDA #:	22-071

This memorandum is in response to a May 21, 2007 request from your Division for a review of the proprietary names [redacted] and [redacted], and review the proposed labels and labeling for terbinafine mini-tablets. The Division requested an expedited review, so a cursory assessment of the proprietary names of [redacted] and [redacted] was submitted via e-mail on May 31, 2007 by Carol Holquist, Division Director of the Division of Medication Errors and Technical Support to Dr. Jill Lindstrom, Team Leader in the Division of Dermatologic and Dental Products. This e-mail detailed the discussion concerning the unacceptability of the modifiers [redacted] and [redacted] it also outlined some concerns DMETS had with the labels and labeling. The Division subsequently sent the labels and labeling for assessment from a medication errors perspective.

b(4

b(4

After a review of the container labels and carton and insert labeling, DMETS has the following comments.

A. GENERAL COMMENTS

1. The Labeling and Nomenclature Committee (LNC) recommended the use of "oral granules" in lieu of "mini-tablets" due to history and standards. Assure that all references to mini-tablets are replaced with oral granules per the LNC's request.

2. The sponsor named their package configuration [redacted] commonly refers to packets that hold sugar and artificial sweeteners for beverages and candy ("Pixie Stixs"). These beverage sweeteners and candy are poured into beverages or directly into the mouth, respectively. To avoid any confusion that this drug product can be added to a beverage or directly poured into the mouth, and to be consistent with currently marketed granule drug products, DMETS recommends the use of "packet" as the descriptor rather than [redacted] Also, we have seen these types of package configuration naming conventions take over as the product name when prescribed. For example, Zithromax Z-PAK is often prescribed as Z-PAK. For this reason, we would also object to the use of [redacted] this designation may lead to less error in administration and prescribing. Revise all labels and labeling accordingly.

b(4

b(4

3. As noted in our May 31, 2007 e-mail to Dr. Jill Lindstrom, DMETS does not recommend separate insert labeling for the two formulations of Lamisil. DMETS acknowledges the Division's concern that combined labeling for the two formulations may lead to dosing confusion or off-label use of Lamisil for the treatment of onychomycosis in pediatric patients. However, off-label use in pediatric patients is already occurring in clinical practice. In addition, from the perspective of DMETS, the separation could lead to a lack of knowledge of the existence of the granule formulation and may result in compounding of the Lamisil tablets for pediatric use. Compounding of medication for pediatric use could result in inaccurate dosing and subsequent side effects. Therefore, DMETS recommends the use of one package insert for the tablet and oral granule formulation.

B. CONTAINER LABELS

1. See General Comment A-1 and A-2.

2. Revise the yellow font color text of the 125 mg product strength label as it is difficult to read on the white background. The text font color utilized should maximize the contrast between the text and the background. Additionally, ensure that the text font color utilized does not overlap or look similar to the purple color used on the 187.5 mg product strength label.

C. CARTON LABELING (14 and 42 count)

1. See General Comment A-1 and A-2 and Comment B-2.

2. Revise the designation of the strength to include "per packet." This designation will help to diminish confusion with regards to the content of each packet. For example, the statement could read "XXX mg terbinafine base equivalent per packet."

3. Under Patient Instructions on the back panel, consider revising the number two instructions to read "tap packet gently to settle contents." The word combination of "tap" and "settle" may be more logical than "shake", which may lead to loss of "granules" after opening.

4. Under Patient Instructions on the back panel (number 4), the practitioner/patient is instructed to pour the contents onto a spoonful of soft food, such as pudding with a notation not to add to applesauce or other fruit-based product. DMETS has two issues with this instruction. The first is the viability for the patient/caregiver to add the entire packet of drug product to one spoonful of food. We question if this could result in a choking hazard for children. Thus, consideration should be given to the amount of food needed for administration.

   The second issue is the lack of definitive options of soft foods to use as a vehicle for administering the drug product. DMETS recommends this be addressed by the inclusion of specific food products (e.g. Lamisil oral granules may only be added to one of the following soft foods: pudding, XXX, XXX). In selection of these foods, the sponsor must consider common allergies (e.g. milk) and provide a variety of food options. The sponsor should then assure that the statement of food products that may not be used as a vehicle for drug administration (i.e. applesauce, beverages) is sufficiently distinguished to avoid a cursory read of the label resulting in misinterpretation. The sponsor should clarify if the drug product may be added to both hot and cold foods. Moreover, the sponsor should consider whether the addition of a warning to "not" add granules to beverages, as this may pose a chocking hazard is needed on the carton and packet.

D. INSERT LABELING

1. See General Comment A-1 through A-3.

2. HIGHLIGHTS OF PRESCRIBING INFORMATION

   a. In the Indication and Usage sub-section, revise to include the studied or approved age for use of [redacted] DMETS believes inclusion of this information will help to ensure the appropriate use of this drug product. b(4)

   b. In the Dosage and Administration sub-section, revise to include complete dosing information.

3. FULL PRESCRIBING INFORMATION

   a. Revise the Dosage and Administration section in accordance with Comment C-4 above. Thus, delete the term of [redacted] as most practitioners and patients/caregivers are not likely to know what food is considered acidic compared to basic (non-acidic). Furthermore, the sponsor should indicate the outcome if not mixed in the correct food product or chewed. For example, chewing of the granules or adding the granules to a food product that is not recommended could result in a bitter or unpleasant taste, but the drug product would still be effective. b(4)

   b. In the Dosage and Administration section, a statement should be added that states "any used portion should be discarded." Otherwise, patients may save unused portions to administer at a later time period.

   c. In the Patient Counseling Information, under bullet number four (4) of the "How are Lamisil oral granules taken?" subsection, see recommendation C-4 and revise accordingly.

We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any communication to the sponsor with regard to this review. DMETS would appreciate feedback of the final outcome of this consult. If you have further questions or need clarifications, please contact Angela Robinson, OSE Project Manager, at 301-796-2284.

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

/s/

Kimberly Culley-Pedersen
6/13/2007 02:29:55 PM
DRUG SAFETY OFFICE REVIEWER

Todd Bridges
6/13/2007 03:14:12 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/13/2007 04:07:59 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: May 9, 2007

To: Kalyani Bhatt, DDDP
Patricia Brown, MD, DDDP

From: Andrew Haffer, DDMAC

Re: Comments on draft labeling for Lamisil
NDA# 22-071

DDMAC has reviewed the draft PI for Lamisil. DDMACs comments are based on the proposed draft labeling distributed by Kalyani Bhatt via email on 5/8/07 at 12:56pm. DDMAC's comments are included directly in the attached document.

If you have any questions about DDMACs comments or would like a copy of the comments in WORD please do not hesitate to call.

12 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Andrew Haffer
5/9/2007 03:51:12 PM
DDMAC REVIEWER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Dermatology and Dental Products

FACSIMILE TRANSMITTAL SHEET

DATE: 4-30-07

To: Paula Rinaldi	From: Kalyani Bhatt
Company: Novartis	
Fax number: 973-781-2565	Fax number: (301) 796-9894
Phone number: 862-778-7712	Phone number: (301)-796-0852

Subject:

Total no. of pages including cover: 3

Document to be mailed: YES (NO)

Appears This Way
On Original

Information Request

1) Please provide any available data to indicate efficacy of griseofulvin microsized dosed at 10-20 mg/kg/day versus placebo.

2) Please provide information regarding the course of untreated tinea capitis and include the rate of spontaneous resolution over time.

3) In the Summary of Clinical Safety, p. 43, a subject is identified that had "clinically significant weight loss plus decreased appetite" on Visit 3. Please provide a case summary and the case report form for this subject or identify in the submission where this information may be found. (This subject does appear to in Study SFO327C 2301.)

4) On page 43 of the Summary of Clinical Safety definitions were provided for notable abnormalities of vital signs as follows:

• Pulse (b/m)	either ≥120 + increase ≥25, or > 130
	either ≤ 50 + decrease ≥ 30, or < 40
• SBP (mmHg)	either ≥180 + increase ≥30, or > 200
	either ≤90 + decrease ≥30, or < 75
• DBP (mmHg)	either ≥105 + increase ≥20, or > 115
	either ≤50 + decrease ≥20, or < 40

Are these definitions set using age corrected values? If not, please provide, if possible, the information in table 2.7.4.7-6.1 "Vital signs meeting notably abnormal criteria, by sign and treatment (Safety population)" using age corrected values (for the definitions of notable vital sign abnormalities).

5) On page 35 of the Summary of Clinical Safety Table 5-1 is as follows:

Table 5-1 Clinically notable hematology values (pivotal studies, pooled safety population)

		Terbinafine N=1042	Griseofulvin N=507
Laboratory test (unit)	**Criterion**	**Total n (%)**	**Total n (%)**
Hematocrit (L/L)	<0.28	928 1 (0.1)	464 1 (0.2)
Hemoglobin (g/L)	<100	949 3 (0.3)	473 2 (0.4)
RBC (10E12/L)	<3.0	949 0 (0.0)	473 0 (0.0)
Absolute Neutrophils (Seg. + Bands) (10E9/L)	<1	958 12 (1.3)	482 13 (2.7)
Absolute Lymphocytes (10E9/L)	<1	958 5 (0.5)	482 3 (0.6)
Absolute Eosinophils (10E9/L)	>0.6	958 111 (11.6)	482 57 (11.8)
Platelet count (direct) (10E9/L)	<100	945 1 (0.1)	471 1 (0.2)
WBC (total) (10E9/L)	<3	958 9 (0.9)	483 5 (1.0)

Source: PT-table 2.7.4.7-5.4

Are age corrected values used for setting the criteria for clinically notable hematology values? If not, please provide, if possible, the information in Table 5-1 using age corrected values (for the criterion of clinically notable hematology values).

6) On page 40 of the Summary of Clinical Safety Table 5-5 is as follows:

Table 5-5 Clinically notable biochemistry values (pivotal studies, pooled safety population)

		Terbinafine N=1042	Griseofulvin N=507	
Laboratory test (unit)	**Criterion**	**Total n (%)**	**Total n**	**(%)**
Alkaline phosphatase, serum (U/L)	>2 ULN	951 2 (0.2)	476	0 (0.0)
Blood Urea Nitrogen (BUN) (mmol/L)	>1 ULN	984 7 (0.7)	495	0 (0.0)
Creatinine (umol/L)	>1 ULN	984 110 (11.2)	495	55 (11.1)
corrected creatinine*		984 4 (0.4)	495	3 (0.6)
SGOT (AST) (U/L)	>2 ULN	958 2 (0.2)	483	0 (0.0)
SGPT (ALT) (U/L)	>2 ULN	978 2 (0.2)	491	2 (0.4)
Bilirubin (total) (umol/L)	>1 ULN	981 4 (0.4)	493	1 (0.2)
Gamma Glutamyltransferase (U/L)	>2 ULN	951 1 (0.1)	475	3 (0.6)

Source: PT-table 2.7.4.7-5.8
Patients with missing baseline values were excluded.
* corrected creatinine does not appear in the source table.

Are age corrected values used for setting the criteria for clinically notable biochemistry values? If not, please provide, if possible, the information in Table 5-5 using age corrected values (for the criteria of clinically notable biochemistry values).

Kalyani

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

Victoria Lutwak

DATE: March 26, 2007

To: Shelia Methias	**From:** Victoria Lutwak for Kalyani Bhatt
Company: Novartis Pharmaceuticals Corporation	Division of Dermatology and Dental Products
Fax number: 862-778-2565 973 781-2865	**Fax number:** 301-796-9895/94
Phone number: 862-778-0847	**Phone number:** (301) 796-2445

Responded VL.

Subject: NDA 22-071 Lamisil

Total no. of pages including cover: 1

Comments: Please provide case summaries for all subjects with the adverse event of dysgeusia. In section 6.2 (p. 43) of the Summary of Clinical Safety (SFO327/Tinea capitis) 4 subjects were identified as having this adverse event. Please also provide, or identify where they may be found in the submission, the case report forms for the two subjects having dysgeusia who were in the terbinafine treatment group. (The case report forms for the two subjects with dysgeusia in the griseofulvin treatment group have been located in the submission.)

If possible, could you respond Fax by close of business 3/29/2007. If not, please provide a time.

Document to be mailed: ☐ YES ☑ NO

This application contains the following items: (*Check all that apply*)

[X]	1. Index
[X]	2. Labeling *(check one)* [X] Draft Labeling [ ] Final Printed Labeling
[X]	3. Summary (21 CFR 314.50 (c))
[X]	4. Chemistry section
[X]	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d)(1); 21 CFR 601.2)
[X]	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
[X]	C. Methods validation package (e.g., 21 CFR 314.50 (e)(2)(i); 21 CFR 601.2)
[X]	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d)(2); 21 CFR 601.2)
[X]	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3); 21 CFR 601.2)
[X]	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d)(4))
[X]	8. Clinical data section (e.g., 21 CFR 314.50 (d)(5); 21 CFR 601.2)
[ ]	9. Safety update report (e.g., 21 CFR 314.50 (d)(5)(vi)(b); 21 CFR 601.2)
[X]	10. Statistical section (e.g., 21 CFR 314.50 (d)(6); 21 CFR 601.2)
[X]	11. Case report tabulations (e.g., 21 CFR 314.50 (f)(1); 21 CFR 601.2)
[X]	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
[X]	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
[X]	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b)(2) or (j)(2)(A))
[X]	15. Establishment description (21 CFR Part 600, if applicable)
[X]	16. Debarment certification (FD&C Act 306 (k)(1))
[X]	17. Field copy certification (21 CFR 314.50 (l)(3))
[X]	18. User Fee Cover Sheet (Form FDA 3397)
[X]	19. Financial Information (21 CFR Part 54)
[ ]	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowlegde are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[X]	**Sheila Mathias, PhD, Senior Associate Director** Drug Regulatory Affairs	**SEPT. 8, 2006**

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Health Plaza East Hanover, New Jersey 07936-1080	**(862) 778-0847**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
NOVARTIS PHARMACEUTICALS CORPORATION	September 8, 2006
TELEPHONE NO. (*Include Area Code*) **(862) 778-0847**	FACSIMILE (FAX) Number (*Include Area Code*) **862.778.2565**
APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued*): One Health Plaza East Hanover, New Jersey 07936-1080	AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (*If previously issued*) **22-071**

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
terbinafine hydrochloride	**LAMISIL**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)

CODE NAME (*If any*) **SFO327C**

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Film coated tablets (mini-tablets)	**125 mg and 187.5 mg**	**Oral**

(PROPOSED) INDICATION(S) FOR USE:
Tinea Capitis

APPLICATION INFORMATION

APPLICATION TYPE (*check one*)
[X] NEW DRUG APPLICATION (21 CFR 314.50) [ ] ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
[ ] BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE [X] 505 (b)(1) [ ] 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (*check one*) [X] ORIGINAL APPLICATION [ ] AMENDMENT TO A PENDING APPLICATION [ ] RESUBMISSION
[ ] PRESUBMISSION [ ] ANNUAL REPORT [ ] ESTABLISHMENT DESCRIPTION SUPPLEMENT [ ] EFFICACY SUPPLEMENT
[ ] LABELING SUPPLEMENT [ ] CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT [ ] OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY [ ] CBE [ ] CBE-30 [ ] Prior Approval (PA)

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (*check one*) [ ] PRESCRIPTION PRODUCT (Rx) [ ] OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS [ ] PAPER [X] PAPER AND ELECTRONIC [ ] ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready is ready for inspection or, if not when it will be ready.

Drug substance-related sites are referred to approved NDA 20-539 for Lamisil Tablets.
For drug product sites, please refer to the attachment: 356hform_attachment.
All the manufacturing, packaging, and control sites are ready for inspection.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 57,093 IND
NDA 20-192; NDA 20-539; NDA 20-749; NDA 20-846; NDA 20-980; NDA 21-124
DMF DMF
The references to the DMFs in the current application are summarized in the attachment: 7005419_R_DMFR_840_1

b(4

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

/s/

Victoria Lutwak
3/26/2007 02:35:43 PM
CSO

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On Original

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-071

INFORMATION REQUEST LETTER

Novartis Pharmaceuticals Corporation
Attention: Sheila Mathias, Ph. D
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. DiDomenico:

Please refer to your September 8, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamisil (terbinafine hydrochloride).

We also refer to your submissions dated November 8, 2006 December 1, 2006 and January 22, 2007.

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 in order to continue our evaluation of your NDA.

Drug Product:

1. **Established Name and Dosage Form Nomenclature:**
   - The proposed drug product name, Lamisil® (terbinafine hydrochloride) mini-tablets is not deemed acceptable. The drug product name recommended is as follows:

     _____ b(4

   - Please provide samples of the drug product (6 units per strength).

2. **Control of Excipients:**
   - The particle size of _____ is considered a critical parameter since the b(4

3. **Manufacturing Process Controls:**
   - Please provide critical process controls used during ——— processes including desired weight gain or ——— level for each ——— layer. b(4)
   - ——— because of the concern for possible not-uniform distribution of the ——— colloidal silicon dioxide ——— b(4) ———. The fill weight can be used as a control for filling only if the aforementioned concern is resolved during production stage.

4. **Quality Control - Testing Monographs:**
   - Please include detailed description on the test method and procedure for the "Appearance" test of the drug product specifications with revised "Appearance" acceptance criterion including "no sticking and broken minitablets".
   - Establish "Moisture Content" specification for the ——— "minitablets" to ensure physical stability of the drug product. b(4)
   - Provide justification and validation for preparing the reference solution **only periodically** for the "Dissolution" test.
   - Explain the following equation used to calculate drug content (assay) based on the bulk level determination ———

b(4)

5. **Reference Standards:**
   - Please provide detailed information on the preparation and characterization of the reference materials, terbinafine hydrochloride and 503-82.

6. **Executed Batch Record:**
   - Please explain the more than ——— yield of ——— granules when there was a loss of the ———, as shown in page 3/35 (theoretical yield of ——— is ——— based on all the ingredients including ——— added; however, the actual amount of ——— obtained was ——— b(4)
   - Was there any material loss during the other unit operations to prepare the final blend for ——— (Theoretical weight: ———, actual weight delivered for ——— b(4)

If you have any questions, call Linda Mullins Athey, Regulatory Health Project Manager for Quality, at 301-796-2096.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Moo-Jhong Rhee
2/6/2007 09:36:43 AM
Chief, Branch III

NOVARTIS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Sheila A. Mathias, MBA, PhD
Sr. Associate Director
Tel: 862-778-0847
Fax: 973-781-2565
email address: sheila.mathias@ novartis.com

January 8, 2007

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

NDA No. 22-071
Lamisil® (terbinafine hydrochloride)
Mini-tablets

120-Day Safety Update

Dear Dr. Walker:

Novartis refers the Agency to NDA 22-071 for Lamisil Mini-tablets, submitted September 8, 2006. In a telephone conversation held with the project manager, Ms. Kalyani Bhatt, on October 31, 2006, Novartis informed Ms. Bhatt of the following:

In regard to the 120-day safety update, the database was locked for study 2301 on the 18th of April and for study 2302 on the 13th of April 2006 and neither database was reopened. In addition, there are no ongoing studies and no CRFs or CRTs to submit. As a result of the information above, Novartis respectfully submits this cover letter for the 120 day safety update.

This submission is being provided in accordance with the guidance for industry titled, *Providing Regulatory Submissions in Electronic Format-NDA's(January 1999).* The relevant technical details of this submission are as follows:

- Submission size: approximately 248 KB
- Electronic media: one compact disc
- Virus scan: Network Associates Incorporated VirusScan version 7.1.0 formerly known as the McAfee VirsuScan). The submission is virus free.

If you have any questions or need any additional information, please contact me, Sheila A. Mathias, Ph.D. at (862) 778-0847 or, in my absence, Eric A. Floyd, Ph.D. at (862) 778-5657.

Sincerely,

Sheila Mathias, PhD
Senior Associate Director
Drug Regulatory Affairs

SAM/ar
Submitted in duplicate
20070108 CV sam Minitabs 120 day

NOVARTIS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Sheila A. Mathias, MBA, PhD
Sr. Associate Director
Tel: 862-778-0847
Fax: 973-781-2565
email address: sheila.mathias@ novartis.com

January 8, 2007

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

NDA No. 22-071
Lamisil® (terbinafine hydrochloride)
Mini-tablets

120-Day Safety Update

Dear Dr. Walker:

Novartis refers the Agency to NDA 22-071 for Lamisil Mini-tablets, submitted September 8, 2006. In a telephone conversation held with the project manager, Ms. Kalyani Bhatt, on October 31, 2006, Novartis informed Ms. Bhatt of the following:

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If you have any questions or need any additional information, please contact me, Sheila A. Mathias, Ph.D. at (862) 778-0847 or, in my absence, Eric A. Floyd, Ph.D. at (862) 778-5657.

Sincerely,

Sheila Mathias, PhD
Senior Associate Director
Drug Regulatory Affairs

SAM/ar
Submitted in duplicate
20070108 CV sam Minitabs 120 day

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: November 14, 2006

To: Sheila A. Mathias, Ph.D. Senior Associate Director	From: Kalyani Bhatt, Regulatory Project Manager
Company: Novartis Pharmaceutical Corp	Division of Dermatologic and Dental Products
Fax number: (973)-781-2565	Fax number: 301-796-9894
Phone number: (862)-778-0847	Phone number: 301-796-2110

Subject: NDA 22-071/ Lamisil (terbinafine hydrochloride)

Total no. of pages including cover: 2

Comments:

Please see the following SEALD Comments

Document to be mailed: ☐ YES ☐ NO

Thank you.

SEALD Comments

Highlights:

- The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(6) and (d)(8)]

- Create bulleted statements throughout the Highlights.

- A "Recent Major Changes" section should be added to contain any changes made to the following sections during the year before approval of this supplement: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions. [See CFR 201.57 (a)(5)]

- The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:
  "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

  Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

- Regarding Contraindications, "theoretical" adverse reactions must not be listed (i.e., hypersensitivity). If the contraindication is not theoretical, then it must be reworded to explain the type and nature of the adverse reaction. The same applies to the Contraindications section in the FPI. [See 21 CFR 201.57(a)(9) and (c)(5)]

- Under Adverse Reactions, you must include the most frequently occurring adverse reactions along with the criteria used to determine inclusion (e.g., incidence rate). Revise Adverse Reactions in Highlights accordingly.
  [See 21 CFR 201.57(a)(11)].

- Under Adverse Reactions, your proposed required statement currently reads:

  [ ] b(4)

  The required statement should read:

  [ ] b(4)

  The Novartis phone number must connect callers directly to a location for voluntary reporting of adverse events. A general phone number that is not specifically designated for adverse event reporting should not be included.
  [See 21 CFR 201.57(a)(11)]

- Since Lamisil has proposed patient labeling, the patient counseling statement should read **See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.**
  [See 21 CFR 201.57(a)(14)]

- The revision date is currently located immediately after Use in Specific Populations in the proposed label. The revision date must appear after the required statement "**See 17 for PATIENT**

COUNSELING INFORMATION and FDA-Approved Patient Labeling" and should be right justified. A space should appear between that statement and the revision date.
[See 21 CFR 201.57(a)(15)]

FPI: Contents:

- The Contents must be limited in length to one-half page, in 8 point type, two-column format. [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- Unbold the section subheadings. Only section headings should be bolded.
[See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- Create subsection headings that identify the content. Avoid using the word ——— as you have proposed in 5.6 under ——————— This also applies to the FPI. b(4)

- Under Adverse Reactions and Use in Specific Populations, revise the headings within subsections. Only section and subsection headings may be numbered. Do not number headings within a subsection. For example, ——————— is not allowed. You may use headings without numbering within subsections of the FPI (e.g., *Clinical Studies Experience*). Such headings should not appear in the Contents. Please correct in both Contents and the FPI. b(4)
[See 21 CFR 201.56(d)(1) for the appropriate section and subsection numbers and names]

- Under Use in Specific Populations, the 8.5 Geriatric Use subsection is missing in the proposed label. This information must be included unless clearly inapplicable. This also applies to the FPI.
[See 21 CFR 201.57 (b) and 21 CFR 201.57 (c)(9)]

- Under 13 Nonclinical Toxicology, 13.1 should read Carcinogenesis, Mutagenesis, Impairment of Fertility, and 13.2 should read Animal Toxicology and/or Pharmacology. This also applies to the FPI.
[See 21 CFR 201.57 (b) and 21 CFR 201.57 (c)(14)]

- The required footnote "*Sections or subsections omitted from the full prescribing information are not listed" should be right justified.
[See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

FPI:

- Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10), please use bold print sparingly. Use another method for emphasis such as italics or underline. [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- Under Adverse Reactions, you refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at http://www.fda.gov/cder/guidance and revise your Adverse Reactions section accordingly.

- Under Adverse Reactions, add appropriate titles to the three tables included in that section.

- Regarding Patient Counseling Information, include information for prescribers to convey to patients to use the drug safely and effectively. Your Patient Counseling Information section is written for the patient, not the prescriber. Please revise accordingly.

  "Information for Patients" is a subsection contained in the old labeling format and is not included in the new PLR format. The proposed 17 **PATIENT COUNSELING INFORMATION** should read:

  17 **PATIENT COUNSELING INFORMATION** b(4)

  17.1 (propose language directed to prescribers) b(4)

  [See 21 CFR 201.57 (c)(18)]

- The company trademark, name and address should be moved from the end of How Supplied/Storage and Handling to the last page of the labeling after the Patient Counseling Information.

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

/s/

Kalyani Bhatt
12/28/2006 02:13:52 PM
CSO

Study Endpoints and Label Development (SEALD) Team
Review of Physician Labeling Rule (PLR) Labeling

Subject: Proposed Labeling Format Review

Application Number: NDA 22-071

Applicant: Novartis

Drug Names: Lamisil (terbinafine hydrochloride)

Receipt Date: 9/8/06
SEALD Review Date: 12/8/06

Project Manager: Kalyani Bhatt
Review Division: Division of Dermatology and Dental Products

SEALD Reviewer: Robin Anderson, RN, MBA
SEALD Director Concurrence: Laurie Burke, RPh, MPH

Executive Summary

This memo provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

SEALD Comments

Highlights:

- The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(6) and (d)(8)]

- Create bulleted statements throughout the Highlights.

- A "Recent Major Changes" section should be added to contain any changes made to the following sections during the year before approval of this supplement: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions. [See CFR 201.57 (a)(5)]

- The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

"(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

- Regarding Contraindications, "theoretical" adverse reactions must not be listed (i.e., hypersensitivity). If the contraindication is not theoretical, then it must be reworded to explain the type and nature of the adverse reaction. The same applies to the Contraindications section in the FPI. [See 21 CFR 201.57(a)(9) and (c)(5)]

- Under Adverse Reactions, you must include the most frequently occurring adverse reactions along with the criteria used to determine inclusion (e.g., incidence rate). Revise Adverse Reactions in Highlights accordingly. [See 21 CFR 201.57(a)(11)].

- Under Adverse Reactions, your proposed required statement currently reads:

[redacted] b(4)

The required statement should read:

[redacted] b(4)

The Novartis phone number must connect callers directly to a location for voluntary reporting of adverse events. A general phone number that is not specifically designated for adverse event reporting should not be included. [See 21 CFR 201.57(a)(11)]

- Since Lamisil has proposed patient labeling, the patient counseling statement should read **See 17 for PATIENT COUNSELING INFORMATION** [redacted] b(4)

[See 21 CFR 201.57(a)(14)]

- The revision date is currently located immediately after Use in Specific Populations in the proposed label. The revision date must appear after the required statement "**See 17 for PATIENT COUNSELING INFORMATION** [redacted] and should be right justified. A space should appear between that statement and the revision date. b(4)
[See 21 CFR 201.57(a)(15)]

FPI: Contents:

- The Contents must be limited in length to one-half page, in 8 point type, two-column format. [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- Unbold the section subheadings. Only section headings should be bolded. [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- Create subsection headings that identify the content. Avoid using the word ——— as you have proposed in 5.6 under ———. This also applies to the FPI. b(4)

- Under Adverse Reactions and Use in Specific Populations, revise the headings within subsections. Only section and subsection headings may be numbered. Do not number headings within a subsection. For example, " ——— is not allowed. You may use headings without numbering within subsections of the FPI (e.g., *Clinical Studies Experience*). Such headings should not appear in the Contents. Please correct in both Contents and the FPI. [See 21 CFR 201.56(d)(1) for the appropriate section and subsection numbers and names] b(4)

- Under Use in Specific Populations, the 8.5 Geriatric Use subsection is missing in the proposed label. This information must be included unless clearly inapplicable. This also applies to the FPI. [See 21 CFR 201.57 (b) and 21 CFR 201.57 (c)(9)]

- Under 13 Nonclinical Toxicology, 13.1 should read Carcinogenesis, Mutagenesis, Impairment of Fertility, and 13.2 should read Animal Toxicology and/or Pharmacology. This also applies to the FPI. [See 21 CFR 201.57 (b) and 21 CFR 201.57 (c)(14)]

- The required footnote "*Sections or subsections omitted from the full prescribing information are not listed" should be right justified. [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

FPI:

- Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10), please use bold print sparingly. Use another method for emphasis such as italics or underline. [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- Under Adverse Reactions, you refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of

Labeling for Human Prescription Drug and Biological Products – Content and Format," available at http://www.fda.gov/cder/guidance and revise your Adverse Reactions section accordingly.

- Under Adverse Reactions, add appropriate titles to the three tables included in that section.

- Regarding Patient Counseling Information, include information for prescribers to convey to patients to use the drug safely and effectively. Your Patient Counseling Information section is written for the patient, not the prescriber. Please revise accordingly.

  "Information for Patients" is a subsection contained in the old labeling format and is not included in the new PLR format. The proposed 17 **PATIENT COUNSELING INFORMATION** should read:

  17 **PATIENT COUNSELING INFORMATION** b(4)

  17.1 (propose language directed to prescribers)

  b(4

  [See 21 CFR 201.57 (c)(18)]

- The company trademark, name and address should be moved from the end of How Supplied/Storage and Handling to the last page of the labeling after the Patient Counseling Information.

Recommendations

After the comments are conveyed to the applicant and revised labeling is submitted, please check to ensure that comments have been addressed and incorporated into the labeling. At the first labeling meeting, use the applicant's updated (revised) draft labeling for review.

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/s/

Robin E Anderson
12/13/2006 12:51:34 PM
CSO

Laurie Burke
12/13/2006 08:36:02 PM
INTERDISCIPLINARY

Department of Health and Human Services
Public Health Service
Food and Drug Administration

MEMORANDUM

Date: December 12, 2006

From: Pediatric Exclusivity Board

Through: John K. Jenkins, M.D.
Chair, Pediatric Exclusivity Board

Subject: Terbinafine Pediatric Exclusivity

To: NDA 22-071

On December 4, 2006, the Pediatric Exclusivity Board (the Board) met to make a pediatric exclusivity determination for terbinafine (Lamisil), sponsored by Novartis Pharmaceuticals (Novartis).

This memorandum addresses the Board's decision-making process for the terbinafine pediatric exclusivity determination.

The original written request was issued to Novartis on Dec 28, 2001. The written request was issued an amendment on four occasions: July 14, 2003 {amendment #1}, October 17, 2003 {amendment #2}, March 16, 2006 {amendment #3}, and May 15, 2006 {amendment #4}.

The Pediatric Exclusivity Board initially met on October 25, 2006 to discuss terbinafine. The review division indicated that they believed that the sponsor fairly met the terms of the written request as a whole, but stated that the ophthalmologic issues identified by Dr. Wiley Chambers, who was unable to attend the Board meeting, needed to be considered further. A follow-up Board meeting was held on November 8, 2006 with Dr. Chambers in attendance. He described the strengths and weaknesses of the color vision and visual field data submitted by the sponsor to evaluate retinal safety. After lengthy discussion, the Board asked that the review division request additional information from the sponsor regarding the various ophthalmologic assessments. At the third and final Board meeting held on December 4, 2006, the review division noted that amendment # 2 served as the basis for designing the sponsor's two pivotal trials. The due date for submission of final study reports was October 1, 2006. On December 21, 2005, the sponsor requested an amendment to the written request to permit additional vision tests to evaluate retinal safety. Amendment #3 was issued approximately three days prior to the completion of the first pivotal study and one month prior to completion of the second pivotal study to include the following vision tests:

- SPP3 test for color vision testing in patients less than 11 years of age;
- Roth 28-hue test for color vision testing in patients less than 11 years of age; and
- Allen test for visual acuity only for children who cannot read.

When the written request was revised to incorporate the additional vision tests, other ophthalmology related terms were inadvertently made stricter. The written request due date remained October 1, 2006, making it impossible for the sponsor to modify the pivotal studies to comply with the revised written request. Amendment #4 was issued in response to the sponsor's request for clarification on the timing of the ophthalmologic testing, but retained the stricter language inserted in amendment #3. Amendment #4 also did not extend the due date for submitting final study reports beyond October 1, 2006.

At the December 4, 2006 meeting, the review division provided the Board with a letter dated June 16, 2006, in which the sponsor acknowledged the changes to the written request for the ophthalmologic testing and reminded the agency that the protocol was based on amendment #2. Dr. Jenkins noted that while the language in amendment #2 was in some ways contradictory, the overall view of the review division and Dr. Chambers, who assessed potential changes in visual field loss and color vision, was that the sponsor fairly responded to the terms of the written request. The Board also agreed that the studies provided were overall well done, were responsive to the written request in all other ways, and provided useful information to inform the safe and effective use of terbinafine in children. In addition, Dr. Jenkins concluded that the ophthalmologic safety data provided, thus far, do not support the concerns that led to the inclusion of these vision tests into the written request. Therefore, after reviewing all these facts, a decision was made to grant pediatric exclusivity.

Since this submission triggers the Pediatric Research Equity Act, it was recommended that the review division require additional safety studies at the time they approve the submission to further refine the ophthalmologic safety database which will be tracked as a required postmarketing commitment. Requiring the studies after approval for pediatric use is also consistent with agency practice in instances where the risk is theoretical, and the available safety database, while not perfect, is deemed adequate and does not support a signal of a safety concern.

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/s/

Debbie Avant
12/12/2006 02:54:30 PM
PHARMACIST

John Jenkins
12/18/2006 04:41:42 PM
MEDICAL OFFICER

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA: 5 /15/2006.
Application Written Request was made to: IND 57,093, NDA 20-192, NDA 20-539, NDA 20-749, NDA 20-846, NDA 21-124, NDA 20-980
Timeframe Noted in Written Request for Submission of Studies: 10/01/2006.
NDA# 22-071 Supplement # Not Applicable Choose one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR
Sponsor: Novartis
Generic Name: Terbinafine mini-tablets Trade Name: Lamisil
Strength: 125 mg, 187.5 mg, 250 mg Dosage Form/Route: mini-tablets/oral
Date of Submission of Reports of Studies 09/08/2006.
Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) ~~10/25/06.~~ 12/7/06

Was a formal Written Request made for the pediatric studies submitted?	Y ✓	N___
Were the studies submitted after the Written Request?	Y ✓	N___
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y ✓	N___
Was the timeframe noted in the Written Request for submission of studies met?	Y ✓	N___
If there was a written agreement, were the studies conducted according to the written agreement? *OR* If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y ✓	N___
Did the studies fairly respond to the Written Request?	Y ✓	N___

SIGNED Patricia C Brown DATE 10/19/06
(Reviewing Medical Officer)

SIGNED [signature] DATE 10/19/06
(Division Director)

Do not enter in DFS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD, HFD-960.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity ✓ **Granted** ___ **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
21-124	4755 34	Dec 30, 2006
21-124	5687849	Oct 28, 2014
21-124	6126314	May 18, 2012
20-980	4755 34	Dec 30, 2006

SIGNED [signature] DATE 12/4/06

(Last revised Jan 11, 2005)

See page 2

Terbinafine Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020846	001	4755534	DEC 30 2006			U-445
020846	001	5681849	OCT 28 2014		Y	
020846	001	5856355	MAY 18 2012		Y	U-540
020846	001	5856355	MAY 18 2012		Y	U-502
020846	001	5856355	MAY 18 2012		Y	U-504
020846	001	6005001	MAY 18 2012		Y	U-540
020846	001	6005001	MAY 18 2012		Y	U-504
020846	001	6005001	MAY 18 2012		Y	U-502
020846	001	6121314	MAY 18 2012		Y	U-504
020846	001	6121314	MAY 18 2012		Y	U-502
020846	001	6121314	MAY 18 2012		Y	U-540

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020749	001	4755534	DEC 30 2006			
020749	001	6121314	MAY 18 2012			U-502

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020539	001	4755534	DEC 30 2006			U-73

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/s/

John Jenkins
12/11/2006 09:29:52 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-071

Novartis Pharmaceuticals Corporation
Attention: Sheila A. Mathias, MBA, Ph.D.
Sr. Associate Director
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Mathias:

Please refer to your September 8, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamisil ® (terbinafine hydrochloride) mini-Tablets, 125 mg and 187.5 mg.

We also refer to your submissions dated November 2 and 8, 2006.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 7, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue. The information submitted with respect to color vision and visual field testing appears to be incomplete and some of the testing requested in the pediatric written request letter does not appear to have been performed. Specific details of the additional information needed were included in the fax sent to you on November 10, 2006.

We are providing the above comment to give you preliminary notice of a potential review issue. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We reiterate our request in the fax dated November 10, 2006 that you submit the following information:

Clinical:

Color vision testing

1. Specify which color vision test was done for each patient.

2. Explain why the number of symbols shown is not constant for all patients.

3. Address our concern that the following explanation that you provided for the missing number of symbols correct/total is incorrect.

> Color vision - the number of symbols correct/total shown will be blank if the method used is Roth 28 or not done. The Roth 28 test is evaluated utilizing the instructions developed by the manufacturer. The test was interpreted by assessing the diagram of the sequence of discs (refer to the Roth 28 instructions). Since 1 misplaced color can cause 2 discs to be misread, it is not possible to record accurately the number of symbols correct.

We believe that your explanation is incorrect because the following patients are all eleven and twelve year olds who should have had a Roth 28 or 40 test, which would have established a "blank" if the above explanation is correct. However, there are symbols shown/seen recorded for them which seems to contradict the statement above. Please clarify.

CSFO327C2302_0351_00005
CSFO327C2301_0513_00004
CSFO327C2301_0556_00009
CSFO327C2302_0113_00005
CSFO327C2302_0157_00004
CSFO327C2301_0302_00011
CSFO327C2301_0404_00005
CSFO327C2301_0402_00017
CSFO327C2301_0402_00019
CSFO327C2301_0405_00002
CSFO327C2301_0517_00019
CSFO327C2301_0310_00006
CSFO327C2302_0106_00006
CSFO327C2302_0131_00003
CSFO327C2302_0131_00013
CSFO327C2301_0401_00001
CSFO327C2302_0355_00001
CSFO327C2301_0506_00003
CSFO327C2301_0513_00002
CSFO327C2301_0513_00010
CSFO327C2301_0525_00006
CSFO327C2302_0103_00010
CSFO327C2302_0253_00005
CSFO327C2301_0702_00014
CSFO327C2302_0503_00012
CSFO327C2301_0302_00005
CSFO327C2301_0302_00007
CSFO327C2301_0303_00001
CSFO327C2301_0403_00006

CSFO327C2301_0517_00012
CSFO327C2302_0401_00002
CSFO327C2302_0401_00029
CSFO327C2302_0401_00036
CSFO327C2302_0601_00007
CSFO327C2301_0301_00011
CSFO327C2301_0303_00010
CSFO327C2301_0402_00022
CSFO327C2301_0405_00017
CSFO327C2301_0405_00025
CSFO327C2301_0511_00003
CSFO327C2301_0551_00005
CSFO327C2301_0803_00019
CSFO327C2302_0355_00026
CSFO327C2302_0355_00028
CSFO327C2302_0502_00032
CSFO327C2302_0123_00016
CSFO327C2302_0310_00006

4. Roth 28 or 40 hue test results should include the area derived from the confused caps. Provide these results.

Visual field testing

1. In the 18-19% of patients for whom visual field testing was recorded as "not done," explain why the testing was not done.

2. Provide the mean threshold value for all patients. If a threshold value cannot be provided, explain why a perimeter was used that cannot provide the threshold value.

We also request that you submit the following information:

Chemistry:

1. The appropriate dosage form name for the proposed product is under review. Provide drug product samples (6 units for each packaging size) for nomenclature evaluation.

Respond only to the above requests for additional 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.

If you have any questions, please call Kalyani Bhatt, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

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

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/s/

Susan Walker
11/20/2006 05:19:37 PM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Fran LeSane, Supervisory Project Manager, DAIDP-HFD-520/Fred Marsik, Micro TL

FROM: Kalyani Bhatt, Project Manager
Dermatological and Dental Drug Products

DATE:	IND NO.	NDA NO.	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
October 24, 2006				September 8, 2006

NAME OF DRUG:	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Lamasil Mini Tablets			Aptril 1, 2006

NAME OF FIRM: Novartis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY

☐ PRE–NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
X Electronic NDA
☐ CONTROL SUPPLEMENT

☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☐ OTHER *(SPECIFY BELOW)*: SM

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILTY STUDIES
☐ PHASE IV STUDIES

☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS Please review the micro content of the electronic NDA . If you have questions, please call Kalyani Bhatt 6-0852.

SIGNATURE OF REQUESTER Kalyani Bhatt, Project Manager	METHOD OF DELIVERY (Check one) ☐ MAIL ☐X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Kalyani Bhatt
11/14/2006 04:55:20 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: November 14, 2006

To: Sheila A. Mathias, Ph.D. Senior Associate Director	From: Kalyani Bhatt, Regulatory Project Manager
Company: Novartis Pharmaceutical Corp	Division of Dermatologic and Dental Products
Fax number: (973)-781-2565	Fax number: 301-796-9894
Phone number: (862)-778-0847	Phone number: 301-796-2110

Subject: NDA 22-071/ Lamisil (terbinafine hydrochloride)

Total no. of pages including cover: 2

Comments:

Please see the following Clinical Pharmacology & Biopharmaceutics Information Request

Document to be mailed: ☐ YES ☐ NO

Thank you.

Clinical Pharmacology Comment:
Please submit or direct us to the location of the following datasets to support the population analysis (RANVR050-051):

All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

- Model codes or control streams and output listings should be provided for all major model building steps, e.g.,

base structural model, covariates models, final model, and validation model. These files should be submitted as

ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

- A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

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/s/

Kalyani Bhatt
11/14/2006 10:41:35 AM
CSO

See My e-mail

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: November 9, 2006

To: Shelia Methias or Eric A. Floyd	**From:** Vickey Lutwak VL For Kalyani Bhatt
Company: Novartis Pharmaceuticals Corp	Division of Dermatology and Dental Products
Fax number: 973-781-2565	**Fax number:** (301) 796-9895
Phone number: 862-778-0847	**Phone number:** (301) 796-2445

Subject: NDA 22-071

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

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NDA 20-071

Please refer to your NDA 20-071 for Lamisil (terbinafine hydrochloride) Mini-tablets dated September 8, 2006 and received September 8, 2006.

We have the following request for information:

Color vision testing

1. Specify which color vision test was done for each patient.
2. Explain why the number of symbols shown is not constant for all patients.
3. The ophthalmology reviewer is concerned that the following statement is incorrect (see below); please address.

color vision - the number of symbols correct/total shown will be blank if the method used is Roth 28 or not done. The Roth-28 test is evaluated utilizing the instructions developed by the manufacturer. The test was interpreted by assessing the diagram of the sequence of discs (refer to the Roth 28 instructions). Since 1 misplaced color can cause 2 discs to be misread, it is not possible to record accurately the number of symbols correct.

These patients for example are all eleven and twelve year olds who should have had a Roth 28 or 40 test, yet there are Letters shown/seen recorded for them:

CSFO327C2302_0351_00005
CSFO327C2301_0513_00004
CSFO327C2301_0556_00009
CSFO327C2302_0113_00005
CSFO327C2302_0157_00004
CSFO327C2301_0302_00011
CSFO327C2301_0404_00005
CSFO327C2301_0402_00017
CSFO327C2301_0402_00019
CSFO327C2301_0405_00002
CSFO327C2301_0517_00019
CSFO327C2301_0310_00006
CSFO327C2302_0106_00006
CSFO327C2302_0131_00003
CSFO327C2302_0131_00013
CSFO327C2301_0401_00001
CSFO327C2302_0355_00001
CSFO327C2301_0506_00003
CSFO327C2301_0513_00002
CSFO327C2301_0513_00010
CSFO327C2301_0525_00006
CSFO327C2302_0103_00010
CSFO327C2302_0253_00005
CSFO327C2301_0702_00014
CSFO327C2302_0503_00012

CSFO327C2301_0302_00005
CSFO327C2301_0302_00007
CSFO327C2301_0303_00001
CSFO327C2301_0403_00006
CSFO327C2301_0517_0001
CSFO327C2302_0401_00002
CSFO327C2302_0401_00029
CSFO327C2302_0401_00036
CSFO327C2302_0601_00007
CSFO327C2301_0301_00011
CSFO327C2301_0303_00010
CSFO327C2301_0402_00022
CSFO327C2301_0405_00017
CSFO327C2301_0405_00025
CSFO327C2301_0511_00003
CSFO327C2301_0551_00005
CSFO327C2301_0803_00019
CSFO327C2302_0355_00026
CSFO327C2302_0355_00028
CSFO327C2302_0502_00032
CSFO327C2302_0123_00016
CSFO327C2302_0310_00006

4. Roth 28 or 40 hue test results should include the area derived from the confused caps. This should be reported.

Visual field testing

1. In the 18-19% of patients for whom visual field testing was recorded as "not done," please explain why the testing was not done.
2. Provide the mean threshold value for all patients. If a threshold value cannot be provided, please explain why a perimeter was used that cannot provide the threshold value.

The above information needs to be received by 22 Nov 06.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-071

Novartis
Attention: Sheila A. Mathias, Ph.D.
Senior Associate Director
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Mathias:

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

Name of Drug Product: Lamisil (terbinafine hydrochloride) Mini-tablets

Review Priority Classification: S

Date of Application: September 8, 2006

Date of Receipt: September 8, 2006

Our Reference Number: NDA 22-071

The application will be filed on November 7, 2006, in accordance with 21 CFR 314.101(a). The user fee goal date will be July 8, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

Center for Drug Evaluation and Research
Division of Dermatology & Dental Products
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Kalyani Bhatt, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Supervisor, Project Management
Division of Dermatology & Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Mary Jean Kozma Fornaro
9/20/2006 08:51:16 AM

22-071

Brown, Patricia C (ODEIII)

From: Lindstrom, Jill
Sent: Thursday, November 09, 2006 9:36 AM
To: Bhatt, Kalyani
Cc: Brown, Patricia C (ODEIII); Chambers, Wiley A; Lutwak, Victoria; Kober, Margaret
Subject: RE: Information request to Novartis re ophthalmology tests done in support of PWR Lamisil mini-tabs, NDA 22-071

Hi Kalyani,

Please revise yesterday's request as follows (revisions in red):

Color vision testing

1. Specify which color vision test was done for each patient.
2. Explain why the number of symbols shown is not constant for all patients.
3. The ophthalmology reviewer is concerned that the following statement is incorrect (see below); please address.

color vision - the number of symbols correct/total shown will be blank if the method used is Roth 28 or not done. The Roth-28 test is evaluated utilizing the instructions developed by the manufacturer. The test was interpreted by assessing the diagram of the sequence of discs (refer to the Roth 28 instructions). Since 1 misplaced color can cause 2 discs to be misread, it is not possible to record accurately the number of symbols correct.

These patients for example are all eleven and twelve year olds who should have had a Roth 28 or 40 test, yet there are Letters shown/seen recorded for them:

CSFO327C2302_0351_00005
CSFO327C2301_0513_00004
CSFO327C2301_0556_00009
CSFO327C2302_0113_00005
CSFO327C2302_0157_00004
CSFO327C2301_0302_00011
CSFO327C2301_0404_00005
CSFO327C2301_0402_00017
CSFO327C2301_0402_00019
CSFO327C2301_0405_00002
CSFO327C2301_0517_00019
CSFO327C2301_0310_00006
CSFO327C2302_0106_00006
CSFO327C2302_0131_00003
CSFO327C2302_0131_00013
CSFO327C2301_0401_00001
CSFO327C2302_0355_00001
CSFO327C2301_0506_00003
CSFO327C2301_0513_00002
CSFO327C2301_0513_00010
CSFO327C2301_0525_00006
CSFO327C2302_0103_00010
CSFO327C2302_0253_00005
CSFO327C2301_0702_00014
CSFO327C2302_0503_00012
CSFO327C2301_0302_00005
CSFO327C2301_0302_00007
CSFO327C2301_0303_00001
CSFO327C2301_0403_00006
CSFO327C2301_0517_00012
CSFO327C2302_0401_00002
CSFO327C2302_0401_00029

CSFO327C2302_0401_00036
CSFO327C2302_0601_00007
CSFO327C2301_0301_00011
CSFO327C2301_0303_00010
CSFO327C2301_0402_00022
CSFO327C2301_0405_00017
CSFO327C2301_0405_00025
CSFO327C2301_0511_00003
CSFO327C2301_0551_00005
CSFO327C2301_0803_00019
CSFO327C2302_0355_00026
CSFO327C2302_0355_00028
CSFO327C2302_0502_00032
CSFO327C2302_0123_00016
CSFO327C2302_0310_00006

4. Roth 28 or 40 hue test results should include the area derived from the confused caps. This should be reported.

Visual field testing

1. In the 18-19% of patients for whom visual field testing was recorded as "not done," please explain why the testing was not done.
2. Provide the mean threshold value for all patients. If a threshold value cannot be provided, please explain why a perimeter was used that cannot provide the threshold value.

The above information needs to be received by 22 Nov 06.

Please send out this information request today, as we need to receive a response NLT 11/22.

Many thanks,

Jill

From: Chambers, Wiley A
Sent: Thursday, November 09, 2006 9:00 AM
To: Lindstrom, Jill; Bhatt, Kalyani
Cc: Brown, Patricia C (ODEIII)
Subject: RE: Information request to Novartis re ophthalmology tests done in support of PWR Lamisil mini-tabs, NDA 22-071

The other thing we need to tell them, particularly since we do not want them to make the same mistake twice is that I believe that the following statement, submitted in their November 2 response is incorrect:

color vision - the number of symbols correct/total shown will be blank if the method used is Roth 28 or not done. The Roth-28 test is evaluated utilizing the instructions developed by the manufacturer. The test was interpreted by assessing the diagram of the sequence of discs (refer to the Roth 28 instructions). Since 1 misplaced color can cause 2 discs to be misread, it is not possible to record accurately the number of symbols correct.

These patients for example are all eleven and twelve year olds who should have had a Roth 28 or 40 test, yet there are Letters shown/seen recorded for them:

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CSFO327C2302_0157_00004
CSFO327C2301_0302_00011
CSFO327C2301_0404_00005
CSFO327C2301_0402_00017
CSFO327C2301_0402_00019

CSFO327C2301_0405_00002
CSFO327C2301_0517_00019
CSFO327C2301_0310_00006
CSFO327C2302_0106_00006
CSFO327C2302_0131_00003
CSFO327C2302_0131_00013
CSFO327C2301_0401_00001
CSFO327C2302_0355_00001
CSFO327C2301_0506_00003
CSFO327C2301_0513_00002
CSFO327C2301_0513_00010
CSFO327C2301_0525_00006
CSFO327C2302_0103_00010
CSFO327C2302_0253_00005
CSFO327C2301_0702_00014
CSFO327C2302_0503_00012
CSFO327C2301_0302_00005
CSFO327C2301_0302_00007
CSFO327C2301_0303_00001
CSFO327C2301_0403_00006
CSFO327C2301_0517_00012
CSFO327C2302_0401_00002
CSFO327C2302_0401_00029
CSFO327C2302_0401_00036
CSFO327C2302_0601_00007
CSFO327C2301_0301_00011
CSFO327C2301_0303_00010
CSFO327C2301_0402_00022
CSFO327C2301_0405_00017
CSFO327C2301_0405_00025
CSFO327C2301_0511_00003
CSFO327C2301_0551_00005
CSFO327C2301_0803_00019
CSFO327C2302_0355_00026
CSFO327C2302_0355_00028
CSFO327C2302_0502_00032
CSFO327C2302_0123_00016
CSFO327C2302_0310_00006

Roth 28 or 40 hue test results should include the area derived from the confused caps. This should be reported.

Wiley

From: Lindstrom, Jill
Sent: Wednesday, November 08, 2006 5:10 PM
To: Bhatt, Kalyani
Cc: Brown, Patricia C (ODEIII); Chambers, Wiley A
Subject: RE: Information request to Novartis re ophthalmology tests done in support of PWR Lamisil mini-tabs, NDA 22-071

Hi Kalyani,

Target timeline from Ped Ex Bd meeting today: information request should go out by tomorrow (Thurs); we need to receive this information from sponsor by 11/22, Div and Ophthal need to send a response to PedEx Bd by 11/29, and they will make a decision by 12/1, and issue letter 12/7.

Thanks,

Jill

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

/s/

Victoria Lutwak
11/9/2006 01:47:52 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Fran LeSane, Supervisory Project Manager, DAIDP-HFD-520/Fred Marsik, Micro TL

FROM: Kalyani Bhatt, Project Manager
Dermatological and Dental Drug Products

DATE:	IND NO.	NDA NO.	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
October 24, 2006				September 8, 2006

NAME OF DRUG:	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Lamasil Mini Tablets			Aptril 1, 2006

NAME OF FIRM: Novartis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY

☐ PRE–NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
X Electronic NDA
☐ CONTROL SUPPLEMENT

☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☐ OTHER *(SPECIFY BELOW)*: SM

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILTY STUDIES
☐ PHASE IV STUDIES

☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS Please review the micro content of the electronic NDA . If you have questions, please call Kalyani Bhatt 6-0852.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Kalyani Bhatt, Project Manager	☐ MAIL ☐X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Kalyani Bhatt
10/24/2006 12:07:49 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: October 23, 2006

To: Sheila A. Mathias, Ph.D. Senior Associate Director	From: Kalyani Bhatt, Regulatory Project Manager
Company: Novartis Pharmaceutical Corp	Division of Dermatologic and Dental Products
Fax number: (973)-781-2565	Fax number: 301-796-9894
Phone number: (862)-778-0847	Phone number: 301-796-2110

Subject: NDA 22-071/ Lamisil (terbinafine hydrochloride)

Total no. of pages including cover: 2

Comments:

Please see the following Ophthalmology Information Request

Document to be mailed: ☐ YES ☐ NO

Thank you.

Please see the following information request:

Please submit corrected and complete dataset.

Please note that the submitted ophthalmology line listing are not complete and contain numerous errors. Many of the columns have blanks instead of the appropriate value. For example, test values may include normal, abnormal (clinically significant or insignificant) or not done. They should not include blanks. The number of letters seen or presented is often missing for visual acuity lines. Approximately 8% of follow-up visits are blank.

Additional evaluation errors include, but are not limited to:

Patient 1, Site 152, Study 2302 has an abnormal color vision on follow-up in each eye. The assessment is "Unchanged" for each eye. The patient evaluation is "Improved" and the final status for the eyes is "Normal."
Patient 18, Site 601, Study 2302 has an abnormal color vision in each eye and is listed as normal.
Patient 24, Site 601, Study 2302 has an abnormal color vision in one eye, abnormal dilated fundus, abnormal visual field and is listed as normal.
Patient 3, Site 101, Study 2302 has an abnormal visual acuity in each eye and is listed as normal.
Patient 13, Site 133, Study 2302 has an abnormal color vision in each eye and is listed as normal.
Patient 1, Site 152, Study 2302 has an abnormal color vision in each eye and is listed as normal.

Additional inconsistencies include variability in the number of letters seen on visual acuity chart yet the visual acuity score is the same. An explanation should be provided.

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

NOVARTIS PHARMACEUTICALS CORP
Angie Young
One Health Plaza
East Hanover NJ 07936
US

2. TELEPHONE NUMBER
862-778-8685

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

22-071

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
Lamisil (terbinafine hydrochloride)

6. USER FEE I.D. NUMBER
PD3006650

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
M. Mitchell	Sr VP ORA	8/1/06

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$767,400.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	October 24, 2005
TIME:	1:00 P.M.
LOCATION:	White Oak building 22, room #1379
APPLICATION:	IND 57,093
DRUG NAME:	Lamisil® (terbinafine HCL) Minitablets
TYPE OF MEETING:	Pre-NDA meeting
MEETING CHAIR:	Stanka Kukich, M.D./Acting Division Director, DDDP
MEETING RECORDER:	Felecia Curtis/Regulatory Management Officer, DDDP

FDA ATTENDEES:

Division of Dermatology and Dental Products
Stanka Kukich, M.D./Acting Division Director, DDDP
Ramesh Sood, Ph.D./Branch Chief, Chemistry, ONDQA
Ernest Pappas, Chemistry Reviewer, ONDQA
Abimbola Adebowale, Ph.D./Pharmacology Reviewer, DDDP
Jill Lindstrom, M.D., Ph.D. / Acting Deputy Director, DDDP
Steve Thomson, Ph.D. / Biostatistics Reviewer, DBIII
Wiley Chambers, M.D., / Deputy Division Director, DAIOP
Felecia Curtis/Regulatory Management Officer, DDDP

EXTERNAL CONSTITUENT ATTENDEES:

Novartis Corporation

Rajesh Bakshi, MD	Clinical Research
Marie Bernasconi, Ph.D.	Project Management
Angela Browne, PharmD	Drug Regulatory Affairs
Bin Cai, MD, MS, MPH	Biostatistics
Emmanuel Faure, PharmD	Drug Regulatory Affairs
Eric Floyd, Ph.D.	Drug Regulatory Affairs
Chin Koerner	Drug Regulatory Affairs, Liaison Office
Friedrich Karl Mayer, Ph.D.	Project Management
Judit Nyirady, MD	Clinical Research
Orin Tempkin, Ph.D.	Drug Regulatory Affairs, CMC
Linda Ann Wraith, MBA	Clinical Research

MEETING OBJECTIVES:

To provide general guidance on the content and format of the proposed new Investigational New Drug Application under 21CFR 312. The pre-meeting briefing document (submitted September 22, 2005) provides background and questions (page 7-19) for discussion.

Chemistry, Manufacturing and Controls:

Reference is made to the Agency's End of Phase 2 meeting minutes dated November 13, 2000, regarding CMC comments, whereby additional CMC information was requested on the Drug Substance and Drug Product. In this regard, the Pre-NDA package did not address these CMC requests. Therefore, the applicant is asked if they have addressed the CMC requests of November 13, 2000.

Regarding CMC Questions for Pediatric Exclusivity Determination:

Sponsor's Question #4:

Does the Agency agree with the proposed level of CMC content for a pediatric exclusivity submission?

Agency's Response:

No; the sponsor's proposal to submit full CMC information at a later date is not acceptable. In this regard, full CMC information should be submitted at the time of the initial filing of the NDA.

Sponsor's Question #5:

Does the Agency agree with the content and format proposed for the Quality Overall Summary and Quality Module (CTD sections 2.3 and Module 3)?

Agency's Response:

Yes; the applicant's proposal for the standard CTD format as listed under Appendix 2 is acceptable. In addition, the CMC information as listed under items (a), (b) and (c) was found acceptable.

Sponsor's Question #6: Supporting documentation for ——— excipient: b(4)

Novartis proposes the CMC documentation outlined below in the NDA to support the use of basic butylated methacrylate copolyme ——— a non-(USP/NF)-compendial but non-novel excipient. Is this acceptable? b(4)

Agency's Response:

Yes; the use of ——— excipient is acceptable. However, a particle size specification should be submitted of ——— and how it is controlled. In addition, please submit information on how ——— is manufactured starting from ——— b(4)

Sponsor's Question #7: Selection of executed production records for the NDA

Novartis proposes to provide the executed production records and analytical data outlined below in the NDA. Is this acceptable to the Agency?

Agency's Response:

Yes; the applicant's proposal to provide the proposed executed production records and analytical data to support the batch records is acceptable.

Sponsor's Question #8: Stability data to support site and scale of commercial ——— filling

Novartis proposes to provide the data below to support the site and scale of commercial ——— filling. Is this acceptable to the Agency?

Agency's Response:

No. The post approval stability commitment should include placing ——— ommercial production batches of each strength under accelerated and long-term storage conditions.

Sponsor's Question #9: Analytical method for dissolution

Novartis proposes the attached method for dissolution of Lamisil Minitablets in ——— s this acceptable to the Agency?

Agency's Response:

The adequacy of the dissolution method will be determined during the review of the NDA. Please submit data related to the development of the dissolution method in the NDA including justification for the choice of media and rotation speed.

The sponsor agreed to submit the CMC information as requested under the Draft Reviewer's Comments of October 24, 2005.

The sponsor indicated that they did not ignore the CMC request after the November 13, 2000 EOP-2 meeting. Some of the points from the EOP-2 meeting may not be relevant as the dosage form since that meeting has changed. However the remaining relevant CMC comments from that meeting will be answered.

The sponsor agrees with the Agency's responses to the CMC questions.

Pharmacology/Toxicology:

Sponsor's Question #10:

To fulfill the nonclinical request listed in the PWR, Novartis will provide the final study report to the juvenile animal study 0470001. Does the Agency agree?

Agency's Response:

Submission of the final study report for the 52 week oral juvenile dog toxicology study with the NDA submission is acceptable and the adequacy of this study will be determined after review of the final study report. Whether this final study report will fulfill the nonclinical request listed in the PWR will be determined by the Pediatric Exclusivity Board.

Sponsor's Question #11:

Does the Agency agree with the content and format proposed for the Nonclinical Overview (CTD section 2.4) and Nonclinical Written and Tabulated Summaries (CTD sections 2.6.2 to 2.6.7)?

Agency's Response:

It is acceptable to cross reference NDA 20-539 and not re-submit nonclinical study reports that have been previously provided to the agency. However, it is not acceptable to only provide a cross reference to NDA 20-539 in the Nonclinical Overview (CTD section 2.4) and Nonclinical Written and Tabulated Summaries (CTD sections 2.6.2 to 2.6.7) sections of the NDA submission. It is recommended that the sponsor provide appropriate summary information and summary tables in the CTD format for the pivotal nonclinical toxicology studies to support the safety of oral terbinafine hydrochloride in the NDA submission.

The sponsor agrees with the Agency's responses to the Pharmacology/Toxicology questions.

Clinical Pharmacology/ Biopharmaceutics:

Sponsor Question #15:

Does the Agency agree with the content and format proposed for the Summary of Biopharmaceutic Studies and Associated Analytical Methods (CTD section 2.7.1) and Summary of Clinical Pharmacology Studies (CTD section 2.7.2)?

Agency's Response:

The content and format proposed for the summary sections is acceptable.

In addition, datasets for each pivotal Clinical Pharmacology and Biopharmaceutics (CPB) study that will be submitted in this NDA should be provided in electronic format as SAS transport files.

The sponsor agrees with the Agency's responses to the Clinical Pharmacology/ Biopharmaceutics questions.

Clinical Microbiology:

1. The clinical microbiology datasets from the two pivotal clinical trials C2301 and C2302 should be provided in the format shown below:

Study no.	Subject ID	MITT or PP	Treatment group	KOH results	Pathogen	Visit	Clinical outcome at TOC	Mycological outcome at TOC

MITT = modified intent to treat population
PP = per protocol population
TOC = test of cure visit.

2. The protocol summaries for the 2 pivotal clinical studies do not indicate if information on *in vitro* susceptibility of clinical isolates to terbinafine were collected. If information on *in vitro* susceptibility is available, the minimum inhibitory concentration data for each isolate per patient should also be included in the same dataset.

The sponsor agrees with the Agency's Clinical Microbiology comments.

Clinical:

Sponsor's Question #1:

Novartis proposes to submit the reports outlined in the Pediatric Written Request (PWR) on or before October 1, 2006 to qualify for pediatric exclusivity extension under Section 505A of the FDA Food, Drug and Cosmetic Act. Does the Agency agree with the content and format proposed?

Agency's Response:

By the sponsor's description of the proposed content of the NDA submission, it appears that such a submission would only be potentially fileable.
It was again discussed that the sponsor needs to submit a complete NDA, and in addition, submit all study reports as outlined in the Pediatric Written Request.

The Pediatric Exclusivity Board, not the Division, will determine whether the sponsor has fulfilled the requirements of the Pediatric Written Request.

Sponsor's Question #2:

The NDA will be compiled as a Common Technical Document in electronic format. A draft sample of the proposed index can be found in Appendix 2. Does the Agency agree with the content and format proposed?

Agency's Response:

Accurate hotlinks are needed to all relevant information within the submission, as per relevant guidances.

Please provide integrated summaries of safety and efficacy and overall summary of risk vs. benefit in module 2.

Sponsor's Question #3:

Novartis proposes to present Lamisil Minitablets in a separate PI from Lamisil Tablets and to include the relevant safety information from the Lamisil Tablets PI to the Lamisil Minitablets PI. Does the Agency agree with this proposal?

Agency's Response:

The rationale for separate PIs is not clear; a single package insert for Lamisil Tablets and Lamisil Minitablets is preferred. The draft package insert and patient package insert should also be provided in MS Word format.

sponsor questions 4, 5, 6, 7, 8, and 9 are for Chemistry, Manufacturing and Controls (see above)
sponsor questions 10, and 11 are for Pharmacology/Toxicology (see above)

Sponsor's Question #12:

Novartis will provide safety data on 'at least 300 children per study completing the course of terbinafine treatment at the to-be-marketed dose or higher' which is defined as patients who had taken >=80% of total dosing accounting for both dose and duration. Does the Agency agree?

Agency's Response:

Safety data should be derived from all study patients who received at least one dose of study drug. Per patient line listings should be provided for all reports of serious adverse events in addition to the case reports, and for any AEs not in the labeling for Lamisil tablets.

Per patient line listings should be provided for all reports of serious adverse events. In addition, the case report forms of patients who died, experienced serious adverse events, or who discontinued the study for any reason should be submitted for all studies conducted in support of this NDA.

Sponsor's Question #13:

Post-treatment changes in visual acuity, visual field, color vision and fundoscopic findings will be compared to baseline and analyzed based on the examining ophthalmologist's opinion as to their clinical significance. Does the Agency agree?"

Agency's Response:

The ophthalmology comments from the June 24, 2005, letter are unchanged. The proposal to have the examining ophthalmologist to decide whether a visual field defect or a missed plate is clinically significant is not acceptable.

Any visual field defect that did not exist at baseline should be considered clinically significant. False positives and false negatives are monitored by the perimeter, and a score for false positives and false negatives is provided in the standard results of the test. If the number of false positives and false negatives is too high, the test is not reliable and should be repeated. If the test is judged to be reliable, any visual field defect that did not exist at baseline should be considered clinically significant. This is particularly true since there is a known learning curve with perimetry.

Any missed number on any plate in the SPP2 test should be considered significant. There is a known learning curve with the SPP2 testing methodology. The bias is toward fewer errors during subsequent tests. Any missed number on any plate in the SPP2 test should be considered significant.

Regarding Table 2-1, the alternative tests used may not be comparable with the protocol-required tests requested in the PWR. The color vision alternative tests either do not make sense or are not equivalent, and therefore are not acceptable. It is not recommended that Novartis deviate from the PWR.

A copy of the Ophthalmology Manual should be included in the NDA

Sponsor's Question #14:

Novartis proposes to submit the DSMC (Data Safety Monitoring Committee) charter and DSMC official meeting reports in Appendix 16.1.4 of the clinical study reports. Does the Agency agree?

Agency's Response:

Yes. Please provide a narrative describing the implementation of any recommendations that the DSMC might have made during the study.

Sponsor's Question #16:

The content of the proposed Summary of Clinical Efficacy (CTD section 2.7.3) will be based on the proposed statistical methodology in Appendix 4 and table shells in Appendix 5. Does the Agency agree?

Agency's Response:

The primary efficacy population should be the MITT with LOCF. The primary efficacy variable should be complete cure. The efficacy results should be reported for each study. In addition, the data from both studies could be combined in a separate analysis.

Efficacy at week-3 and week-6, not pre-specified in the protocol, would not be appropriate primary efficacy variables, and would have little regulatory utility. However, the analysis of these might produce interesting data.

The Per-Protocol population should include patients who had very good compliance with treatment (at least 80% of doses, page 58), as opposed to the proposed "at least one-week of treatment" (page 57).

Please supply a summary of patients who were protocol violators for each of the following:

-wrong study treatment was dispensed during the whole study.
-wrong dose of study drug was dispensed during the whole study
-study drug was switched to a different arm for more than 50% during the trial.

The applicability to the US of study data from subjects demographically different from the US population will be a review issue (e.g. causative organism, personal grooming).

A list of subjects discontinued for administrative reasons should be provided, and the reason for each administrative reason should be properly coded and clearly described.

Please report MICs on dermatophyte isolates recovered during the study.

The Biostatistical plan should agree with the pre-specified plan for primary analysis (please see Biostatistics additional comments below).

Sponsor's Question #17:

Novartis proposes to submit a Summary of Clinical Safety (CTD section 2.7.4), which captures all the safety information and analyses normally contained in a conventional Integrated Summary of Safety (ISS). Does the Agency agree with the proposal?

Agency's Response:

The safety results should be presented separately for each study. A comprehensive analysis of safety should also be provided.

Sponsor's Question #18:

Novartis will provide SAS datasets of efficacy and safety for each pivotal study. Instructions on pooling the data for the summary of efficacy and safety will also be provided. The inferential efficacy programs for the primary efficacy variable will be provided during review only upon request. Is this acceptable to the Agency?

Agency's Response:

The sponsor should submit line listings in an additional format with column headers as follows: Subject number, a column for each visit, with subheadings (also arranged in a columnar fashion) for each of the following:

- KOH result
- Culture result by species
- Signs & Symptoms
- Doses administered
- Subjects' weight
- Subjects age
- Treatment administered
- Concurrent treatments, both OTC and prescription.
- *Laboratory tests*
- Visual test conducted.

The sponsor should provide site-breakdown of the data from the two pivotal multi-center studies.

It is recommended that the sponsor provide efficacy and safety subset analysis for each of the following populations in their studies:

- Racial background
- Age Groups (4-7 and 8-12 for safety)

- Gender

Sponsor's Question #19:

Novartis proposes to provide an electronic representation of the CRF and SAE narratives that are relevant to the proposed population and indication as described below. Novartis also proposes to provide patient profiles during review upon request. Is this acceptable to the Agency?"

Agency's Response:

Please also include CRF and SAE narratives for patients who discontinue from the trial. Please include narratives for patients experiencing adverse events not already described in labeling for Lamisil tablets, regardless of severity.

Additional Agency Comments:

Please provide a copy of any materials used in the training of participating investigators, their assessment and the results of such assessment.

PDF documents should not be editable rather than image

Biostatistics:

Sponsor's Question #16:

The content of the proposed Summary of Clinical Efficacy (CTD section 2.7.3) will be based on the proposed statistical methodology in Appendix 4 and table shells in Appendix 5. Does the Agency agree?

Agency's Response:

The statistical methodology should be acceptable and does seem to fit that requested in the Pediatric Written Request.

Sponsor's Question #17:

Novartis proposes to submit a Summary of Clinical Safety (CTD section 2.7.4), which captures all the safety information and analyses normally contained in a conventional Integrated Summary of Safety (ISS). Does the Agency agree with the proposal?

Agency's Response:

From a statistical perspective, this seems to be acceptable.

The sponsor agrees with the Agency's responses to the Biostatistics questions.

Sponsor's Question #18:

Novartis will provide SAS datasets of efficacy and safety for each pivotal study. Instructions on pooling the data for the summary of efficacy and safety will also be provided. The inferential efficacy programs for the primary efficacy variable will be provided during review only upon request. Is this acceptable to the Agency?

Agency's Response:

Annotated case report forms noting the source of variables in the SAS data sets and descriptions of derived variables can be very helpful when analyzing the data. Either SAS data sets or SAS transport data sets are requested for the review of this application.

The sponsor agrees with the Agency's responses to the Biostatistics questions.

Administrative Comments

1. The Agency and the sponsor agree to have a follow-up telecon to further discuss issues related to Ophthalmology.

2. For applications submitted after February 2, 1999, the applicant is required to either certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

3. Comments shared with you 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 the information submitted to the IND might identify additional comments or informational requests.

4. The sponsor is reminded of the Pediatric Research Equity Act of 2003, which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

5. The sponsor is reminded to please submit appropriate patent certification at the time of NDA submission.

Attach: sponsor handout of table entitled, "Patients tested with PWR-specified Visual Acuity and Color Vision Tests as of October 21st 2005"

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

/s/

Stanka Kukich
11/22/2005 06:08:06 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 22-071	Efficacy Supplement Type SE- N/A	Supplement Number N/A	
Drug: LAMISIL (terbinafine hydrochloride) Oral Granules(125 mg/packet and 18.5 mg/packet)		Applicant: Novartis Pharmaceuticals	
RPM: Kalyani Bhatt		HFD-540	Phone # 301-7969-0852

Application Type: **(x)** 505(b)(1) **( )** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **( )** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	**(X)** Standard **( )** Priority
• Chem class (NDAs only)	3S
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	September 26, 2007
❖ Special programs (indicate all that apply)	**(X)** None Subpart H **( )** 21 CFR 314.510 (accelerated approval) **( )** 21 CFR 314.520 (restricted distribution) **( )** Fast Track **( )** Rolling Review **( )** CMA Pilot 1 **( )** CMA Pilot 2
❖ User Fee Information	
• User Fee	**(X)** Paid UF ID number **3006650**
• User Fee waiver	**( )** Small business **( )** Public health **( )** Barrier-to-Innovation **( )** Other (specify) N/A
• User Fee exception	**( )** Orphan designation **( )** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) **( )** Other (specify) N/A
❖ Application Integrity Policy (AIP)	

• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• 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.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III 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).	**N/A**
• [505(b)(2) applications] For each paragraph IV 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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) **N/A** (no paragraph IV certification) ( ) 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? (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)? *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 box below (Exclusivity).* *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 ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the 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)? *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 box below (Exclusivity).* *If "**No,**" continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the 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). *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 box below (Exclusivity).* *If "**Yes,**" a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *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.*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (X) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Yes
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	09-08-06
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC(05-09-07); DMETS (6-13-07)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Yes 9-17-07
• Applicant proposed	09-08-06
• Reviews	Medical Review for Label 9-24-07
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	July 23, 2001
• Pre-NDA meeting (indicate date)	November 11, 2005
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Team Leader Review 9/24/07
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	MO 6/29/07/
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Page 104 in Clinical Review: No New Clinical Information
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	9/24/07
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	09/10/07
❖ Biopharmaceutical review(s) *(indicate date for each review)*	05/15/07
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	No DSI inspection
• Bioequivalence studies	No DSI inspection
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	06/13/07
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	06/05/07
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (X) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	04/13/07
❖ Nonclinical inspection review summary	No
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	No
❖ CAC/ECAC report	No

Appendix A to NDA/Efficacy Supplement Action Package Checklist

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

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Meeting Date: July 2, 2002 Time: 1030 Location: N225
Meeting ID# 8775

Lamisil (terbinafine HCl) Tablets, 250 mg

Indication: Tinea pedis

Sponsor: Novartis Pharmaceuticals Corporation

Pediatric Written Request Meeting

Meeting Chair: Markham Luke, M.D., Ph.D., Acting for Jonathan K. Wilkin, M.D., Division Director

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Markham Luke, M.D., Ph.D., Clinical Team Leader, DDDDP, HFD-540
Barbara Hill, Ph.D., Pharmacology/Toxicology Reviewer, DDDDP, HFD-540
Dennis Bashaw, Pharm.D., Biopharmaceutics Team Leader, DPEIII, HFD-880
Jenny J. Zheng, Ph.D., Pharmacometric Reviewer, DPEIII, HFD-880
Lisa Mathis, M.D., Medical Officer, DDDDP, HFD-540
Mary Jean Kozma-Fornaro, Supervisor, Project Management Staff, DDDDP, HFD-540
Frank H. Cross, M.A., CDR., Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Rajesh Bakshi, M.D., Clinical Research
Bin Cai, M.D., M.S., M.P.H., Biostatistics
Chin Koerner, Drug Regulatory Affairs
Volker Fischer, Ph.D., Preclinical Safety
Soraya Madani, Ph.D., Clinical Pharmacology
Frederichkarl Mayer, Ph.D., Project Management
Aruna Mehra, M.D., Ph.D., Clinical Safety and Epidemiology
Patricia McGovern, Drug Regulatory Affairs
Jerry Nedelman, Ph.D., Biostatistics
Jack Weet, Ph.D., Drug Regulatory Affairs

With reference to the December 28, 2001 and June 12, 2002, Pediatric Written Request and Meeting Briefing Package, respectively, the following discussion took place:

Agency:

Pharmacology/Toxicology:

1. It is not acceptable to delete the following statements from the information included in the "Additional information required" section of the Pediatric Written Request for Lamisil.

    a. It is not appropriate to delete the following portion of the first sentence, "covering the period of maturation in a nonrodent species". This is a critical stage for toxicology studies conducted in juvenile animals.

b. It is not appropriate to delete the fourth sentence in this section that reads "These studies will reveal possible rare events that may occur in maturing animals and are required because tinea capitis is non-life threatening condition." The pediatric committee felt it was important to clarify why this nonclinical study was being recommended for Lamisil for the tinea capitis indication.

2. The conduct of the proposed 3 month study in juvenile monkey may be acceptable if the design of this study provides for drug product exposure covering the period of maturation in the monkey. In addition to monthly ophthalmoscopic evaluations, the following toxicity measurements are recommended for inclusion in the repeat dose juvenile monkey toxicology study. It is recommended that the repeat dose juvenile monkey toxicology study include complete clinical pathology (serum chemistry and hematology), histopathology (all standard tissues for all animals in all dose groups) and toxicokinetics. It is recommended that the protocol for this study be submitted to the division for evaluation prior to initiation of the study.

Sponsor:

The Sponsor proposed to conduct the juvenile nonrodent study in dogs instead of monkeys.

Agency

The Agency advised the Sponsor to submit a protocol for evaluation along with a supporting rationale for conduct of the juvenile nonrodent study in dogs instead of monkeys.

Biopharmaceutics:

Due to the safety concern, the uncertainty in PPK analysis was found not acceptable.

1. The full time vs. concentration profile which consists of 285 plasma samples from adults were used to determine the structure model for pediatric subjects. The bias caused by borrowing information from adults for children was not estimated.

2. Most of samples were collected from 1-4 hours after dose. Only trough concentrations were collected from elimination phase. This design was not optimal to characterize pharmacokinetic of the drug (such as clearance (CL)).

3. According to the model, the estimated CL for an adult (Body weight: 65 kg) was significantly lower than estimated CL from Study 306 (mean body weight: 64 kg). The estimated CLs were 26.1 L/h and 74 L/h for study T201 and 306, respectively. The average CL for adult in the label is 54.8 L/h. Using underestimated CL for adult as reference might over estimate the CL in children.

4. As described by the Sponsor in study 306, pharmacokinetic of the drug are different between adult and children after single dose but the difference disappeared at steady state. The PPK analysis for study T201 did not take this aspect into consideration.

The Pharmacokinetic study as required in the Pediatric Written Request is necessary. The study design should be adequate to characterize pharmacokinetic of terbinafine in pediatric subjects. It is recommended that the samples be collected after steady states given per comment #4 above.

Discussion:

In regards to the first comment, the Sponsor responded that in the model used, the Sponsor had included co-variates for age and body weight that would allow for the consideration of the pooled dataset. In replying to this comment the Agency indicated that the bias we were referring to was the *a priori* decision by the Sponsor that the disposition model (i.e., 1,2, 3, or 4-compartment) used was the same in children as it is in adults. To force the pediatric data to fit the adult 4-compartment model, without independent verification of disposition similarity, represents an introduction of bias that could not accounted for in their covariates. In response to this discussion the Sponsor inquired about the use of model-independent (i.e., non-compartmental) pharmacokinetic data analysis. This approach was acceptable to the Agency provided that the Sponsor included sufficient data points in their sampling scheme so as to be valid.

After further discussion between the Sponsor and the Agency on these issues it was agreed that the Sponsor would initiate a new pK study designed to evaluate the pharmacokinetics (i.e., exposure) of higher doses of terbinafine to children. These doses being required as it appears that children do not have comparable systemic levels (i.e., decreased) to adults following scaled doses. The Sponsor was also encouraged to develop a true pediatric dosage form as the development of true pediatric dosage forms is one of the goals of the Pediatric Rule. In such a case it was agreed that a bridging pharmacokinetic study would be considered and presented to the Pediatric Implementation Team (PedIT) after it had been submitted and reviewed. There is a possiblity that this study could be conducted in adult subjects to link this new pediatric formulation to the currently marketed/studied material.

Clinical:

1. Changes to the Pediatric Written Request Requested by the Sponsor from Sponsor's June 12, 2002, Meeting Briefing Package:

Sponsor:

a. Under heading "Type of study to be conducted:", page 5 of June 12, 2002, Meeting Briefing Package:

Study 1: Systemic exposure study in affected patients at steady state utilizing an appropriate formulation or the oral tablets to establish bioavailability. This study is to be performed prior to conducting Studies 2 and 3 in order to assess the systemic exposure in the target population with the appropriate dose. Pharmacokinetic information must be assessed by the Division of Dermatologic and Dental Drug Products prior to the initiation of Studies 2 and 3 studies. Alternatively the systemic exposure with the appropriate dose in the pediatric population can be assessed by using sparse sampling and population pK methods during study 2 and/or study 3.

Study 2 and 3: Clinical safety and efficacy study in tinea capitis

Under heading "Study Design:" page 5 of June 12, 2002, Meeting Briefing Package:

Study 1: The pharmacokinetic study should be run in patients with tinea capitis who should be treated for 6 weeks to ensure adequate treatment of *Microsporum canis*-infected patients. The pharmacokinetic evaluation should last 6 weeks, which should be adequate given that steady state is reached with Lamisil in approximately 2 weeks.

This study should be a multiple dose pharmacokinetic study with a pharmacokinetic sampling plan covering the first dose as well as pharmacokinetic sampling at steady state.

The treatment regimen used and the general study design features (inclusion criteria, exclusion criteria, severity index, dosing regimen, etc.) should be the same as is planned for the clinical efficacy trials. The study should be run at the doses to be used in Studies 2 and 3. These doses can be selected based on the established pK of terbinafine in children. This study can be run as a stand alone trial or could be incorporated into Study 2 or 3 using population pK methods.

The pK data for terbinafine in children and the proposed doses to be used in Studies 2, and 3 Studies 2 and 3: These studies should be randomized, investigator-blinded, active comparator-controlled, safety and efficacy trials. The terbinafine dose will be determined after review of the full pK for terbinafine in children.

The comparator griseofulvin should be used at the maximum dose labeled.

An Independent Data Safety Monitoring Committee should be used to establish and monitor stopping rules.

Under heading "Endpoints:" page 5 of June 12, 2002, Meeting Briefing Package:

Pharmacokinetic Study 1: Study 1 should provide confirmation of the estimate of any dosing adjustments that may be needed in pediatric patients based on available pK data for terbinafine in children.

Agency:

i. The pK study plan in the WR included an incremental increase in the terbinafine dose with analysis at each level to ensure that the systemic exposure for pediatric patients did not exceed that of adult patients. It appears that studies 306 and T201, already performed by the Sponsor, may support the requirements for the first part of the pK studies if more pediatric patients are enrolled. This would provide sufficient pediatric data so that the Sponsor does not have to rely on data extrapolated form adult patients.

ii. Due to the known adverse event profile, and the adverse events seen in the small number of patients in Study T201 (total patients 176, 8 were gastrointestinal, 3 were headache, hyperasthesia, and moderate leukopenia) and T202 (total patients 133, 6 drug related AEs with one urticaria and one leukopenia), exposing large numbers of patients in Studies 2 and 3 with higher doses is not appropriate without prior pK data as requested in the Original Pediatric Written Request.

iii. It may be reasonable to limit the pK study to 4 weeks as steady state is achieved at this point, however, patients will need to be followed for safety until the therapy for their tinea capitis is completed (6 weeks).

Sponsor:

b. Under heading "Number of patients to be studied or power of study to be achieved:" page 5 of June 12, 2002, Meeting Briefing Package:

Study 1: The sample size for study 1 should be based on the known pK parameters for terbinafine in children and should provide 80% power to detect 30% clearance in children compared to adults. The total volume of blood to be drawn and the pharmacokinetic methods to

be employed in the data analysis should be determined a priori and stated in the protocol. If sparse sampling methods, i.e., population pharmacokinetics are employed, blood samples should be dispersed through out the absorption and elimination phases of the drug concentration time profile to ensure proper parameter estimation.

Studies 2 and 3: Each of the studies should be individually powered with a probability of 95% that events from terbinafine that occur at 1%, or more will be observed during the course of the trial. Therefore, each study should have at least 300 patients enrolled at the to-be-marketed dose or higher per treatment arm to provide at least 220 evaluable patients. The primary statistical analysis should be to demonstrate non-inferiority with a test of hypothesis using a one-sided 97.5% CI. A second analysis to demonstrate superiority should be performed if the first analysis is successful.

Agency:

i. The Agency agrees to discuss the change "1% or less" to "1% or more" with the PedIT as long as the studies are powered with a probability of 99% that events from terbinafine that occur at 1% or more. There is still concern that to make this change may allow the studies to be powered to detect the "more." The drug specific safety concerns are such that the Division was interested in adverse events that are less common, and may occur in 1% or less of the patients. In addition, the Sponsor requested that the Division consider arriving at the probability of 99% with **pooled data** rather than the probability from the individual studies. The Division expressed concern with this approach, but agreed to discuss the issue with the PedIT once the Sponsor submitted information about this approach.

(Please refer to corrigendum, below)

ii. Because of the reported low efficacy rates of the labeled dose of griseofulvin, the agency does not believe that it is in the best interest of the Public Health to evaluate another drug based on non-inferiority – especially given the potential for serious adverse events. The studies in the WR will remain superiority studies.

Sponsor:

c. Under heading "Drug information:" page 5 of June 12, 2002, Meeting Briefing Package:

Route of administration: Oral

Dosage form: One of the existing tablet formulations or another formulation that is appropriate for the pediatric population should be used. The active comparator griseofulvin should be specified by drug product and manufacturer.

Regimen: Once daily for six weeks

Agency:

The Agency appreciates that the tablet form of terbinafine is being used off-label for the treatment of tinea capitis, and that a tablet form is not the most appropriate formulation for patients under the age of 6-years-

In order to fulfill the requirements of the Pediatric Written Request, the Sponsor must develop and study an age appropriate formulation. If there is a chemistry/ manufacturing rational for not developing a pediatric formulation, this information must be provided to the Agency. Currently, the Division has 2 INDs for terbinafine that may prove suitable for pediatric administration – the rapid dissolution and the minitablet.

Sponsor:

d. Under heading "Age group on which studies should be performed:" page 5 of June 12, 2002, Meeting Briefing Package:

Study 1: Pharmacokinetic parameters should be obtained/confirmed in children of the same age range as that to be used in studies 2 and 3. Within this age subset there should be a sufficient distribution to ensure adequate numbers of subjects at the lower end of the range.

Studies 2 and 3: The studies should include patients ages 6-12 years. The Sponsor may alternatively propose methods to study the adverse events associated with terbinafine (i.e. visual color effects and visual field defects) in order to conduct this study in the youngest population that is feasible down to the age of 36 months.

If the Sponsor conducts any studies in pediatric patients less than 6 years of age, then there must be an adequately designed pharmacokinetic study in this population to determine dosing prior to initiation of this study.

Agency:

As noted in the introduction of the Pediatric Written Request issued December 28, 2001, the Agency is aware that tinea capitis occurs in patients 3-9 years of age. The ages of patients included in the Pediatric Written Request were not restricted based on incidence rates of tinea capitis; they were restricted based on safety concerns. The briefing packet contains information that complete eye examinations, to include examination of the lens, retina, color vision, and visual fields) can be successfully performed in patients younger than age 6 years. There is still some question regarding compliance with visual field testing in younger patients, and it is unlikely that all 3-year-old patients know their colors sufficiently to reliably be tested for color vision.

The Sponsor must provide adequate evidence that this specific safety monitoring can be performed in these age groups (i.e., literature, expert consensus statements). This information, once formally submitted and reviewed by the Division, would be discussed with the PedIT.

Sponsor:

The Sponsor presented a brief overview of a new method for assessing ocular function and inquired as to its acceptability to the Agency.

Agency:

The Sponsor should submit the referenced methodology for Agency review and comment.

Sponsor:

e. **Under heading "Study evaluation:" page 5 of June 12, 2002, Meeting Briefing Package:**

Study 1: Biweekly to include an end-of-treatment evaluation. Safety, tolerability, LFTs and CBCs should be performed at each evaluation including end of treatment.

For Studies 2 and 3: Biweekly to include an end-of-treatment evaluation as well as final assessment at 10 weeks to assess efficacy. LFTs and CBC should be performed at each evaluation to include end of treatment.

Studies should include assessments for changes in vision (visual field loss, color vision), as well as food diaries and weight monitoring in order to assess taste disturbances at all visits.

Agency:

i. It appears reasonable to exclude efficacy assessment from the pk study because efficacy results will be available from studies 2 and 3. Those patients who receive the to-be-marketed dosage and duration of therapy with terbinafine could be used in the safety population.

ii. Because of the large number of blood draws for the studies, the Division would offer a revision that would allow for blood draws to occur at baseline, week 3 and week 6 rather than at baseline and then every 2 weeks. This would ensure adequate safety data and may also help in recruitment and compliance.

Sponsor:

f. **Under heading "Statistical information:" page 5 of June 12, 2002, Meeting Briefing Package:**

Pharmacokinetic Study 1: Descriptive statistics (mean, median, co-efficient of variance, etc.) for the primary patient parameters (AUC, C max, T max, CI/F) where appropriate.

Clinical Studies 2 & 3: The primary efficacy variable (complete cure) will be analyzed using a 1-sided 97.5% CI and confirmed by Cochran Mantel Haenszel (CMH) test, stratified by center.

All efficacy analyses will be presented for the ITT and mITT populations. In addition, non-inferiority will be assessed using the per protocol population.

Agency:

i. The numbers for the clinical studies should be changed to studies 2 and 3 as noted by the Sponsor.

ii. As noted earlier, the study design in the WR will remain a superiority trial.

Sponsor:

g. **Under heading "Additional information required:" page 5 of June 12, 2002, Meeting Briefing Package:**

It is recommended that a juvenile study be conducted at doses to a maximum tolerated dose (MTD). The species selected should be the species that best expresses the toxicities already seen in humans and which has metabolism most similar to humans. A study in monkeys would be desirable because the monkeys exhibited the ocular effects, but the sponsor could propose a rationale for a study in dogs.

This study is recommended to support the use of terbinafine in the pediatric tinea capitis population and is recommended for inclusion with the NDA submission.

Agency:

See Pharmacology/Toxicology comments above.

Sponsor:

h. **Under heading "Timeframe for submitting reports of the studies:" page 5 of June 12, 2002, Meeting Briefing Package:**

Reports of the above mentioned studies must be submitted to the Agency on or before December 30, 2006, the date listed in the Orange Book as the last applicable unexpired patent for terbinafine. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired or been previously granted a pediatric extension at the time you submit your reports of studies in response to this Pediatric Written Request.

Agency:

The date may be changed from July 14, 2004, to December 30, 2006, in order to give the Sponsor adequate time to perform the pK studies as outlined and in order to develop a pediatric formulation – both issues that will influence safe dosing of terbinafine. This extension of the date has been agreed upon to give the Sponsor adequate time to perform the studies required to fulfill the Pediatric Written Request. The original wording will remain the same with only changes made to the date.

Sponsor:

2. Registration Question, page 5 of June 12, 2002, Meeting Briefing Package: **Adequacy** of fulfillment of the WR requirements, with a positive outcome for Studies 2 and 3, to achieve registration for Lamisil in tinea capitis.

Agency:

The Sponsor has not provided a specific question. It is anticipated that the studies in the Pediatric Written Request will or will not support the safety and efficacy of terbinafine for the indication of tinea capitis in pediatric patients.
Registration, or approval, for this indication will be based on the data from the studies.

Sponsor:

3. Labeling Question, page 5 of June 12, 2002, Meeting Briefing Package: "Acceptability of including labeling resulting from the pediatric exclusivity trials in the Lamisil Tablets label if registration for tinea capitis is not achieved."

Agency:

The Sponsor has not provided a specific question. The studies in the Pediatric Written Request have been structured to provide information that will be helpful to clinicians. Any useful information on dosage, safety, and/or efficacy will be incorporated into labeling.

Sponsor:

The Sponsor presented a proposal to perform the required safety monitoring during their proposed Phase 3 Clinical Trials. Said proposal would not involve clinical oversight.

Agency:

The Data Safety Monitoring Board was included in the Pediatric Written Request because of the drug specific safety concerns. The Sponsor should submit the proposal for Agency review and comment.

Biostatistics:

1. On page 9 of the submission, the original Pediatric Written Request states: "Each of the studies should be powered with a probability of 95% that events from terbinafine that occur at 1% or less will be observed during the course of the trial. . . . " The sponsor proposes to modify the "1% or less" to "1% or more".

Agency:

The Agency agrees with the Sponsor's change in wording, however, following the Medical Officer, (above) the probability that one or more subjects have the event should be 0.99, not 0.95.

2. Complete cure is defined using signs and symptoms and mycological evaluation. These are evaluated at weeks 2, 4, 6, and 10 (4 week follow-up).

Agency:

One time point should be chosen to be the primary endpoint, otherwise there needs to be a penalty for multiple comparisons.

3. The Sponsor modified the original superiority test of terbinafine over griseofulvin to a non-inferiority test. If the hypothesis of inferiority test is rejected, the sponsor proposes to test superiority over griseofulvin.

Agency:

Following the Medical Officer, the test of noninferiority above is not useful. The test should be formulated as a test of superiority of terbinafine over griseofulvin. For this test the mITT group is most appropriate. However results should not be driven by the method of dealing with dropouts.

4. The Sponsor indicates that secondary variables will only be assessed descriptively.

Agency:

This seems like a reasonable approach, and would not require adjustment for multiple comparisons. However, if any claims are to be made based on the results of any of these variables, appropriate attention to multiple comparisons would be required.

Additional comments:

The Sponsor has proposed major revisions for the Pediatric Written Request. Because of the magnitude of requested changes, the Sponsor should submit these requested changes formally, considering all of the concerns discussed at this meeting. The Division will review the submission and present planned revisions to the Pediatric Implementation Team for discussion. The discussion between the Sponsor and the Division regarding these proposed changes will not be considered as agreements until a Revised Pediatric Written Request is issued.

Corrigendum:

To garner an adequate safety determination, the studies should be powered to detect adverse events that occur in 1% or less of patients with the sought indication, exposed to Lamisil at the dose proposed for marketing with a 95% confidence interval."

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

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

/s/

Markham Luke
8/30/02 12:00:28 PM
Note to Sponsor: Addendum included in minutes.

MEMORANDUM OF A MEETING

Date: November 13, 2000 Meeting Number # 6297

Participants:
Members from Novartis Pharmaceutical Corporation:
Bea Abrams, Ph.D., Clinical Research
Peter Donatsch, Ph.D., Preclinical Safety
Stefan Hirsch, Ph.D., Technical Research and Development
Friedrich Mayer, Ph.D., Project Management
Soraya Madani, Ph.D., Clinical Pharmacology
Patricia McGovern , Regulatory Affairs
Marianne Notter, Ph.D., Biostatistics
Carle Paul, M.D., Clinical Research

JAN 23 2001

Members from the Food and Drug Administration:
Jonathan Wilkin, M.D., DDDDP, HFD-540
Susan Walker, M.D., DDDDP, HFD-105
Markham Luke, M.D., Ph.D., DDDDP, HFD-540
Abigail Jacobs, Ph.D., DDDDP, HFE-540
Kumar Mainigi, D.V.M., Ph.D., DDDDP, HFD-540
James Vidra, Ph.D., DDDDP, HFD-540
Steve Thomson, Ph.D., DOBIII, HFD-725
Dennis Bashaw, Pharm.D.,DPEIII, HFD-880
Sousan Altaie, Ph.D., DAIDP, HFD-520
Kevin Darryl White, DDDDP, HFD-540

Subject: End-Of-Phase 2 meeting for LAMISIL (terbinafine hydrochloride tablets) for the treatment tinea capitis in children (IND 57,093)

The purpose of this meeting was to provide regulatory guidance on the Sponsor's proposed Phase 3 development plan in support of a marketing application for terbinafine tablets for the treatment of tinea capitis in children. The Applicant's pre-meeting briefing package (Serial #011; dated 10/12/00) provided background information and questions (Section 4: pg. 8-21) for discussion. A summary of this meeting is provided below.

Chemistry, Manufacturing and Controls (CMC):

Although this submission contained no specific CMC questions, the following are CMC requests generally submitted for the End-of- Phase 2 Meeting.

A. Drug Substance:

No additional CMC comments on terbinafine HCl will be made since this drug substance has been previously reviewed and approved in the past five (NDAs 20-539, 20-192, 20-749, 21-214 & 20-846) recently-approved NDAs. However, a statement is requested that the sponsor's manufacturing process for terbinafine hydrochloride has not changed since its approval on 12/6/96.

B. Drug Product:

1. **Composition**: The composition of the drug product should list all compendial excipients. In addition, a Certificate of Analyses and specification should be submitted for each non-compendial excipient. All Type IV Drug Master Files for non-compendial excipients should also be referenced, if they exist, with their respective Letters of Authorization.
   On the page 24 table, the percentage difference of the two coatings is relatively small. Does such a small difference impact significantly on tablet disintegration?
2. **Specifications:** Submit the specifications for this drug product.
3. **Dissolution Data**: Submit the comparison between the adult and child dissolution data. Also include the physical dimensions of the adult and child's tablets.
4. **Manufacturing & Packaging**: A detailed description of the new manufacturing process, which includes the new coating process, should be submitted. A diagram of the manufacturing process would be helpful.
5. **Controls**: The controls for the new coating process should be submitted.
6. **Container Closure System**: A description of the new container closure system, to include any child-resistant closure, should be submitted.
7. **Stability Studies**: Please submit the actual stability data generated to date that will cover the Phase 2 and 3 treatment periods. There should be a minimum of 12 months of stability data generated on three individual batches at the NDA Filing.

Please read both 21 CFR 312.23(a)(7)(iv)(b) and GUIDANCE FOR INDUSTRY: CMC Content and Format of INDs for Phases 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products for additional details on Phase 2 and 3 clinical studies.

Pharmacology/Toxicology:

Question #4.1 (Briefing Package, p. 8)
Response: The 26-week and 52-week oral studies of terbinafine in dogs should be submitted to the IND. If these studies were not conducted at a maximal tolerated dose and did not cover both the juvenile period and the period of sexual maturation of the dog, then such a study in dogs will needed to support an NDA for a juvenile indication. Pharmacokinetic (AUC) data for dogs should also be supplied. The proposed protocol should be submitted to the Division for review.

Biopharmaceutics:

A. Change from [redacted] Coating to [redacted] b(4)

The sponsor has conducted an in vivo bioequivalency trial (W-252) between the marketed tablets and fast dissolving tablets with [redacted] The to-be-marketed material is composed of [redacted] aterial. While not directly applicable, the SUPAC-MR document allows for changes in rate controlling excipients not to exceed a total of 5%. Such changes requiring additional multi-media disolution testing. In keeping with the spirit of SUPAC on the pre-approval side, the data from study W-252 would be acceptable along with the additional multi-media dissolution testing called for under the SUPAC-MR, rate-controlling excipients, Level 2 change provision. b(4)

B. Determination of Relative Bioavailability in Adults:

The Agency does allow sponsors to determine relative bioavailability in adults provided that determination is linked to further work in the target pediatric population.

C. Use in Pediatrics:

At the present time the sponsor has conducted two trials in children with tinea capitis, Study 306 was a trial involving healthy adults and children with tinea capitis between the ages of 5 and 11. In this trial significant differences were noted in the pharmacokinetics between children and adults (i.e. clearance). In Study 302, children between the ages of 3 and 11 had single trough plasma concentrations taken at week 0, 3 and 4. Only very broad conclusions can be drawn from this trial given the lack of pharmacokinetic samples taken. Since significant differences were noted between the adults and children from 5-11, there is insufficient data to extend the dosing regimen down to 2 years of age based on the results of Study 302. As a general rule, the Agency is willing to extrapolate information in children up but not down in age. A new trial along the line of Study 306 should be initiated in the target population down to the age of 2.

Clinical:

A. Comments on the Sponsor's drug/indication:

The indication being sought is the treatment of tinea capitis.

The Sponsor is proposing studying a new formulation of terbinafine HCl tablet (a fast disintegrating tablet with polymer coated granules). On page 9 of the Investigator's brochure, the Sponsor states the following: "The tablets dissolve into micro-particles within the mouth or in small amounts of water. This facilitates drug administration to young children. Parents or caregivers can pre-dissolve the tablet in a teaspoon of water prior to administration."

The Sponsor should provide assurance that the placebo tablet has similar dissolution characteristics to the drug product. Provided there are no pharmacokinetic concerns regarding such a means of administration (pre-dissolution), each investigator should note if this is the route of administration for each subject. Subgroup analysis should be performed for this route of administration.

The two tablets are ——— 125 mg. Adequate precautions should be taken to clearly denote the tablets as the two mm diameter difference between the two may allow for confusion during dosing. b(4)

The tablets contain aspartame in the formulation. The Sponsor should address issues related to the use of the product in patients with hypersensitivity or other intolerance (e.g. PKU patients) to this excipient.

The tablets should be enclosed in a child-proof container during the study.

B. Comments on demonstration of adequate safety information to proceed with human trials:

The Sponsor is referred to Pharm/Tox and Biopharm comments.

C. Comments on dose ranging:

The Sponsor has only addressed the element of duration in its dose ranging studies. The elements of dose and frequency may not have been adequately addressed for the disease under consideration. The Sponsor may wish to address this concern in its final protocol submission.

D. Comments on protocols submitted:

The first study is titled: A randomized, double-blind, double-dummy, parallel group study to compare the efficacy and safety of 2-week Lamisil treatment (pediatric formulation) versus 6-week griseofulvin (pediatric suspension) treatment in children from 2 to 18 years of age with tinea capitis due to *Trichophyton* species.

The Sponsor proposes one trial for *Trichophyton* genera and an open-labeled study for *Microsporum* genera. Species should be referred to by the full name.

The second study is titled: A 16-week, open-labeled, multicenter, evaluation of the safety and efficacy of Lamisil pediatric formulation (with stratified doses per weight) in children from 2 to 18 years of age with tinea capitis due to *Microsporum* species.

In general, a minimum of two adequate and well-controlled Phase 3 trials need to be conducted to support approval of an NDA.

A trial conducted in a foreign country is subject to the regulations outlined in 21 CFR 312.120 and 314.106. The Sponsor should show that the data submitted is applicable to the U.S. population and U.S. medical practice. The demographics of the study population will be an important issue. Hair care habits may differ among populations. Such differences should be noted. In addition any differences between non-U.S. and U.S. dermatophytes causing tinea capitis should be highlighted (including prevalence pattern and drug resistance)

The Applicant should submit rationale for assuming the applicability of any foreign data in the submission to the U.S. demographics. The relevance of using patients exposed to European variants of *T. tonsurans* and *M. canis* may be questionable. Separate analysis of the U.S. sites is requested. Based on Sponsor's provided comparability data or lack thereof, the European data may or may not be used to make a determination for efficacy with the drug product.

The Sponsor should clarify the timepoint for assessing the primary endpoints, i.e., at the End of Therapy visit or at the Set of Cure. The Sponsor is reminded that traditionally the Agency assesses the endpoints at the Test of Cure visit.

The Sponsor plans to measure fungal load as part of efficacy assessments. It is not clear how fungal load relates to efficacy in a fungal infection. Please submit the methodology by which the fungal load is determined and linkage to efficacy.

The Sponsor should use different sites for its two Phase 3 multicentered, placebo-controlled trials. The patients enrolled in Phase 3 studies should be different from those in the Phase 2 studies.

E. Comments on Overall Study Design:

The Sponsor was advised to consider a revised study design more consistent with current clinical practices. This new study design would allow for enrollment of all patients with clinical diagnosis of tinea capitis regardless of the causative agent as well as allowing for return of culture results to determine the treatment duration so that the true safety and efficacy rates for this product can be assessed.

Please note that the drug products are labeled for treatment of infections due to microorganism designated by genus and species' name. The division would not grant approval for organisms designated only by the genus name.

Phase 3 studies should mimic actual use conditions as closely as possible. While separating the organisms for study into two trials may be appropriate for Phase 2 exploratory studies,

Phase 3 studies should have Use Conditions that resemble actual clinical conditions. Thus, it is not possible for an investigator to have culture results before treatment begins nor should an ITT delayed exclusion be performed for any species of dermatophyte causing tinea capitis in the trials.

The Sponsor should identify the type of micronized griseofulvin suspension used in the active treatment arm by Manufacturer, Tradename, Lot Number, and Expiration Date. It is assumed from the dosages suggested that a formulation containing micronized griseofulvin will be used. The Sponsor should identify a standardized method for culture.

F. Comments on Inclusion/Exclusion criteria:

The Sponsor appears to be only enrolling children from 2 to 18 years old into its Phase 3 studies. Also, no patients that are immunocompromised are being enrolled. The studies as designed may not allow for extrapolation for efficacy and safety to other populations.

The Sponsor is excluding kerions requiring immediate treatment or treatment with systemic corticosteroids and/or systemic antibiotics.

The Sponsor is reminded that the label will reflect the populations studied in Phase 3.

What is the Sponsor's rationale for excluding males planning to father children (page 60 of Briefing)?

History of hepatitis or other hepatic disease should be an exclusion criterion.

G. Comments on Safety:

The Sponsor should use MedDRA or COSTART terms to describe adverse events. The Sponsor should define withdrawal criteria (e.g. development of elevated serum hepatobiliary laboratory markers) for its subjects. During follow-up, subjects should be asked specific questions regarding change in vision, including color vision, change in taste, in addition to constitutional questions.

H. Comments on Endpoints:

Endpoints for evaluation should be static. The assessment of efficacy by patient is not needed. Dichotimization for success/failure will use patients with Complete Cure (ITT population). Subgroup analysis for each of the dermatophytes as determined by fungal culture is needed. A specific Point of Cure should be clearly identified in the protocol (e.g. four weeks after completion of treatment).

With respect to the use of active controls, the appropriate comparisons between terbinafine and griseofulvin for approval would be:

1. Demonstration of superiority between terbinafine and griseofulvin (micronized) when used as labeled, or
2. Demonstration of non-inferiority between terbinafine and griseofulvin (micronized) at a dose of 20 mg/kg.

It is noted that the Sponsor has a secondary endpoint of fungal load. It would be greatly appreciated if the Sponsor could clarify the relationship between fungal load and infectivity, and identify the point in treatment at which infectivity is decreased.

I. Regulatory Review of Sponsor's Submission:

For Phase 3 development, the Sponsor should propose at least two adequate and well-controlled studies investigating the use of its new formulation of terbinafine for the treatment of tinea capitis.

The Sponsor should clearly define its Point of Cure (i.e., the point in time when final definitive evaluation for presence or absence of tinea capitis is conducted).

J. Sponsor's Additional Questions:

Question #4.2 (Briefing Package, p. 11)
Response: In general, based upon information from dose ranging, the Sponsor should aim for maximum cure rates with minimal toxicity. Only the summary of the data was reviewed. It is noted that only dose ranging of time of treatment studies were performed. Based on that review, it appears that a 2-week treatment with terbinafine may provide the needed information regarding relative efficacy to placebo. However, it is not clear that a 2-week treatment with terbinafine will allow for an adequate demonstration of superiority to the labeled dose of micronized griseofulvin. (Refer to Page 49 – table)

Question #4.3 (Briefing Package, p. 12)
Response: From the time ranging study performed with terbinafine in Phase 2 for *Microsporum* it appears that greater efficacy was achieved from griseofulvin (20 mg/kg/day for 12 weeks) than Lamisil tablets at any duration (6, 8, 10, or 12 weeks) of treatment.

Question #4.4 (Briefing Package, p. 13)
Response: The Phase 3 study should reflect, as close as possible, actual clinical use conditions. The study as proposed appears to be somewhat artificial, not mimicking clinical use conditions, due to the inclusion of only *Trichophyton* species. Current clinical practice does not include speciation of dermatophyte prior to initiating treatment for tinea capitis.
Question #4.5 (Briefing Package, p. 15)

Response: It is preferable that two separate pivotal trials be conducted that would mimic clinical use conditions. Subgroup analysis may be performed for the different species of dermatophytoses causing tinea capitis.

Question #4.6 (Briefing Package, p. 16)
Response: See comments for Questions 4.4 and 4.5. Efficacy in tinea capitis caused by *Microsporum* species should be investigated in controlled studies against placebo or active control. If an active control arm is used, superiority should be demonstrated against griseofulvin micronized suspension used as labeled, or non-inferiority against griseofulvin at the 20 mg/kg dose level (clinical standard).

Question #4.7 (Briefing Package, p. 17)
Response: The Sponsor should stratify for different pediatric age groups. Any stratification scheme may be supported by epidemiological data regarding incidence of tinea capitis in that age group in the United States.

The Sponsor is reminded that the demographics of the population enrolled should be similar to that seen in the United States with regard to the occurrence of tinea capitis.

Question #4.8 (Briefing Package, p. 18)
Response: If the Sponsor is proposing that its fast disintegrated tablets be used in a fashion whereby the tablet is dissolved in water prior to administration, adequate data to support this method of use should be provided. Subgroup analysis of efficacy and safety from Phase 3 studies for those patients using this method of administration should be performed.

Question #4.9 (Briefing Package, p. 20)
Response: There should not be any delayed exclusions (ITT population) for speciation of dermatophyte as this does not reflect current clinical practice. (See Biostatistics comments)

Question #4.10 (Briefing Package, p. 21)
The Sponsor should request a waiver or deferral for the Pediatric Rule with the actual NDA submission. Current data for the age group under consideration, regarding incidence and treatment options, should be provided by the Sponsor at that time.

K. General Comments:

Study reports for Phase 1, 2, and 3 studies should clearly indicate the composition/formulation of the drug product and placebo used in the trials.

Biostatistics:

1. Note that neither study includes a control arm. As noted by the Medical Officer, a course in Griseofulvin may provide an adequate "gold standard" of efficacy. However, in general, the

lack of a control group makes it difficult to make a causal interpretation of any observed treatment effect. Even a small control group might be helpful.

2. The proposed primary end-point for both trials is to be "complete cure" at the end of study, defined as negative microscopy and culture and a total signs and symptoms score equal to 0. This total signs and symptoms score is defined as the sum of the signs and symptoms scales for erythema, desquamation/scaling, papules, and pustules, however details about these scales were not included in this submission. Also, presumably the last measurement is scheduled at the end of the follow-up period (week 10 or week 16 for each study, respectively) but this does not seem to be made explicit in this submission.

3. Following the Medical Officer's comments, one or more superiority or noninferority trials may be needed. . For a superiority comparison, either to placebo or to an active control, following ICH guidelines, the Intent-to-Treat (ITT) population is generally preferred. However, the preferred definition for the ITT population by the Division of Dermatological and Dental Drug Products (DDDDP) is all patients randomized and dispensed treatment, NOT limited to those with one or more follow-up visits. For noninferiority trials, the Per Protocol population should be used as the primary analysis and analysis based on the ITT population should be presented as a supportive analysis. Handling of dropouts in the ITT analysis should be done in such a way, which ensure minimum bias in the estimates of treatment effect.

4. For fungal infections the definition of ITT has been modified to allow those subjects with NO confirmed (KOH or culture) fungal infection to be excluded from the efficacy analysis. Since culturing the fungus usually occurs after randomization, subjects with no infection can be excluded even after randomization. Such an allocation has been called a "Modified Intent-to-Treat" (MITT) population. Again, however, following the Medical Officer's comments, results from speciation have not been considered appropriate for excluding subjects from the analysis.

5. Also, in the T301 study, the sponsor proposes to assess noninferiority using the Anderson and Hauck (1983) correction to the variance of the difference in proportions, where this variance is estimated using the DerSimonian and Laird (1986) procedure. Fundamentally this seems to be a promising approach, however we would also like to see the standard confidence intervals around the difference in proportions using simple binomal/CMH approximations.
6. Using simpler models this reviewer was able to essentially confirm the sponsor's power/sample size calculations in the T301 study. However, if we disallow exclusions due to speciation as noted in paragraph 4 above, then under the same assumptions as made by the sponsor, one would expect that the percentage of delayed exclusions should be less than the 20% specified by the sponsor.

General Comments:

The Food and Drug Administration Modernization Act [FDAMA] of 1997, Section 111, Pediatric Studies of Drugs, effective April 1, 1999, requires the following:

Per 21 CFR 314.50(d)(7), NDA applications are required to contain "A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section, and information required to be submitted under Section 314.55."

In addition, per 21 CFR 314.55(a), each NDA "application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective...." Under 21 CFR 314.55(d) "this section does not apply to any drug for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter."

A waiver can be requested in accordance with 21CFR 314.55(c).

Financial Disclosure:

For applications submitted after February 2, 1999, in accordance with 21 CFR 54.3 and 21 CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.

Labeling:

If the Applicant has an Information for Patients leaflet/labeling, please submit it with the NDA.

Signature, minutes preparer:_____

Chair concurrence:_____

Attachments:

cc:
HFD-540
HFD-540Wilkin
HFD-540/Walker
HFD-540/Luke
HFD540/Vidra
HFD-540/DeCamp
HFD-520/Altaie
HFD-540/ Jacobs
HFD-540/Mainigi
HFD-880/Bashaw
HFD-725 /Alosh
HFD-725/Thomson
HFD-540/White

MEETING MEMO

/s/

Kevin White
1/24/01 11:51:08 AM