

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-484

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

**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

22-484

NAME OF APPLICANT/NDA HOLDER

Stiefel Laboratories, Inc.

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)

Hyphanox

ACTIVE INGREDIENT(S)

Itraconazole

STRENGTH(S)

200 milligrams

DOSAGE FORM

Oral tablet

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.

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

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 7,081,255	b. Issue Date of Patent 07/25/2006	c. Expiration Date of Patent 05/12/2017
d. Name of Patent Owner Janssen Pharmaceutica, N.V.	Address (of Patent Owner) Turnhoutsweg 30	
	City/State Beerse, BELGIUM B-2340	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
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) Devin G. Buckley c/o Stiefel Laboratories, Inc.	Address (of agent or representative named in 1.e.) 255 Alhambra Circle	
	City/State Coral Gables, FL	
	ZIP Code 33134	FAX Number (if available)
	Telephone Number (305) 443-3800	E-Mail Address (if available) dbuckley@stiefel.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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).	<input type="checkbox"/> Yes	<input type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 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.)	<input type="checkbox"/> Yes	<input type="checkbox"/> 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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent) 12, 13	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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 proposed labeling.) Once daily treatment of fungal infections through oral administration.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug 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 the manufacture, use, or sale of the drug product.	<input type="checkbox"/> Yes
---	------------------------------

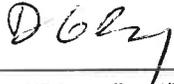
6. Declaration Certification

6.1 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



3/16/09

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

Devin G. Buckley, c/o Stiefel Laboratories, Inc.

Address

255 Alhambra Circle

City/State

Coral Gables, FL

ZIP Code

33134

Telephone Number

(305) 443-3800

FAX Number (if available)

E-Mail Address (if available)

dbuckley@stiefel.com

The public reporting burden for this collection of information has been estimated to average 20 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 supplement 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. Sending 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 April 2007) 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.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.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 (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

- 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.

**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

22-484

NAME OF APPLICANT/NDA HOLDER

Stiefel Laboratories, Inc.

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)

Hyphanox

ACTIVE INGREDIENT(S)

Itraconazole

STRENGTH(S)

200 milligrams

DOSAGE FORM

Oral tablet

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.

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

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 6,509,038	b. Issue Date of Patent 01/21/2003	c. Expiration Date of Patent 05/12/2017
d. Name of Patent Owner Janssen Pharmaceutica, N.V.	Address (of Patent Owner) Turnhoutsweg 30	
	City/State Beerse, BELGIUM B-2340	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
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) Devin G. Buckley c/o Stiefel Laboratories, Inc.	Address (of agent or representative named in 1.e.) 255 Alhambra Circle	
	City/State Coral Gables, FL	
	ZIP Code 33134	FAX Number (if available)
	Telephone Number (305) 443-3800	E-Mail Address (if available) dbuckley@stiefel.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input type="checkbox"/> No		

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use 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

2.7 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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
2, 3	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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 proposed labeling.) Once daily treatment of fungal infections through oral administration.
--	--

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug 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 the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 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



3/16/09

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

Devin G. Buckley, c/o Stiefel Laboratories, Inc.

Address

255 Alhambra Circle

City/State

Coral Gables, FL

ZIP Code

33134

Telephone Number

(305) 443-3800

FAX Number (if available)

E-Mail Address (if available)

dbuckley@stiefel.com

The public reporting burden for this collection of information has been estimated to average 20 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.
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- Form 3542 should be used after NDA or supplement 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. Sending 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 April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
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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.
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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 (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

- 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.

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

*For Each Patent That Claims a Drug Substance
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and/or Method of Use*

NDA NUMBER

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Stiefel Laboratories, Inc.

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ACTIVE INGREDIENT(S)

Itraconazole

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DOSAGE FORM

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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
6,488,939

b. Issue Date of Patent
12/03/2002

c. Expiration Date of Patent
12/03/2019

d. Name of Patent Owner
Abbott Laboratories

Address (of Patent Owner)
100 Abbott Park Road, Dept. 0377, Bldg. AP6A-1

City/State
Abbott Park, IL

ZIP Code
60064

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

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)

Address (of agent or representative named in 1.e.)
255 Alhambra Circle

City/State
Coral Gables, FL

ZIP Code
33134

FAX Number (if available)

 Devin G. Buckley
c/o Stiefel Laboratories, Inc.

Telephone Number
(305) 443-3800

E-Mail Address (if available)
dbuckley@stiefel.com

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

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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).	<input type="checkbox"/> Yes	<input type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 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.)	<input type="checkbox"/> Yes	<input type="checkbox"/> 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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input type="checkbox"/> 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 proposed labeling.)	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug 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 the manufacture, use, or sale of the drug product.	<input type="checkbox"/> Yes
---	------------------------------

6. Declaration Certification

6.1 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



3/16/09

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

Devin G. Buckley, c/o Stiefel Laboratories, Inc.

Address

255 Alhambra Circle

City/State

Coral Gables, FL

ZIP Code

33134

Telephone Number

(305) 443-3800

FAX Number (if available)

E-Mail Address (if available)

dbuckley@stiefel.com

The public reporting burden for this collection of information has been estimated to average 20 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 supplement 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. Sending 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 April 2007) 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.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.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 (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

- 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.

EXCLUSIVITY SUMMARY

NDA # 22-484

SUPPL #

HFD # 540

Trade Name Tradename Tablets, 200 mg

Generic Name itraconazole

Applicant Name Stiefel Laboratories, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

NA

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

NA

d) Did the applicant request exclusivity?

YES NO

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

3 years

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA# 20083

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 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

Phase 3 Trial BT0300-302-INT

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Phase 3 Trial BT0300-302-INT

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 #69,847 YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

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

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

If yes, explain:

=====

Name of person completing form: Nichelle Rashid

Title: Regulatory Health Project Manager

Date: 11/27/09

Name of Office/Division Director signing form: Susan Walker

Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

STIEFEL
LABORATORIES
INC

HYPHANOX 200MG FILM-
COATED TABLETS

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

/s/

NICHELLE E RASHID
04/28/2010

SUSAN J WALKER
04/28/2010

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 022484 BLA #	NDA Supplement # NA BLA STN #	If NDA, Efficacy Supplement Type: NA
Proprietary Name: TRADENAME Established/Proper Name: itraconazole Dosage Form: Tablet, 200 mg		Applicant: Stiefel Laboratories, Inc. Agent for Applicant (if applicable): NA
RPM: Nichelle Rashid		Division: Division of Dermatology and Dental Products
<p><u>NDA's:</u> NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p style="text-align: center;"><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>	
❖ User Fee Goal Date Action Goal Date (if different)		April 30, 2010 April 29, 2010
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)		<input checked="" type="checkbox"/> None
❖ Promotional Materials (<i>accelerated approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC</p> <p>Comments: _____</p>	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____	10/29/09
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

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

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

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

Yes No

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

If "Yes," skip to question (4) below. If "No," continue with question (2).

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

Yes No

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

If "No," continue with question (3).

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

Yes No

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

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

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

Yes No

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

If "No," continue with question (5).

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

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	05/03/10
--	----------

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s): Approved, 04/29/10
---	--

Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	04/28/10
<ul style="list-style-type: none"> Original applicant-proposed labeling 	08/28/09
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 8/26/09

<ul style="list-style-type: none"> Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	04/28/10
<ul style="list-style-type: none"> Original applicant-proposed labeling 	08/28/09
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	04/21/10; 04/27/10
❖ Proprietary Name	
<ul style="list-style-type: none"> Review(s) (<i>indicate date(s)</i>) Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	09/22/09 09/24/09
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 05/19/09 <input checked="" type="checkbox"/> DMEDP 11/06/09 <input checked="" type="checkbox"/> DRISK 03/05/10 <input checked="" type="checkbox"/> DDMAC 02/26/10 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (e.g., RPM Filing Review ⁴ /Memo of Filing Meeting) (<i>indicate date of each review</i>)	08/07/09
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> PeRC (<i>indicate date of mtg; approvals only</i>) 	<input type="checkbox"/> Not applicable 10/28/09
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>) 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 02/04/09
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 12/08/05

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 8/26/09

<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04/28/10
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 03/29/10
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	Refer to CDTL review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	04/28/10 03/29/10
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	See Clinical review dated 04/28/10 p. 6
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	See Clinical review dated 03/29/10 p. 17
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None 08/11/09
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo (<i>indicate date</i>) Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 11/16/09 (Letters – 11/06/09, 11/23/09)
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/02/09
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/02/09
Clinical Pharmacology <input type="checkbox"/> None	

⁵ Filing reviews should be filed with the discipline reviews.
Version: 8/26/09

❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/13/09
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/24/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Product quality review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/17/09
• ONDQA Biopharmaceutics review (<i>indicate date for each review</i>)	NA
• BLAs only: Facility information review(s) (<i>indicate dates</i>)	<input checked="" type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology (<i>indicate date of each review</i>)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	11/17/09
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)	Date completed: 12/11/09 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

<ul style="list-style-type: none">• BLAs:<ul style="list-style-type: none">○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed

Appendix A to Action Package Checklist

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

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

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

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

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

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

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

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

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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

STIEFEL
LABORATORIES
INC

HYPHANOX 200MG FILM-
COATED TABLETS

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/s/

NICHELLE E RASHID

05/03/2010

MEMORANDUM OF TELECON

Date: April 19, 2010
Time: 9:30 a.m.
Application: NDA 22484, Itraconazole Tablets
Meeting Chair: David Kettl, M.D., Clinical Team Leader
Meeting Recorder: Nichelle Rashid, Regulatory Project Manager

FDA Participants:

David Kettl, M.D., Clinical Team Leader, DDDP
Snezana Trajkovic, M.D., Clinical Reviewer, DDDP
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Seongeun Cho, Ph.D., Clinical Pharmacology Reviewer, DCP 3
Kerry Snow, M.S., Microbiologist, DAIOP
Denise V. Baugh, PharmD, BCPS, Safety Evaluator, OSE
Nichelle Rashid, Regulatory Project Manager, DDDP

Sponsor:

Stiefel Laboratories, Inc.

Koen Van Rossem, M.D. - Project Physician
David Angulo, M.D. - Clinical Research
Charles Barranco - Clinical Operations
Steve Young - Clinical Operations
Devon Allen, Sr. Director, Regulatory Affairs
Salisa Hauptmann, VP, Global Regulatory Affairs - Regulatory Affairs
Alicia Tatro, Associate Director, Regulatory Affairs Labeling

Background:

Original NDA 022484, TRADENAME (itraconazole) Tablets, 200mg was submitted on March 31, 2009. The Agency conveyed proposed labeling on March 24, 2010. The sponsor submitted their proposed labeling with questions and concerns.

The following points were discussed:

Carton/Blister Labeling

The Agency requested that the established name on the carton labeling be bolded to increase its prominence. The Agency also requested that the statement, “(Each tablets contains.....” on the blister labeling required be bolded to increase its prominence.

The sponsor agreed.

The Agency requested that the artwork of the carton/blister labeling be submitted to the Agency by noon, Tuesday, April 20, 2010, followed by an official submission once we have agreed upon labeling.

The Agency inquired about the submission of the proprietary name.

The sponsor acknowledged that the resubmission of the proprietary name was sent as of April 16, 2010.

Labeling

In Section 6.1, Table 1, under INFECTIONS and INFESTATIONS the Agency is proposing a value of 7.3% incidence in the placebo group for upper respiratory tract infections. Our calculations suggest that this value should be (b) (4). Additionally under GASTROINTESTINAL DISORDERS, the Agency is proposing a value of 1.0% incidence in the placebo group for abdominal pain. Our calculations suggest that this value should be (b) (4). Please clarify.

Response:

The Agency acknowledged that the basis for calculations of adverse events differs from that of the sponsor. The Agency requested that the sponsor provides a table with listed and System Organ Class and preferred terms used for calculations of rates of adverse event in their proposed labeling.

In Section 7.1, the Agency is proposing language that itraconazole is a “strong inhibitor of P-glycoprotein transporter and may result in increased plasma concentrations of drugs whose gastrointestinal absorption is regulated by P-gp.” Given that we have no information to support this and the language is not in the current version of the Sporanox PI, can the Agency please provide the source of this information?

Stiefel accepts the proposed language around the additional drug-drug interactions in Sections 7.1 and 7.2. However, given the similarities between our itraconazole 200 mg tablets and Sporanox capsules, we request that the labels of all itraconazole manufacturers be revised to reflect these additional DDIs as soon as possible. This would ensure that the labeling is consistent and would not put Stiefel’s itraconazole tablet at a disadvantage in the marketplace.

Response:

The Agency acknowledged that it has been well documented in the literature that itraconazole is a P-gp inhibitor. Given there are no established criteria regarding the potency of the inhibition,

the Agency will remove the word "strong" and modify it to read "itraconazole is also an inhibitor of P-glycoprotein transporter and ..."

In Section 7.2 under the discussion of Opiate Analgesics, we have removed the second paragraph discussing methadone. We believe that this statement is providing contradictory advice given that methadone is specifically listed as a contraindicated concomitant drug in the Highlights section, the Black Box Warning, and in Sections 4 and 5.2 and in Table 4 of the Full Prescribing Information of this package insert.

Response:

The Agency agreed with the proposal change that the second paragraph under Opiate Analgesics regarding methadone be removed.

(b) (4)

Response:

The Agency did not agree with the proposed changes.

In Section 13.1, Carcinogenesis, Mutagenesis, Impairment of Fertility FDA's proposed paragraph discussing the carcinogenicity results is not consistent with the information that we directly referenced from the Sporanox label. Can you please confirm the source of FDA's information and why it is changed from what is in the SPORANOX label?

Response:

The Agency acknowledged that the information provided in Section 13.1 of the Itraconazole label is derived from the Sporanox NDA. This section of the label reflects the information available concerning Carcinogenesis, Mutagenesis, Impairment of Fertility for itraconazole based on the information available in the Sporanox NDA. The wording in this section of the label is slightly different than what is in the Sporanox label because it has been updated to today's standards for labeling. The multiples of human exposure calculations in this section of the label have been changed from a mg/kg basis to a body surface area comparison (i.e., mg/m² comparison) because this is more appropriate for small molecules that are widely distributed in

the body. Even though the wording in Section 13.1 of the itraconazole label has been slightly modified compared to the Sporanox label, the overall contents of this section is consistent with what is in the Sporanox label.

The sponsor accepted the Agency's explanation.

In Section 14, Table 6, we note that the itraconazole capsule results have been removed by the FDA reviewers. The Phase 3 clinical trial (BT0300-302-INT) from which the data in this Table were taken is a non-inferiority clinical trial that was agreed to with the Agency in the Special Protocol Assessment (SPA) Meeting of 24 July 2006 and the End of Phase 2 Meeting of 8 December 2005. Under the SPA, the Division required that this trial demonstrate that the itraconazole tablets were non-inferior to the itraconazole capsules while being superior to placebo. The trial results did demonstrate that itraconazole tablets were non-inferior to itraconazole capsules and were superior to placebo. Stiefel considers all these data fundamental to the outcome the trial. For these reasons, we believe that presenting the full set of efficacy data in this table, including all treatment groups, is essential to correctly reflect the purpose and outcome of the study. We, therefore, respectfully request that the itraconazole capsule results be added back to the table and we have revised it accordingly. Additionally, as discussed in (Scher, et. al., June 2007), the normal appearance of a nail plate after a full course of itraconazole treatment is not always attainable, a fact commonly accepted among physicians. Therefore, we consider the Clinical Improvement data valuable information for prescribers and request that it remain in Table 6 of the label.

For ease of reference, we have highlighted in yellow the new statements that we believe are applicable across all itraconazole package inserts and should be subsequently modified for those products.

Response:

The Agency stated that a decision had not been made on the best approach for presenting the information in this section of the labeling (table vs. sentence format). The Agency also stated that there were some concerns with future marketing claims. The Agency acknowledged that further discussion will be required prior to reaching a decision.

The discussion ended amicably.

ADDENDUM:

The sponsor submitted the requested information for Table 1 in section 6.1 and the artwork for the carton/blister labeling on Monday, April 19, 2010.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

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HYPHANOX 200MG FILM-
COATED TABLETS

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/s/

DAVID L KETTL
04/28/2010

From: Rashid, Nichelle E
Sent: Monday, April 12, 2010 2:40 PM
To: 'Devon L Allen'
Cc: Owens, Margo; Gould, Barbara; Rashid, Nichelle E
Subject: Labeling/NDA 22484/Itraconazole tablets

Ms. Allen,

The Agency found the following changes were not made based upon our recommendations:

- 1) On the blister card and carton labeling, increase the established name taking into account all pertinent factors, including typography, layout, contrast and other printing features in accordance with 21 CFR 201.10(g)(2).
- 2) On the blister card and carton labeling, increase the prominence of the statement beginning with "Each tablet contains . . ." to help minimize the potential for misinterpreting the strength of a tablet.
- 3) On the carton labeling, the dosage form should be on the same line as the established name (see example below), which is required by the CFR.

TRADENAME
(itraconazole) Tablets 200 mg

Please submit a corrected mockup of the blister card and carton labeling by close of business tomorrow, Tuesday, April 13th.

Thanks,

Nichelle E. Rashid
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Tel: (301) 796-3904
Fax: (301) 796-9895
nichelle.rashid@fda.hhs.gov

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

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HYPHANOX 200MG FILM-
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/s/

NICHELLE E RASHID

04/27/2010

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

MEMORANDUM

DATE: April 1, 2010
TO: Review #1 of NDA 22-484
FROM: Christopher Hough, Ph.D.
SUBJECT: **Final Recommendation**

Previous Review # noted two pending issues; 1) Final recommendation from the Office of Compliance, and 2) Issues on container/carton labels.

Establishment Evaluation: The Office of Compliance issues an overall “Acceptable” recommendation on 11-Dec-2009. See Addendum A for the Report.

Labeling Issues: The Agency has received the Sponsor’s response to its final proposed changes to the carton and immediate packaging labels for NDA 22-484 drug product on 21-Apr-2010 (SD-014). They now contain all the required information and are adequate. See Addendum B for blister pack and carton label mockups.

Recommendation: Therefore, from the CMC perspective, this NDA is now recommended for approval.

Addendum A

Establishment Evaluation Request Detail Report

Application:	NDA 22484/000	Action Goal:	
Stamp Date:	31-MAR-2009	District Goal:	02-DEC-2009
Regulatory:	31-JAN-2010		
Applicant:	STIEFEL LABS INC 20 TW ALEXANDER DR RESEARCH TRIANGLE PARK, NC 27709	Brand Name:	HYPHANOX 200MG FILM-COATED TABLETS
Priority:	5	Estab. Name:	ITRACONAZOLE 200MG FILM-COATED TABLETS
Org. Code:	540	Generic Name:	ITRACONAZOLE 200MG FILM-COATED TABLETS
Application Comment:	THE CONTACT FOR THE NDA APPLICANT IS MS. DEVON ALLEN, PH: 919-990-6207, EMAIL: DEVON.ALLEN@STIEFEL.COM. (on 13-NOV-2009 by J. DAVID () 301-796-4247)		
FDA Contacts:	J. DAVID	Project Manager	301-796-4247
	C. HOUGH	Review Chemist	301-796-0323
	S. DING	Team Leader	301-796-1349
Overall Recommendation:	ACCEPTABLE	on 11-DEC-2009	by E. JOHNSON (HFD-320) 301-796-3334

2 pages of Draft Carton and Container Labels have been Withheld in Full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22484	ORIG-1	STIEFEL LABORATORIES INC	HYPHANOX 200MG FILM-COATED TABLETS

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/s/

CHRISTOPHER J HOUGH
04/22/2010

MOO JHONG RHEE
04/22/2010
Chief, Branch III



NDA 22-484

PDUFA GOAL DATE EXTENSION

Stiefel Laboratories, Inc.
Attention: Devon Allen, MS, RAC
Director, Regulatory Affairs
20 T.W. Alexander Drive
P.O. Box 14910
Research Triangle Park, NC 27709

Dear Ms. Allen:

Please refer to your March 31, 2009 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME (itraconazole) Film-Coated Tablets, 200 mg.

Your submission dated and received January 15, 2010, constitutes a major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 30, 2010.

If you have any questions, call Nichelle Rashid, Regulatory Project Manager, at (301) 796-3904.

Sincerely yours,

{See appended electronic signature page}

Barbara Gould, M.B.A.H.C.M.
Chief, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

STIEFEL
LABORATORIES
INC

HYPHANOX 200MG FILM-
COATED TABLETS

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/s/

BARBARA J GOULD
01/27/2010

REQUEST FOR CONSULTATION

TO (Office/Division): Office of Surveillance and Epidemiology/
Division of Risk Management
Attention: Janet Anderson

FROM (Name, Office/Division, and Phone Number of Requestor):
Nichelle Rashid, RPM /DDDP (301) 796-3904
Snezana Trajkovic (Clinical reviewer) (301) 796-4782
David Kettl (Clinical Team leader) (301) 796-2105

DATE
01/26/10

IND NO.
NA

NDA NO.
22-484

TYPE OF DOCUMENT
Original NDA

DATE OF DOCUMENT
March 31, 2009

NAME OF DRUG
TRADENAME
(Itraconazole) 200 mg Film-coated Tablets

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG
5

DESIRED COMPLETION DATE
February 12, 2010

NAME OF FIRM: Stiefel Laboratories, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): NEW NDA |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

Original NDA submitted for the treatment of onychomycosis of the toenail (b) (4)
Hyphanox is a new formulation of an already approved drug marketed under the name of Sporanox.

eCTD application and available on edr site for NDA 22-484, Hyphanox (itraconazole) 200 mg Film-coated Tablets at the following network location: <\\CDSESUB1\EVSPROD\NDA022484\022484.ENX>

We would like to request top-line, unvetted search for cases of anaphylaxis or hypersensitivity to itraconazole. PLR labeling rules suggest that theoretical hazards not be included. If actual cases are reported, then it must be worded to explain the type and nature of the adverse reaction. If there are no cases in the AERS search, we would not include the statement, "Tradename itraconazole should not be administered to individuals who are hypersensitive to

itraconazole " as was typically included in older labels.

If you are any questions, please contact me at (301) 796-3904, Snezana Trajkovic (medical reviewer) at (301) 796-4782, or David Kettl (Medical Team leader) at (301) 796- 2105.

SIGNATURE OF REQUESTOR

Nichelle Rashid

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

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HYPHANOX 200MG FILM-
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/s/

NICHELLE E RASHID

01/28/2010

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH
Division: DOED
Mail Code: HFZ-460
Consulting Reviewer Name: Eric Mann, MD
Building/Room #: 66/2438
Phone #: (301) 796-6460
Fax #:
Email Address: Eric.Mammn@fda.hhs.gov
RPM/CSO Name and Mail Code: Pauline Fogarty

From (Originating Center):

Center: CDER
Division: Division of Dermatology and Dental Products
Mail Code: HFD-540
Requesting Reviewer Name: Snezana Trajkovic
Building/Room #: WO WO 22 Rm# 5164
Phone#: 301-796-4782
Fax #:
Email Address: Snezana.Trajkovic@fda.hhs.gov
RPM/CSO Name and Mail Code: Nichelle Rashid (HFD-540)
Requesting Reviewer's Concurring Supervisor's Name: David Kettl

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 01/14/10 Requested Completion Date: **01/22/10**
Submission/Application Number: NDA 22-484 Submission Type: NDA
Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product
Submission Receipt Date: 03/31/09 Official Submission Due Date: 12/10/09
Name of Product: Itraconazole Tablets, 200 mg Name of Firm: Stiefel Laboratories, Inc.

Intended Use: Oral treatment of onychomycosis of the toenail (b) (4)

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Documents to be returned to Requesting Reviewer? π Yes π No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Itraconazole tablet 200mg is a new formulation of already marketed drug Sporanox. In postmarketing experience of Sporanox temporary as well as permanent hearing loss were reported and included in the Sporanox label. Sporanox did not have audiology evaluation during their trial.

Itraconazole tablet label is mostly derived from Sporanox label to which they have Right of Reference.

The sponsor of the Itraconazole tablet included hypoacusis as adverse event in their table of adverse events, but the rate is the same as placebo.

We would like your opinion on sponsor's claim that results of audiology evaluation was similar between Itraconazole 200mg tablet and placebo groups.

We know that this is a short notice for this consult. We would appreciate your preliminary opinion before the end of next week."

Type of Request: Consultative Review π Collaborative Review

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

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/s/

NICHELLE E RASHID

01/15/2010

MEMORANDUM OF TELECON

DATE: January 11, 2010 2:06pm

APPLICATION NUMBER: NDA 022484

BETWEEN:

Name: Devon Allen, Vice-President of Operations and Product Development
Phone: (919) 990-9206
Representing: Stiefel Laboratories, Inc.

AND

Name: Nichelle Rashid, Regulatory Health Project Manager
Division of Dermatology and Dental Products, HFD-540

SUBJECT: Requested Information

Background: A clinical pharmacology information request was sent to sponsor on December 23, 2009 for NDA 22-484 for Itraconazole Tablets, 200 mg. A response was submitted on January 7, 2010 and received on January 7, 2010. Upon reviewing the response, the clinical pharmacology reviewer noted that the actual articles were not included in the submission. A teleconference was held to request the missing information.

Call: The Agency requested that the sponsor send the actual articles and rationale for drugs that were included in the drug interaction section of the labeling. The Agency requested that information be submitted to the Division of Dermatology and Dental Products as soon as possible. The Agency also requested that the information be faxed to RPM's attention at (301) 796-9895. The Agency stated that if the sponsor had any questions that she was to contact the Project Manager for this IND at (301) 796-3904. The call was concluded.

Nichelle E. Rashid
Regulatory Health Project Manager
Division of Dermatology & Dental Products

ADDENDUM:

The sponsor submitted official copies of the responses to the information requests on January 13 and 15, 2010.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

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/s/

NICHELLE E RASHID
03/02/2010



NDA 22-484

INFORMATION REQUEST

Stiefel Laboratories, Inc.
Attention: Devon Allen, MS, RAC
Director, Regulatory Affairs
20 T.W. Alexander Drive
P.O. Box 14910
Research Triangle Park, NC 27709

Dear Ms. Allen:

Please refer to your March 31, 2009 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hyphanox™ (itraconazole) Film-Coated Tablets, 200 mg.

We are reviewing your response to our 11/05/09 information request related to drug-drug interactions.

We are concerned that there are unlabeled drug-drug interactions in your proposed labeling. Provide proposed labeling additions, and any additional information to support safety labeling in the drug interactions section 7, and other sections of the label as appropriate, that reflects current scientific information, or a rationale as to why certain products should not be included.

Please submit the information above by Thursday, January 7, 2009.

If you have any questions, call me at (301) 796-3904.

Sincerely,

{See appended electronic signature page}

Nichelle E. Rashid
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

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/s/

NICHELLE E RASHID
12/23/2009

REQUEST FOR CONSULTATION

TO (Office/Division): **Office of Regulatory Policy**
Attention: **Emily Thakur**
Kristine Bina

FROM (Name, Office/Division, and Phone Number of Requestor):
Nichelle Rashid, RPM /DDDP (301) 796-3904
Snezana Trajkovic (Clinical reviewer) (301) 796-4782
David Kettl (Clinical Team leader) (301) 796-2105

DATE 12/04/09	IND NO. NA	NDA NO. 22-484	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT March 31, 2009
NAME OF DRUG Hyphanox (Itraconazole) 200 mg Film-coated Tablets		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG 5	DESIRED COMPLETION DATE December 18, 2009

NAME OF FIRM: **Stiefel Laboratories, Inc.**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|---|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): NEW NDA |
|--|---|---|

II. BIOMETRICS

- | | |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

Original NDA submitted for the treatment of onychomycosis of the toenail (b) (4)
Hyphanox is a new formulation of an already approved drug marketed under the name of Sporanox.

Please advise on the following question:

NDA 22-484 Hyphanox was submitted under the 505(b)(1) pathway. The applicant has indicated that they have a right of reference to the clinical and nonclinical data from the Sporanox NDA, and the right of reference is not limited or restricted. Sporanox was originally approved in 1992, but now carries a boxed warning from 2002 for cardiac effects. Though the applicant conducted their own Phase 3 study, the annotated labeling provided for Hyphanox contains verbatim wording from the Sporanox labeling in many sections, including the boxed warning and extensive sections on drug interactions. Does having a right of

reference to data in an NDA authorize use of wording from the labeling of the referenced product?

If you are any questions, please contact me at (301) 796-3904, Snezana Trajkovic (Clinical reviewer) at (301) 796-4782, or David Kettl (Clinical Team leader) at (301) 796- 2105.

SIGNATURE OF REQUESTOR Nichelle Rashid	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

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/s/

NICHELLE E RASHID
12/08/2009

MEMORANDUM OF TELECON

DATE: November 17, 2009 11:30 am

APPLICATION NUMBER: NDA 22-484, Hyphanox (itraconazole) Tablets, 200mg

BETWEEN:

Name: David Angulo, MD, Executive Director, Global Clinical Research
Salisa Hauptmann, MPH, RAC, VP, Global Regulatory Affairs
Devon Allen, MPH, RAC, Senior Director, Regulatory Affairs
Isabel Drzewiecki, Consultant, Regulatory Affairs
Charles Barranco, Clinical Project Leader
Stephen Young, Director, Clinical Operations
Harry Klauda, PhD, Distinguished Research Fellow, Research and
Preclinical Development
Xue "Snow" Ge, PhD, Associate Director, DMPK/Bioanalytical
Sara Johnson, Manager, Global Portfolio and Project Management
Phone: (888) 637-4753
Representing: Stiefel Laboratories, Inc.

AND

Name: David Kettl, M.D., Clinical Team Leader, DDDP
Snezana Trajkovic, M.D., Clinical Reviewer, DDDP
Abimbola Adebowale, Ph.D., Clinical Pharmacology Reviewer, DCP 3
Seongeun Cho, Ph.D., Clinical Pharmacology Reviewer, DCP 3

SUBJECT: Clinical Pharmacology Information Request

This teleconference was requested by the Agency to discuss the applicant's response to the Agency's November 5, 2009 Information Request regarding information on drug interaction involving itraconazole for NDA 22-484 Hyphanox Tablets.

The Agency asked for clarification on the following points:

- Whether the applicant had access to the clinical trials that studied drug interaction with itraconazole (e.g. SPORANOX) and any clinical implications as this information should be included in the DRUG INTERACTIONS section of the labeling.
- If the applicant does not have access to the drug interaction studies, to what degree does the applicant have access to the data from those studies given their right of reference to SPORANOX.

The applicant stated that they did have right of reference; however, they do not have ready access to the clinical data.

The Agency asked the applicant to conduct a comprehensive and inclusive literature search on drug interaction studies involving itraconazole and provide a summary of the updated drug list to be incorporated into the labeling.

The applicant agreed.

The Agency requested that the applicant submit their response to the information request by close of business Monday, November 23, 2009 by facsimile, followed by an official submission to the NDA.

The applicant agreed.

The discussion ended amicably.

ADDENDUM

The applicant submitted information regarding drug interaction studies involving itraconazole on November 23, 2009, via email. The official response was submitted to the Agency on December 8, 2009.

Abimbola Adebawale, Ph.D.
Clinical Pharmacology Reviewer, DCP 3

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

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/s/

ABIMBOLA O ADEBOWALE
12/10/2009



NDA 22-484

INFORMATION REQUEST

Stiefel Laboratories, Inc.
Attention: Devon Allen, MS, RAC
Director, Regulatory Affairs
20 T.W. Alexander Drive
P.O. Box 14910
Research Triangle Park, NC 27709

Dear Ms. Allen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tradename (itraconazole) Film-Coated Tablets, 200 mg.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA. Please respond no later than close of business, Wednesday, November 11, 2009.

The drug substance establishment information provided to-date in the NDA is inconsistent with DMF 10725. Submit the drug substance establishment information to the NDA again with a complete and accurate list of facilities that are involved in manufacturing/testing of the drug substance. Amend your NDA with all necessary contact information for each establishment with contact name, address, phone and fax numbers, and email addresses.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Nichelle Rashid, Regulatory Project Manager in the Division of Dermatology and Dental Products (Nichelle.Rashid@fda.hhs.gov).

If you have any questions with regard to this information request letter, contact Jeannie David, Regulatory Project Manager, at (301) 796-7472.

Sincerely,

{See appended electronic signature page}

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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

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/s/

MOO JHONG RHEE
11/10/2009
Chief, Branch III



NDA 22-484

INFORMATION REQUEST

Stiefel Laboratories, Inc.
Attention: Devon Allen, MS, RAC
Director, Regulatory Affairs
20 T.W. Alexander Drive
P.O. Box 14910
Research Triangle Park, NC 27709

Dear Ms. Allen:

Please refer to your March 31, 2009 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hyphanox™ (itraconazole) Film-Coated Tablets, 200mg.

Itraconazole is a strong CYP3A4 inhibitor and there exist vast amounts of information on drug interaction involving itraconazole either as a modulator or a substrate. As such, the Section 7 Drug Interaction in your proposed label, which you adopted from the current label for Sporanox, is not adequate. Provide the following information as specified below:

1. A table grouping drugs based on the level of evidence on drug interaction potential

Group 1: Drugs for which the clinical studies evaluating drug interactions with itraconazole were actually conducted.

Group 2: Drugs for which drug interactions were reported in the literature

Group 3: Drugs having drug interaction potentials based on prediction

For Group 1, provide a brief description of the study and results.

For Group 2, provide reference of the literature.

2. A separate table listing all contraindicated drugs with itraconazole
3. There exist several classes of hypoglycemic agents. Clarify the section below in your proposed label by including the names of specific drugs (or drug classes).

7.16 Oral Hypoglycemic Agents

Please provide the information for our review by close of business, Tuesday, November 10, 2009.

If you have any questions, call me at (301) 796-3904.

Sincerely,

{See appended electronic signature page}

Nichelle E. Rashid
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

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ORIG-1

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/s/

NICHELLE E RASHID

11/05/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 022484

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Stiefel Laboratories, Inc.
20 T.W. Alexander Drive
P.O. Box 14910
Research Triangle Park, North Carolina 27709

ATTENTION: Devon Allen
Director, Regulatory Affairs

Dear Ms. Allen:

Please refer to your New Drug Application (NDA) dated March 31, 2009, received March 31, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Itraconazole Tablets, 200 mg.

We also refer to your June 26, 2009, correspondence, received June 26, 2009, requesting review of your proposed proprietary name, Hyphanox. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

(b) (4)

We acknowledge that our conclusion differs from the conclusion reached in the External Name Study you submitted in support of the proposed name. However, this difference is attributable to the lack of comparative analysis with [REDACTED]^{(b) (4)} as a potential source of confusion.

We note that you have proposed an alternate proprietary name in your submission dated June 26, 2009. In order to initiate the review of the alternate proprietary name, [REDACTED]^{(b) (4)}, submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Nichelle Rashid at (301) 796-3904.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

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INC

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/s/

CAROL A HOLQUIST

09/24/2009



NDA 22-484

INFORMATION REQUEST

Stiefel Laboratories, Inc.
Attention: Devon Allen, MS, RAC
Director, Regulatory Affairs
20 T.W. Alexander Drive
P.O. Box 14910
Research Triangle Park, NC 27709

Dear Ms. Allen:

Please refer to your March 31, 2009 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hyphanox™ (itraconazole) Film-Coated tablet, 200mg.

We are reviewing the CMC section of your submission and have the following information requests:

1. Provide the study report for the forced degradation studies of the drug product.
2. Provide a translation of the Flemish operation SOP 101-149.
3. While solution stability studies were mentioned in validating the HPLC in-house assay analytical method for itraconazole, the studies themselves were not given. Please describe these studies and give the data, and conclusions made from them.
4. Likewise, the solution stability studies in validating the HPLC in-house related substances analytical method for itraconazole were not given. Please describe these studies and give the data and conclusions made from them.

We are also reviewing the labeling section of your submission and have the following information request:

1. Submit a mock-up of the carton labeling and the blister card representative of the packaging configuration you intend to introduce into the marketplace.

We request a prompt written response by August 21, 2009 for labeling request, and by September 1, 2009 for CMC requests in order to continue our evaluation of your NDA.

.

If you have any questions, call me at (301) 796-3904.

Sincerely,

{See appended electronic signature page}

Nichelle E. Rashid
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

NICHELLE E RASHID
08/18/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-484

Stiefel Laboratories, Inc.
Attention: Devon Allen, MS, RAC
Director, Regulatory Affairs
20 T.W. Alexander Drive
P.O. Box 14910
Research Triangle Park, NC 27709

Dear Ms. Allen:

Please refer to your new drug application (NDA) dated March 31, 2009, received on March 31, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Hyphanox™ (itraconazole) Film-Coated Tablets, 200mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 31, 2009.

During our filing review of your application, we identified the following potential review issues:

CMC:

1. Clarify whether the proposed to-be-marketed container/closure system is child resistant.
2. Provide representative samples packaged in the to-be-marketed container/closure system for visual examination of the product.

Clinical Pharmacology:

1. A study report documenting cross-validation of two analytical methods (HPLC-UV and HPLC MS/MS) was not provided. The referenced documents, BTM-1054-R0, is regarding a method development for HPLC/MS/MS. Submit the cross-validation analytical study report.

Biostatistics:

1. In your study report you state the following, “During the course of the study, there were subjects for whom the study drug dispensation information was temporarily available to blinded personnel”. Based upon the electronic data sets, this appears to have occurred for 93 subjects enrolled in 7 centers. The date of enrollment for these 93 subjects ranged from December 7, 2006 to September 12, 2007.

It should be noted that these 7 centers enrolled a total of 301 subjects of which 287 subjects were enrolled between December 7, 2006 and September 12, 2007. The trial as a whole enrolled approximately 90% of subjects between these two dates.

The study report provides little details about the nature of the unblinding, and it is unclear how this may impact the study findings. You should provide all relevant information about the potential break of the blind. This information should include, but not be limited to, the following:

- Clarify how the blind was broken and the date and time it was discovered.
 - Define the corrective action taken to put the blind back in place and the date when this occurred for each center.
 - Define the role of the personnel who became unblinded.
 - Clarify why the blind was only broken for some subjects within a center and not other centers.
 - State whether or not the Agency was made aware of the unblinding issues prior to NDA submission.
2. The Define.XML files for the listing of data sets and descriptions of individual data sets cannot be printed fully using Microsoft Internet Explorer (or any other known FDA supported software). Submit Define.PDF files to the NDA.

We are providing the above comments to give you preliminary notice of potential review issues. 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 are also reviewing the draft labeling submitted in Physician’s Labeling Rule (PLR) format, and have identified the following formatting issues:

In the Highlights section:

1. According to 21 CFR 201.57(d)(8), the Highlights must be limited in length to one-half page.
2. According to 21 CFR 210.57(a)(4), the boxed warning is not to exceed a length of 20 lines.

3. Do not use the “TM” symbols after the drug names.
4. Do not include the pregnancy category C, see comment #34 to Preamble.
5. For pregnancy category C drugs, list pregnancy under Use in Specific Populations in the Highlights section followed by the following statement: “Based on animal data, may cause fetal harm,” or “No human or animal data. Use only if clearly needed. If a pregnancy registry exists, state “Pregnancy registry available.” Conclude the entire statement with a cross-reference to Pregnancy subsection (8.1).
6. The revision date should be the month/year that the application is approved.

In the Contents (Table of Contents) section:

7. The same title for the boxed warning that appears in the HL and FPI must also appear at the beginning of the Table of Contents in upper-case letters and bold type.
8. Avoid using acronyms, CHF and HMG, in subsection headings. These acronyms should be spelled out.

In the Full Prescribing Information (FPI) Section:

9. The cross-references should be the section heading followed the numerical identifier. The cross-reference should be in brackets. The use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print.
10. Use “TM” symbol only once in the content of labeling.
11. Other than the required bolding in 21 CFR 201.57(d)(1), (d)(5) and (d)(10), use bold print sparingly. Use another method for emphasis such as italics and underline.
12. Do not include NDC Numbers in the DOSAGE FORMS AND STRENGTHS section.
13. Do not include “How Supplied” information (i.e. packaging) in the DOSAGE FORMS AND STRENGTHS section.
14. Include following statement (or appropriate modification) preceding presentation of adverse reactions from clinical trials in the ADVERSE REACTIONS section:
“Because clinical trials are conducted under widely varying conditions, adverse reaction rate observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
15. Reference the Patient Packaging Insert (PPI) in the Patient Counseling Information section.

Address the identified labeling deficiencies/issues and re-submit labeling by August 31, 2009. This updated version of labeling will be used for further labeling discussions.

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

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Nichelle Rashid, Regulatory Project Manager, at (301) 796-3904.

Sincerely,

{See appended electronic signature page}

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

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/s/

Susan Walker

6/5/2009 02:57:40 PM



NDA 22-484

INFORMATION REQUEST LETTER

Stiefel Laboratories, Inc.
Attention: Devon Allen, MS, RAC
Director, Regulatory Affairs
20 T.W. Alexander Drive
P.O. Box 14910
Research Triangle Park, NC 27709

Dear Ms. Allen:

Please refer to your March 31, 2009 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hyphanox™ (itraconazole) Film-Coated Tablets, 200 mg.

We are reviewing your submission and have the following information requests. We request a prompt written response by June 15, 2009 in order to continue our evaluation of your NDA.

Biostatistics:

In your study report you state the following, "During the course of the study, there were subjects for whom the study drug dispensation information was temporarily available to blinded personnel". Based upon the electronic data sets, this appears to have occurred for 93 subjects enrolled in 7 centers. The date of enrollment for these 93 subjects ranged from December 7, 2006 to September 12, 2007.

It should be noted that these 7 centers enrolled a total of 301 subjects of which 287 subjects were enrolled between December 7, 2006 and September 12, 2007. The trial as whole enrolled approximately 90% of subjects between these two dates as well.

The study report provides little details about the nature of the unblinding, and it is unclear how this may impact the study findings. You should provide all relevant information about the potential break of the blind. This information should include, but not be limited to the following:

- Clarify how the blind was broken and the date and time it was discovered.
- Define the corrective action taken to put the blind back in place and the date when this occurred for each center.
- Define the role of the personnel who became unblinded.
- Clarify why the blind was only broken for some subjects within a center and not other centers.

- State whether or not the Agency was made aware of the unblinding issues prior to NDA submission.

If you have any questions, call Nichelle Rashid, Regulatory Project Manager, at 301-796-3904.

Sincerely,

{See appended electronic signature page}

Margo Owens
Project Management Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margo Owens

6/1/2009 05:02:27 PM

REQUEST FOR CONSULTATION

TO (Office/Division): Office of Surveillance and Epidemiology/
Division of Risk Management
Attention: Janet Anderson

FROM (Name, Office/Division, and Phone Number of Requestor):
Nichelle Rashid, RPM /DDDP (301) 796-3904
Snezana Trajkovic (Clinical reviewer) (301) 796-4782
David Kettl (Clinical Team leader) (301) 796-2105

DATE
05/12/09

IND NO.
NA

NDA NO.
22-484

TYPE OF DOCUMENT
Original NDA

DATE OF DOCUMENT
March 31, 2009

NAME OF DRUG
Hyphanox (Itraconazole)
200 mg Film-coated Tablets

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG
5

DESIRED COMPLETION DATE
August 15, 2009

NAME OF FIRM: Stiefel Laboratories, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): NEW NDA |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

Original NDA submitted for the treatment of onychomycosis of the toenail (b) (4)
Hyphanox is a new formulation of an already approved drug marketed under the name of Sporanox.

eCTD application and available on edr site for NDA 22-484, Hyphanox (itraconazole) 200 mg Film-coated Tablets at the following network location: <\\CDSESUB1\EVSPROD\NDA022484\022484.ENX>

Please review the attached package insert and patient package insert. The PDUFA date is January 31, 2010.

If you are any questions, please contact me at (301) 796-3904, Snezana Trajkovic (medical reviewer) at (301) 796-4782, or David Kettl (Medical Team leader) at (301) 796- 2105.

SIGNATURE OF REQUESTOR Nichelle Rashid	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Nichelle Rashid
5/14/2009 04:19:32 PM

REQUEST FOR CONSULTATION

TO (Office/Division): **Office of Surveillance and Epidemiology/
Division of Medication Error Prevention and Analysis
Attention: Janet Anderson**

FROM (Name, Office/Division, and Phone Number of Requestor):

**Nichelle Rashid, RPM /DDDP (301) 796-3904
Snezana Trajkovic (Clinical reviewer) (301) 796-4782
David Kettl (Clinical Team leader) (301) 796-2105**

DATE 05/12/09	IND NO. NA	NDA NO. 22-484	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT March 31, 2009
NAME OF DRUG Hyphanox (Itraconazole) 200 mg Film-coated Tablets		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG 5	DESIRED COMPLETION DATE August 15, 2009

NAME OF FIRM: **Stiefel Laboratories, Inc.**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): NEW NDA |
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II. BIOMETRICS

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| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
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III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
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IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

Original NDA submitted for the treatment of onychomycosis of the toenail (b) (4)
Hyphanox is a new formulation of an already approved drug marketed under the name of Sporanox.

eCTD application and available on edr site for NDA 22-484, Hyphanox (itraconazole) 200 mg Film-coated Tablets at the following network location: <\\CDSESUB1\EVSPROD\NDA022484\022484.ENX>

Please review the attached package insert, patient package insert and carton labeling. The PDUFA date is January 31, 2010.

If you are any questions, please contact me at (301) 796-3904, Snezana Trajkovic (medical reviewer) at (301) 796-4782, or David Kettl (Medical Team leader) at (301) 796- 2105.

SIGNATURE OF REQUESTOR Nichelle Rashid	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Nichelle Rashid
5/14/2009 04:10:09 PM

REQUEST FOR CONSULTATION

TO (Office/Division): Office of Medical Policy/
Division of Drug Marketing, Advertising and
Communications
Attention: Paul Loebach

FROM (Name, Office/Division, and Phone Number of Requestor):
Nichelle Rashid, RPM/DDDP (301) 796-3904
Snezana Trajkovic (Clinical reviewer) (301) 796-4782
David Kettl (Clinical Team leader) (301) 796- 2105

DATE 05/12/09	IND NO. NA	NDA NO. 22-484	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT March 31, 2009
NAME OF DRUG Hyphanox (Itraconazole) 200 mg Film-coated Tablets		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG 5	DESIRED COMPLETION DATE August 15, 2009

NAME OF FIRM: Stiefel Laboratories, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): NEW NDA |
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II. BIOMETRICS

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| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
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III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

Original NDA submitted for the treatment of onychomycosis of the toenail (b) (4)
Hyphanox is a new formulation of an already approved drug marketed under the name of Sporanox.

eCTD application and available on edr site for NDA 22-484, Hyphanox (itraconazole) 200 mg Film-coated Tablets at the following network location: <\\CDSESUB1\EVSPROD\NDA022484\022484.ENX>

Please review the attached package insert, patient package insert and carton labeling. The PDUFA date is January 31, 2010.

If you are any questions, please contact me at (301) 796-3904, Snezana Trajkovic (medical reviewer) at (301) 796-4782, or David Kettl (Medical Team leader) at (301) 796- 2105.

SIGNATURE OF REQUESTOR Nichelle Rashid	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Nichelle Rashid
5/14/2009 04:07:26 PM

REQUEST FOR CONSULTATION

TO (Office/Division):
Division of Cardiovascular and Renal Products
Attn: Ed Fromm

FROM (Name, Office/Division, and Phone Number of Requestor):
Nichelle Rashid, RPM /DDDP (301) 796-3904
Snezana Trajkovic (Clinical reviewer) (301) 796-4782
David Kettl (Clinical Team leader) (301) 796-2105

DATE 05/04/09	IND NO.	NDA NO. 22-484	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT 03/31/09
NAME OF DRUG Hyphanox (Itraconazole) 200 mg Film-coated Tablets		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG 5	DESIRED COMPLETION DATE August 15, 2009

NAME OF FIRM: Stiefel Laboratories, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
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<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): NEW NDA |
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II. BIOMETRICS

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| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
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III. BIOPHARMACEUTICS

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|--|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

Original NDA submitted for the treatment of onychomycosis of the toenail (b) (4) Hyphanox is a new formulation of an already approved drug marketed under the name of Sporanox.

eCTD application and available on edr site for NDA 22-484, Hyphanox (itraconazole) 200 mg Film-coated Tablets at the following network location: <http://CDSESUB1\EVSPROD\NDA022484\022484.ENX>

Please evaluate cardiac adverse events and EKG findings for this NDA product. Sporanox, a related product, has a boxed warning for congestive heart failure, and Warnings for negative inotropic effects.

If you are any questions, please contact me at (301) 796-3904, Snezana Trajkovic (medical reviewer) at (301) 796-4782, or David Kettl (Medical Team leader) at (301) 796- 2105.

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

Nichelle Rashid	<input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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this page is the manifestation of the electronic signature.**

/s/

Nichelle Rashid
5/5/2009 04:28:25 PM

REQUEST FOR CONSULTATION

TO (Office/Division):
Division of Anti-Infectives
Frances LeSane, CPMS/ Maureen Dillion-Parker, CPMS

FROM (Name, Office/Division, and Phone Number of Requestor):
Nichelle Rashid, RPM /DDDP (301) 796-3904
Snezana Trajkovic (Clinical reviewer) (301) 796-4782
David Kettl (Clinical Team leader) (301) 796- 2105

DATE 04/10/09	IND NO.	NDA NO. 22-484	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT 03/31/09
NAME OF DRUG Hyphanox (Itraconazole) 200 mg Film-coated Tablets		PRIORITY CONSIDERATION May 15, 2008 (filing date)	CLASSIFICATION OF DRUG 5	DESIRED COMPLETION DATE Request filing issues for filing meeting (will be scheduled by RPM) if filed submission may be on 10 month goal date of January 31, 2010.

NAME OF FIRM: Stiefel Laboratories, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): NEW NDA |
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II. BIOMETRICS

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| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
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IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

Original NDA submitted for the treatment of onychomycosis of the toenail (b) (4) Hyphanox is a new formulation of an already approved drug marketed under the name of Sporanox.

eCTD application and available on edr site for NDA 22-484, Hyphanox (itraconazole) 200 mg Film-coated Tablets at the following network location: <\\CDSESUB1\EVSPROD\NDA022484\022484.ENX>

Please review for Clinical Microbiology issues to include labeling, if filed.

If you are any questions, please contact me at (301) 796-3904, Snezana Trajkovic (medical reviewer) at (301) 796-4782, or David Kettl (Medical Team leader) at (301) 796- 2105.

SIGNATURE OF REQUESTOR Nichelle Rashid	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Frances LeSane

4/14/2009 01:22:15 PM



NDA 22-484

NDA ACKNOWLEDGMENT

Stiefel Laboratories, Inc.
Attention: Devon Allen, MS, RAC
Director, Regulatory Affairs
20 T.W. Alexander Drive
P.O. Box 14910
Research Triangle Park, NC 27709

Dear Ms. Allen:

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

Name of Drug Product: Hyphanox™ (itraconazole) Film-Coated Tablets, 200mg

Date of Application: March 31, 2009

Date of Receipt: March 31, 2009

Our Reference Number: NDA 22-484

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 30, 2009 in accordance with 21 CFR 314.101(a).

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

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dental Products
5901-B Ammendale Road

Beltsville, MD 20705-1266

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

If you have any questions, call me at (301) 796-3904.

Sincerely,

{See appended electronic signature page}

Nichelle E. Rashid
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Nichelle Rashid
4/10/2009 12:30:33 PM

REQUEST FOR CONSULTATION

TO (Office/Division):
Division of Special Pathogen and Transplant Products
Judith Milstein
Diana Willard

FROM (Name, Office/Division, and Phone Number of Requestor):
Nichelle Rashid, RPM /DDDP (301) 796-3904
Snezana Trajkovic (Clinical reviewer) (301) 796-4782
David Kettl (Clinical Team leader) (301) 796- 2105

DATE 01/08/09	IND NO.	NDA NO. 22-484	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT 03/31/09
NAME OF DRUG Hyphanox (Itraconazole) 200 mg Film-coated Tablets		PRIORITY CONSIDERATION May 15, 2008 (filing date)	CLASSIFICATION OF DRUG 5	DESIRED COMPLETION DATE 01/22/09

NAME OF FIRM: Stiefel Laboratories, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
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<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): NEW NDA |
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II. BIOMETRICS

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|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
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<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

An original NDA for Hyphanox (itraconazole) Tablets, 200mg for the treatment of onychomycosis of the toenai (b) (4) has been submitted to DDDP. Hyphanox is a new formulation of an already approved drug marketed under the name of Sporanox.

The sponsor included into Hyphanox labeling several drugs that are reported in literature to have drug-drug interaction with Sporanox, as requested by DDDP. The sponsor also requested to have the same done for all itraconazole containing drugs (including Sporanox). DDDP would like the opinion of Special Pathogen Team on this subject as well on other parts of Hyphanox label that are taken from Sporanox label under ROR. We would like to invite TL, MO, Biopharm, Pharm/Tox, and Clin. Microbiology to take part in labeling meeting on Wednesday, January 13, 2010.

Please review the attached labeling.

eCTD application and available on edr site for NDA 22-484, Hyphanox (itraconazole) 200 mg Film-coated Tablets at the following network location: <\\CDSESUB1\EVSPROD\NDA022484\022484.ENX>

If you have any questions, please contact me at (301) 796-3904, Snezana Trajkovic (medical reviewer) at (301) 796-4782, or David Kettl (Medical Team leader) at (301) 796- 2105.

SIGNATURE OF REQUESTOR Nichelle Rashid	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

17 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

STIEFEL
LABORATORIES
INC

HYPHANOX 200MG FILM-
COATED TABLETS

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/s/

NICHELLE E RASHID
01/12/2010