

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-026

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

13.0 Patent Information

The following information is provided in accordance with 21CFR314.53.

Patent Number: 4,911,932
Issue Date: March 27, 1990
Patent Expires: March 27, 2007

Type of Patent: Drug Product Composition

Patent Owner: Johnson & Johnson

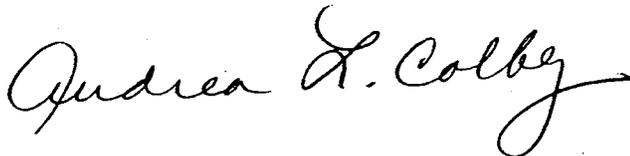
The undersigned declares that Patent 4,911,932 covers the formulation, composition, and/or method of use of 0.25% miconazole nitrate ointment (PEDIASSTATTM). This product is the subject of this application for which approval is being sought.

To the best of our knowledge there are no patents which claim the drug or the drug product or method of using the drug product which could reasonably assert a claim of patent infringement upon this product.

14.0 Certification

Paragraph III Certification

In our opinion and to the best of our knowledge the product which is the subject of this application is protected by patent number 4,911,932 which will expire on March 27, 2007. This certification is made in accordance with Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act.



Andrea L. Colby
Office of General Counsel
Johnson & Johnson

Item 13
Patent Information

The following information is provided in accordance with 21CFR314.53

Patent Number: 4,911,932
Issue Date: March 27, 1990
Patent Expires: March 27, 2007

Type of Patent: Drug Product Composition

Patent Owner: Johnson & Johnson

Exclusive Licensee: Barrier Therapeutics, Inc.

The undersigned declares that Patent 4,911,932 covers the formulations, composition, and/or method of use of 0.25% Miconazole nitrate ointment (ZIMYCANTM). This product is the subject of this application for which approval is being sought.

To the best of our knowledge there are no patents which claim the drug or the drug product or method of using the drug product which could reasonably assert a claim of patent infringement upon this product.

Item 14
Patent Certification

Paragraph III Certification

In our opinion and to the best of our knowledge the product which is the subject of this application is protected by patent number 4,911,932 which will expire on March 27, 2007. This certification is made in accordance with Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act.



Albert C. Bristow
General Counsel
Barrier Therapeutics, Inc.

EXCLUSIVITY SUMMARY

NDA # 21-026

SUPPL #

HFD # 540

Trade Name Vusion Ointment

Generic Name miconazole nitrate 0.25%, zinc oxide 15%, white petrolatum ointment 81.35%

Applicant Name Barrier Therapeutic, Inc

Approval Date, If Known February 16, 2006 (PDUFA date)

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)(2)

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.

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

d) Did the applicant request exclusivity?

YES NO

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

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#

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# 17-494	Monistat Cream
NDA# 17-450	Monistat Vaginal Cream
NDA# 18-040	Monistat IV

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:

BT100USA/100

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

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: Millie Wright

Title: Project Manager

Date:

Name of Office/Division Director signing form: Stanka Kukich, M.D.

Title: Acting Division Director

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

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

/s/

Stanka Kukich
2/9/2006 04:26:03 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA#:21-026 _____ Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: August 16, 2005 _____ Action Date: February 16, 2006 _____

HFD-540 _____ Trade and generic names/dosage form: TRADENAME VUSION(0.25% miconazole nitrate ointment, 15% zinc oxide, 81.35% white petrolatum ointment) .

Applicant:Barrier Therapeutics, Inc. _____ Therapeutic Class: 3S

Indication(s) previously approved: N/A

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

Number of indications for this application(s): 1

Indication #1 : Indicated for the adjunctive treatment of diaper dermatitis only when complicated by candidiasis, as documented by microscopic evidence of pseudohyphae and/or budding yeasts, in immunocompetent pediatric patients 4 weeks and older.

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

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

____ Age/weight range being partially waived: 3-18 years

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

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

X Other: PREA requirement has been met

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

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

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

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

Section D: Completed Studies

Age/weight range of completed studies: 2 weeks to 2 years

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

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

This page was completed by:

{See appended electronic signature page}
Millie Wright _____
Regulatory Project Manager

cc: NDA 21-026
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

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

Indication #2: _____

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

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

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

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

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-026
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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

/s/

Stanka Kukich
2/2/2006 05:38:00 PM

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: <u>21026</u>	Trade Name: <u>PEDIASTAT (MICONAZOLE NITRATE)OINT</u> <u>0.25%</u>
Supplement Number:	Generic Name: <u>MICONAZOLE NITRATE</u>
Supplement Type:	Dosage Form: <u>Ointment; Topical</u>
Regulatory Action: <u>NA</u>	Proposed Indication: <u>Indicated for infants with diaper dermatitis.</u>

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication, but is inadequate to support pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy -
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Please refer to the NA letter issued 6/28/99. This AZ was submitted 1/21/00 in response to the 6/28/99 NA letter. No new clinical studies submitted. NA letter to be issued 7/24/00. MAW 7/19/00

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MILDRED WRIGHT

Mildred A. Wright

Signature

7/19/00

Date

cc
 Orig NOA 21026
 HFD-540/Div file
 HFD-540/M Wright

JW 7/19/00

Item 16
Debarment Certification

Barrier Therapeutics, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Name: Isabel Drzewiecki

Title: Global Head, Regulatory Operations

Signature: *Isabel Drzewiecki*

Date: October 27, 2004

Appears This Way
On Original

AUG 24 1998

16.0 Certification of Debarment

This is to certify that to the best of my knowledge, neither Johnson & Johnson Consumer Companies, Inc. (hereinafter referred to as "Company") nor any person employed thereby has been debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetic Act.

No debarred person will in the future be employed by the Company in connection with any work to be performed for, or on behalf of Johnson & Johnson Consumer Companies, Inc., which may later become part of any application for approval of a drug or biologic by the Food and Drug Administration.

The company is also not aware of any outside contract laboratory, consultant or contract research organization or employees thereof engaged by the Company being debarred.

If at any time after execution of this certification, the Company becomes aware that the Company or any person employed by the Company is in the process of being debarred, the Company hereby certifies that the Company will so notify the Food and Drug Administration.

Sincerely,



Robert B. Armstrong, M.D.
Vice President, Regulatory Affairs

Appears This Way
On Original

016 00001



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-026

Barrier Therapeutics, Inc.
Attention: Isabel Drzewiecki, Global Head, Regulatory Operations
600 College Road East, Suite 3200
Princeton, New Jersey 08540

Dear Ms. Drzewiecki:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for miconazole nitrate ointment, 2%.

The purpose of the teleconference was to discuss the expiration date for you pending NDA amendment.

The official minutes of that teleconference are enclosed.

If you have any questions, call Millie Wright, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

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

Enclosure

**Appears This Way
On Original**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Barrier Therapeutics, Inc.	DATE OF SUBMISSION February 15, 2006
TELEPHONE NO. (Include Area Code) 609-945-1200	FACSIMILE (FAX) Number (Include Area Code) 609- 945-1216
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 600 College Road East Suite 3200 Princeton, NJ 08540	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 021-026		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) 0.25% Miconazole Nitrate	PROPRIETARY NAME (trade name) IF ANY	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any) ZOOM	
DOSAGE FORM: Ointment	STRENGTHS: 0.25%	ROUTE OF ADMINISTRATION: Topical

(PROPOSED) INDICATION(S) FOR USE:
Treatment of diaper dermatitis complicated by candidiasis

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER

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

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

REASON FOR SUBMISSION

Response to Phase 4 Commitment Requests

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

NUMBER OF VOLUMES SUBMITTED 1 Volume THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

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

Janssen Pharmaceuticals, N.V. (Janssen, Geel) Turnhoutseweg 30 B-3240 Beerse, Belgium	Noramco, Inc. (Noramco) 1440 Olympic Drive Athen, GA 30601	DSM Pharmaceuticals, Inc. 5900 Greenville Blvd. Greenville, NC 27834
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Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 21,542.
NDA17-450, NDA17-494, NDA18-040, NDA18-520

b(4)

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

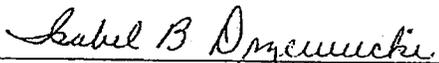
<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A.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

CERTIFICATION

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

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

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Isabel Drzewiecki Vice President Regulatory Affairs	DATE: February 15, 2006
ADDRESS (Street, City, State, and ZIP Code) 600 College Road East Suite 3200 Princeton, NJ 08540		Telephone Number (609) 945-1247

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services Food and Drug Administration CDER, HFD-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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Barrier Therapeutics Inc.
A Vision for Innovative Medicine

Waiting for special submission

February 15, 2006

Stanka Kukich, MD, Acting Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation 3, HFD-540
5901-B Ammendale Road
Beltsville, MD 20700

NDA 21-026
Miconazole Nitrate 0.25% Ointment

Indication: Diaper Dermatitis
complicated by Candidiasis

Response to Draft Labeling Proposal

Dear Dr. Kukich,

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to our submission dated February 9, 2006 in which we submitted our Physician's Package Insert in draft form which reflected our understanding and acceptance of all of the changes proposed by the Division in their fax of February 8, 2006, and the additional changes that were discussed during the teleconference on February 8, 2006. We also refer to a teleconference on February 15, 2006 during which you requested additional changes to the Clinical Studies Section of the Physician's Package Insert.

We have enclosed with this submission both a red-lined and strike-through version and a clean version of our proposed response to the labeling. In the strike-through version, deleted text has a strike-through through it and new text is underlined. We have identified each proposed change by line number.

- Lines 56: Removed period at end of sentence
- Lines 57: Removed space between paragraphs
- Line 58: Deleted the words at the beginning of the sentence, added the word to the beginning to the sentence, and attached the entire sentence to the end of the sentence on Line 56, thereby combining the two sentences into one.
- Lines 62-64: Deleted the words
- Line 72-73: Deleted the word and added the words to the beginning of the sentence.

b(4)

Barrier Therapeutics, Inc.
NDA 21-026, Miconazole Nitrate 0.25% Ointment

This submission consists of 1 volume, including a CD containing Word versions of the Physician's Package Insert, and is being submitted in duplicate with a signed FDA form 356h. Each CD has a label to confirm that it was checked on February 15, 2006 for viruses by Network Associates McAfee VirusScan Enterprise 8.0.0 and is deemed virus free. We understand that this submission and all information contained herein unless otherwise made public by Barrier Therapeutics, Inc., is CONFIDENTIAL. We are available at your convenience if you have any further questions. Please do not hesitate to contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,


Isabel B. Drzewiecki
Vice-President of Regulatory Affairs

Appears This Way
On Original



Barrier Therapeutics Inc.

A Vision for Innovative Medicine

Waiting for official submission

February 15, 2006

Stanka Kukich, MD, Acting Director
Division of Dermatologic & Dental Drug
Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, HFD-540
5901-B Ammendale Road
Beltsville, MD 20705

NDA 21-026

Miconazole Nitrate 0.25% Ointment

**Indication: Candidiasis Complicated by
Diaper Dermatitis**

**Response to Phase 4 Commitment
Requests**

Dear Dr. Kukich:

Reference is made to NDA 21-026 for Miconazole Nitrate 0.25% Ointment and to the Agency's Fax of February 3, 2006 regarding the Division's request for Phase 4 Commitments. We also refer to a teleconference held on February 15, 2006 between yourself, Shalini Jian of your Division and representatives of Barrier Therapeutics. At this time we are responding to your requests. Please find below the Agency's requests in **bold text**, followed by Barrier's responses in plain text. The only change is to add the actual dates to the agreed upon timelines.

1. An open label study to assess the systemic absorption and safety of the marketed formulation of topically applied 0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum ointment in infants with moderate to severe diaper dermatitis when complicated by Candidiasis.

Protocol to be submitted April 30, 2006

Study Start Dated August 30, 2006

Final Report Submission August 30, 2007

Barrier Therapeutics agrees to conduct this study, and to adhere to the above requested timelines.

2. A prospective 2-year longitudinal study to assess for miconazole resistance in *Candida* spp. with repeated treatment courses of the marketed formulation of topically applied .25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum ointment in infants with recurrent moderate to severe diaper dermatitis with Candidiasis. Clinical isolates of *Candida* spp. should be obtained from patients who fail to improve with marketed formulation of 0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white

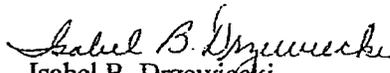
petrolatum ointment treatment followed by properly conducted in-vitro susceptibility testing. Isolates should be saved in the event that further investigation is necessary.

**Draft Protocol submitted June 30, 2006
Protocol submitted December 30, 2006
Study Start Date February 28, 2007
Final Report submitted February 28, 2009**

Barrier Therapeutics agrees to conduct this study. We agree to submit a draft Protocol June 30, 2006 and a final protocol December 30, 2006. We also agree to a study start date of February 28, 2007. As agreed to by the Agency, in order to allow for a 6-month enrollment period, we will finish the study August 30, 2009 and submit the final report November 30, 2009.

This submission consists of 1 volume and is being submitted in duplicate with a signed FDA form 356h. We understand that this submission and all information contained herein unless otherwise made public by Barrier Therapeutics, Inc. is CONFIDENTIAL. If you should have any questions, please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,


Isabel B. Drzewiecki
Vice President Regulatory Affairs

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MEMORANDUM OF TELECON

DATE: February 14, 2006

Application: NDA 21-026/Vusion

Sponsor: Barrier Therapeutic, Inc.

Topic: Sponsor's Expiration Date for pending NDA

FDA Attendees:

Moo-Jhong Rhee, Ph.D., Branch Chief
Steve Hathaway, Ph.D., Reviewing Chemist
Millie Wright, Project Manager,

Barrier Therapeutics, Inc. Participants:

Charles Nomides, B.S., COO
Mat Nunes, PhD., CM&C
Isabel Drzewiecki, Global Head, Regulatory Operations

Background

Barrier has a pending application, PDUFA date is February 16, 2006. During the review of the amendment, the chemistry team noted that the submitted stability data only supported a 1 year expiration date. The teleconference was initiated to inform the Sponsor.

Discussion

The Sponsor was informed that in order for the chemistry team to be able to recommend an approval action, the NDA could only be approved with a 1 year expiration date.

Barrier informed the Agency that they now have real time data to support a expiration date. They acknowledged that this data had not been submitted to the Agency for review.

Agreements reached:

1. The CMC review team can recommend an approval from a CMC perspective with a 1 expiration date.
2. Immediately after the action letter is issued, the Sponsor can submit a CBE-0 supplement with the additional data which will support the expiration date.

b(4)

Signature, minutes preparer: _____

Chair concurrence (or designated signatory): _____

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

/s/

Moo-Jhong Rhee
2/14/2006 02:27:45 PM


Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

February 14, 2006

*W. Walters for
Mildred Wright*

Stanka Kukich, MD, Acting Director Division of Dermatologic & Dental Drug Products Food and Drug Administration Center for Drug Evaluation and Research Office of Drug Evaluation III, HFD-540 5901-B Ammendale Road Beltsville, MD 20705	NDA 21-026 Miconazole nitrate 0.25% Ointment Indication: Candidiasis Complicated by Diaper Dermatitis Acceptance of Expiration Dating
--	---

Dear Dr. Kukich:

Reference is made to NDA 21-026 for Miconazole Nitrate 0.25% Ointment and to a teleconference on February 14, 2006, between representatives of the Office of New Drug Chemistry, Mildred Wright of your Division and representatives of Barrier Therapeutics including myself regarding the expiration dating for Miconazole Nitrate 0.25% Ointment.

This letter is to advise that Barrier Therapeutics, Inc accepts a one-year expiration dating period for VUSION™ (0.25% miconazole nitrate, 15% zinc oxide and 81.35% white petrolatum) Ointment as agreed to during the teleconference.

We trust this is satisfactory for your needs. This submission consists of 1 volume and is being submitted in duplicate with a signed FDA Form 356h. We understand that this submission and all information contained herein unless otherwise made public by Barrier Therapeutics, Inc is CONFIDENTIAL. If you have any questions, please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,

Isabel B. Drzewiecki
 Isabel B. Drzewiecki
 Vice President, Regulatory Affairs

Wright, Mildred

From: Peat, Raquel
nt: Monday, February 13, 2006 12:51 PM
Wright, Mildred
cc: Colangelo, Kim M
Subject: CLEARED: 505(b)(2) NDA 21-026, Vusion with a goal date of February 16, 2006

Hello Millie:

You are cleared to act on this application (NDA 21-026) by IO and ORP with OCC notification. Please contact us if you have any questions or concerns.

Happy Action!
Raquel

LT Raquel Peat, MS, MPH, USPHS
Regulatory Project Officer
FDA/CDER/OND, Immediate Office
301-796-0700 (OND IO main)
301-796-0517 (direct)
Fax: 301-796-9858

Address:
10903 New Hampshire Ave.
Bldg #22, Room 6469
Silver Spring, MD 20993

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Barrier Therapeutics, Inc.

ORIGINAL

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ORIG AMENDMENT

RECEIVED

FEB 15 2006

FEB 13 2006

February 9, 2006

CDER White Oak DR1

N-000-BL

CDER CDER

Stanka Kukich, MD, Acting Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation 3, HFD-540
5901-B Ammendale Road
Beltsville, MD 20700

NDA 21-026
Miconazole Nitrate 0.25% Ointment
Indication: Diaper Dermatitis
complicated by Candidiasis
Response to Draft Labeling Proposal

Dear Dr. Kukich,

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to the fax dated February 8, 2006 from the Agency regarding the Division's proposed changes to the Labeling for VUSION™ Ointment. As discussed in a teleconference on February 8, 2006 between Barrier Therapeutics and the Agency, we herewith submit our Physicians' Package Insert in draft form which reflects our understanding and acceptance of all of the changes proposed by the Division in this fax and the additional changes that were discussed during the teleconference on February 8, 2006.

We have enclosed with this submission both a red-lined and strike-through version and a clean version of our proposed response to the labeling. In the strike-through version, deleted text has a strike-through through it and new text is underlined. We have identified each proposed change by line number. Specific comments are delineated below.

We have agreed to the Agency's request to change to list of ingredients on all tubes and cartons so that it matches the list of ingredients in the Package Insert. We will change the to "Chemoderm® 1001/B fragrance", and we will switch the order of the inactive ingredients so that they are in the same order as shown in the Package Insert.

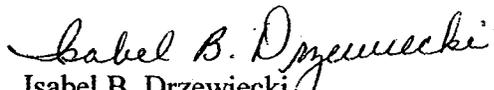
b(4)

We hereby submit both printed copies and a CD containing PDF files of the final artwork reflecting this change to the carton and tube text. As agreed to in the February 8 teleconference, effective immediately, all cartons will be printed in accordance with this finalized artwork. Also, as per our agreement in this teleconference, all tubes will be in conformance with this change by the end of 4 months from the approval date of this drug, in order to allow Barrier to use the first batch of tubes that has already been manufactured. We have also provided both printed copies and a CD containing the Word File of the Package Insert. We will also send it electronically for your ease of review.

- Line 29: Added “®” in superscript at the end of “Chemoderm” and added a footnote number at the end of the line. The footnote is printed at the bottom of the page.
- Lines 91-94: Removed bolding to match the first part of the paragraph
- Lines 225-227: Removed bolding to match the rest of the paragraph **b(4)**
- Line 252: Added a period at the end of the line
- Line 253: Deleted the words
- Line 262: Added “www.barriertherapeutics.com”
- Line 263: Changed the month
- Line 370: Deleted the words
- Line 374: Added “®” in superscript at the end of “Chemoderm”
- Line 385: Changed the month

This submission consists of 1 volume, including a CD containing both Word and PDF versions of the labeling, and is being submitted in duplicate with a signed FDA form 356h. Each CD has a label to confirm that it was checked on February 9, 2006 for viruses by Network Associates McAfee VirusScan Enterprise 8.0.0 and is deemed virus free. We understand that this submission and all information contained herein unless otherwise made public by Barrier Therapeutics, Inc., is CONFIDENTIAL. We are available at your convenience if you have any further questions. Please do not hesitate to contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,


Isabel B. Drzewiecki
Vice-President of Regulatory Affairs

FDA Fax Memorandum

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Date: February 8, 2006

Subject: NDA 21-026/ VUSION (0.25% miconazole nitrate, 15% zinc oxide,
and 81.35% white petrolatum) Ointment
Division's proposed labeling

Hi Isabel,

Attached you will find the Division's proposed wording. We can all use this for our t-
con discussion this afternoon

Isabel, if you have questions, please call.

Respectfully,
Millie

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10 Page(s) Withheld

 Trade Secret / Confidential

8 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-

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

/s/

Mildred Wright
2/8/2006 12:12:19 PM
CSO



A Vision for Innovative Medicine

February 7, 2006

Stanka Kukich, MD, Acting Director
 Division of Dermatologic & Dental Drug
 Products
 Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation III, HFD-540
 5901-B Ammendale Road
 Beltsville, MD 20705

NDA 21-026
 Miconazole Niti

Indication: Cal
 Diaper Dermatitis

Response to Phase 4 Commitment
 Requests

*Secretary for
 Official
 Submission*

Dear Dr. Kukich:

Reference is made to NDA 21-026 for Miconazole Nitrate 0.25% Ointment and to the Agency's Fax of February 3, 2006 regarding the Division's request for Phase 4 Commitments. At this time we are responding to the Agency's requests. Please find below the Agency's requests in bold text, followed by Barrier's responses in plain text.

1. An open label study to assess the systemic absorption and safety of the marketed formulation of topically applied 0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum ointment in infants with moderate to severe diaper dermatitis when complicated by Candidiasis.

Protocol to be submitted by April 2006
 Study Start Dated by August 2006
 Final Report Submission by August 2007

Barrier Therapeutics agrees to conduct this study, and to adhere to the above requested timelines.

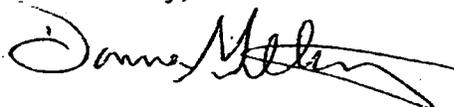
2. A prospective 2-year longitudinal study to assess for miconazole resistance in *Candida* spp. with repeated treatment courses of the marketed formulation of topically applied .25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum ointment in infants with recurrent moderate to severe diaper dermatitis with Candidiasis. Clinical isolates of *Candida* spp. should be obtained from patients who fail to improve with marketed formulation of 0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum ointment treatment followed by properly conducted in-vitro susceptibility testing. Isolates should be saved in the event that further investigation is necessary.

Draft Protocol submitted by June 2006
Protocol submitted by December 2006
Study Start Date by February 2007
Final Report submitted by February 2009

Barrier Therapeutics agrees to conduct this study. We agree to submit a draft Protocol by June 2006 and a final protocol by December 2006. We also agree to a study start date of February 2007. As agreed to by the Agency, in order to allow for a 6-month enrollment period, we will finish the study by August 2009 and submit the final report in November 2009.

This submission consists of 1 volume and is being submitted in duplicate with a signed FDA form 356h. We understand that this submission and all information contained herein unless otherwise made public by Barrier Therapeutics, Inc. is CONFIDENTIAL. If you should have any questions, please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,



For Isabel B. Drzewiecki
Vice President Regulatory Affairs

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Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

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FEB - 8 2006

CDER White Oak DR1

N-000 54

ORIG AMENDMENT

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FEB 07 2006

CDR/CDER

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February 6, 2006

Stanka Kukich, MD, Acting Director
Division of Dermatologic & Dental Drug
Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, HFD-540
5901-B Ammendale Road
Beltsville, MD 20705

**NDA 21-026
Miconazole Nitrate 0.25% Ointment**

**Indication: Candidiasis Complicated by
Diaper Dermatitis**

Final Safety Update Report

Dear Dr. Kukich:

ORIGINAL

Reference is made to our Amendment to our Unapproved New Drug Application (NDA 21-026) which was submitted on November 24, 2004 and to a telephone conversation on February 6, 2006 with Mildred Wright of the Agency in which she requested a Final Safety Update Report for this product.

Our November 24, 2004 Amendment contained all of the safety data that was available from all of the studies included in that Amendment. This study, Protocol Number BT100USA/001 had already been completed by the time of that submission, and since that time, there have been no additional clinical or non-clinical studies conducted, and no new patients have been treated. There is no additional safety information to report at this time. Based on this information, there have not been any significant changes or findings in the safety profile of Miconazole Nitrate 0.25% Ointment.

This submission consists of 1 volume and is being submitted in duplicate with a signed FDA form 356h. We understand that this submission and all information contained herein unless otherwise made public by Barrier Therapeutics, Inc. is **CONFIDENTIAL**. If you should have any questions, please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,

Isabel B. Drzewiecki

Isabel B. Drzewiecki
Vice President Regulatory Affairs

FDA Fax Memorandum

Date: February 3, 2006

Subject: NDA 21-026/miconazole nitrate/amendment
Phase 4 Commitments

Hi Isabel,

The Division has the following Phase 4 commitment requests:

1. An open label study to assess the systemic absorption and safety of the marketed formulation of topically applied 0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum ointment in infants with moderate to severe diaper dermatitis when complicated by candidiasis

Protocol to be submitted by April 2006.
Study Start Date by August 2006
Final Report Submission by August 2007.

2. A prospective 2-year longitudinal study to assess for miconazole resistance in *Candida* spp. with repeated treatment courses of marketed formulation of topically applied 0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum ointment in infants with recurrent moderate to severe diaper dermatitis with candidiasis. Clinical isolates of *Candida* spp. should be obtained from patients who fail to improve with marketed formulation of 0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum ointment treatment followed by properly conducted in vitro susceptibility testing. Isolates should be saved in the event that further investigation is necessary.

Draft Protocol submitted by June 2006
Protocol submitted by December 2006
Study Start Date by February 2007
Final Report submitted by February 2009.

Isabel, you will need to submit your agreement to conduct the above to the NDA, the timelines. If you do not agree with the Division's proposals, please call.

If you have questions, please call.

Respectfully,
Millie

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

/s/

Mildred Wright
2/3/2006 01:00:52 PM
CSO



Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

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FEB 8 2006

CDR/CDER

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FEB - 6 2006

CDER White Oak DR 1

February 2, 2006

Stanka Kukich, MD, Acting Director
Division of Dermatologic & Dental Drug
Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, HFD-540
5901-B Ammendale Road
Beltsville, MD 20705

NDA 21-026
Miconazole Nitrate 0.25% Ointment

**Indication: Candidiasis Complicated by
Diaper Dermatitis**

General Correspondence

Dear Dr. Kukich:

ORIG AMENDMENT

N-000(BM)

Reference is made to our Information Amendment: Clinical, Serial No. 056, in response to the Agency's Fax of January 31, 2006 regarding questions on Protocol Number BT0100-201-INT, "An Open Label Study to Assess the Systemic Absorption and Safety of Topically Applied 0.25% Miconazole Nitrate Ointment in Infants with Moderate to Severe Diaper Dermatitis." which was submitted to IND 21,542 for Miconazole Nitrate 0.25% Ointment on February 2, 2006. In order to keep all correspondences up-to-date and to maintain a complete file, we are submitting a copy of this submission to the corresponding NDA 21-026 for Miconazole Nitrate 0.25% Ointment.

This submission consists of 1 volume and is being submitted in duplicate with a signed FDA form 356h. We understand that this submission and all information contained herein unless otherwise made public by Barrier Therapeutics, Inc. is CONFIDENTIAL. If you should have any questions, please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,

Isabel Drzewiecki
Isabel B. Drzewiecki
Vice President Regulatory Affairs

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On Original

ORIGINAL

Department Of Health and Human Services Public Health Service Food And Drug Administration		Office Of Drug Safety Post-Marketing Safety Review	
To: Stanka Kukich, M.D., Acting Director Division of Dermatologic and Dental Drug Products (DDDDP), HFD-430		From: Nagla Wahab, Pharm.D., Post-Marketing Safety Evaluator Division of Drug Risk Evaluation HFD-430	ODS PID # D 050741
Completed: January 24, 2006		Through: Mark Avigan, M.D., C.M, Director Division of Drug Risk Evaluation, HFD – 430 Office of Drug Safety	
Date Received: December 27, 2005			
Drug: Miconazole 0.25%+Zinc oxide 15%+White Petrolatum 81.35%		NDA/IND#: 21-026	SPONSOR: Barrier Therapeutics, Inc
Drug Name (Trade); Vusion®		Therapeutic Classification: Antifungal Agent	
Event: Hepatic Adverse Events Reported with topical miconazole or miconazole suppositories			
Executive Summary: This document summarizes all AERS reports containing any hepatic adverse event reported with the topical or suppository use of miconazole nitrate (hereafter, miconazole). The information provided in this document was presented at the January 18, 2006 labeling meeting for Vusion®, NDA 21-023, an ointment composed of miconazole nitrate 0.25% + zinc oxide 15% + white petrolatum 81.35%. The Office of Drug Safety searched the AERS database on December 28, 2005 for all reports containing any hepatic adverse event term submitted for miconazole topical, or miconazole suppositories. The search found 47 reports, of which 40 were excluded from final review. The excluded reports either listed the intravenous formulation (33), or an oral formulation (7). We included in our final review 7 cases (US-4, Foreign -3) reporting hepatic adverse events. Although, the seven cases had coded outcomes of death + hospitalization (1), hospitalization (5), and other (1), none of these serious outcomes were strongly associated with the topical or suppository use of miconazole. The 7 cases reported hepatic adverse events that included hepatitis (4), increased bilirubin (1), hepatic encephalopathy (1), and elevated ALT/AST (1). All the cases were confounded by existing medical conditions, or the concomitant use of oral agents that may be more strongly associated with the development of adverse hepatic events. Only two AERS cases were potentially associated with miconazole use. The first case was a literature report that described a patient who developed acute hepatitis after intercourse with her husband, who had used miconazole on his penis. This case reported a positive dechallenge and rechallenge response because the patient had two previous similar hospitalizations while using miconazole and clotrimazole vaginal tablets. However, this case is confounded because the patient was concomitantly using oral metronidazole and ornidazole, both labeled for adverse hepatic events. The second case was of a female who had multiple hospitalizations for infectious patches on the labia associated with the use of Monistat® vaginal cream. This second case also reported a positive dechallenge response, but was confounded because the patient was positive for hepatitis E antibody with unknown onset. In summary, we reviewed seven cases of hepatic adverse events in patients who were using miconazole either topically, or as a suppository. We included a brief narrative of the seven cases in the Appendix. Of the seven cases, two were potentially related to topical miconazole use. Although both cases reported positive dechallenge responses, both cases were confounded, and as such did not provide a compelling new safety signal for hepatic toxicity. DDRE recommends continued monitoring of adverse events report submitted for the topical use of miconazole.			
Relevant Product Labeling: Hepatotoxicity and hepatic adverse events are not listed in the label of topical miconazole drug products. Miconazole is only available in topical or suppository form in the Unites States. The oral gel form is not approved.			
Search Date: December 28, 2005		Search Type(s): <input checked="" type="checkbox"/> AERS <input type="checkbox"/> Literature	
Search Criteria: Drug Names: Miconazole, miconazole nitrate, Monistat, M-Zole, Daktarin, Daktacort MedDRA Terms: Hepatic failure (PT), hepatic necrosis (PT), hepatitis (PT), hepatic and hepatobiliary disorders (HLGT), hepatobiliary investigations (HLGT), liver transplant (PT)			
Methods and Search Results: On December 28, 2005 we searched the AERS database for all adverse event reports for topical miconazole and miconazole suppositories reporting a hepatic adverse event term. The search was for all reports submitted from marketing of the drug products. The search retrieved 47 reports, of which 40 were excluded. The excluded reports included 33 reports of parenteral miconazole and 7 reports of oral miconazole. We reviewed seven cases (US-4, Foreign-3). There were two male cases and five female. The patients ranged in age from 3 years to 63 years, with a median of 38 years (n=5). Miconazole was used as the topical formulation in 4 cases and as a suppository in 1 case. The two remaining cases did not report the formulation of miconazole used. Miconazole was used to treat			

oral candidiasis (1), vaginal candidiasis (3) and unreported indications (3). The adverse events reported included hepatitis (4), increased bilirubin (1), hepatic encephalopathy (1), and elevated ALT/AST (1). One case had a coded outcome of death + hospitalization, 5 cases had coded outcomes of hospitalization, and one case was coded other. Two cases had positive dechallenge, one of which reports positive rechallenge. All cases were confounded by one or more of the following factors: preexisting medical condition (3), concomitant use of other systemic drugs that may be more strongly associated with hepatic adverse events (6), possible use of routes other than topical or suppository (3), or ethanol and drug abuse (1).

Discussion/Conclusion:

Our search of the AERS database found 7 cases of hepatic adverse events associated with the topical or suppository use of miconazole. All seven cases were confounded by one or more factors. In one case, miconazole topical lotion (Monistat®) was used orally. In six cases, the patients used concomitant medications that were listed as co-suspect agents and may have played a role in the reported hepatic events. Other confounders included an AIDS patient with a pre-existing liver condition (liver cirrhosis and hepatitis B and C). One case reported isolated elevated enzymes without reporting the institution's normal range. In addition, this patient was also taking other oral drugs known to cause elevated liver enzymes. In the case coding death as an outcome, the patient had an elevated alcohol level and a positive drug screen. This patient also had multiple concomitant oral medications some of which have strong association with hepatic adverse events. Only two of the 7 cases were possibly related to topical miconazole use, and both reported hepatitis. One of the 2 hepatitis cases (literature report) was of a female patient who developed acute hepatitis after having intercourse with her husband, who had applied miconazole cream to his penis. The patient had a history of chronic trichomonal and candidal vaginitis infections. Although this case reported a positive dechallenge response, it was confounded by the fact that the patient had a previous history of similar hospitalization while using oral metronidazole, oral Ornidazole (nitroimidazole), miconazole and clotrimazole vaginal tablets. The second case occurred in a patient who had 3 to 4 hospitalizations while using Monistat® vaginal cream. The patient was diagnosed with hepatitis (positive hepatitis E antibody). This case reported a positive dechallenge and rechallenge response, but to the oral and vaginal ulcers and not to the hepatitis event. This case also did not provide adequate information regarding past medical history, and concomitant medications.

In summary, we reviewed seven cases of hepatic adverse events in patients who were using miconazole nitrate either topically, or as a suppository. Of the seven cases, two were potentially related to topical miconazole use. Although both cases reported positive dechallenge responses, both cases were confounded, and as such did not provide a compelling new safety signal for hepatic toxicity. DDRE recommends continued monitoring of adverse events report submitted for the topical use of miconazole.

Reviewer's Signature: *Nagla Wahab, Pharm.D.*

Date:

Team Leader: *Marilyn R. Pitts, Pharm.D.*

Date:

Division Director Signature: *Mark Avigan, M.D., C.M.*

Date:

cc: NDA# 21-026

HFD-540 Kukich/Carr/Wright/Division File

HFD-430 Avigan/Johann-Liang/Pitts/Beam

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Hepatic Events Reported with Miconazole Topical and Suppositories products
AERS Search Date: Dec 28, 2005

AERS Case #	MCN	Report Year	Location	Age/Gender	Outcome	Hepatic event type	Narrative
4358984	Direct report	1982	US	3-yr M	Hosp Still under treatment at the time of report.	Hepatitis	<p>This 3 year old male was applied Monistat topical lotion orally BID for 3 months to treat oral candidiasis. After an unspecified time, the patient developed biopsy-confirmed hepatitis. The patient was concomitantly using nystatin, metaprel, amoxicillin (for 7 days), and Cephlor (cefactor) for 10 days. The patient had a history of cartilage hair hypoplasia with T lymphocyte deficiency.</p> <p><i>Reviewer Comment: Elevated liver enzymes have been reported with cefactor and amoxicillin. Cefactor has been associated with cholestatic jaundice. Also, miconazole was used orally for prolonged period of time and systemic absorption is possible.</i></p>
4706308	MON301	1990	US	24-yr F	Hosp	Hepatitis	<p>The patient had 3 or 4 hospitalizations secondary to labial infections. Upon questioning the patient, it was found out that she had been using Monistat 7 vaginal cream each time. Her last hospitalization was significant for increasing rash in her lips, vagina, and hands. Lab results revealed LDH of 190, with normal bilirubin. Repeat hepatitis study revealed positive HPE antibody, another positive (unknown) antibody and negative surface antigen. This case also reports positive dechallenge and positive rechallenge. Monistat was discontinued. She was diagnosed with vaginitis, vasculitis, hepatitis and stomatitis.</p> <p>Concomitant medications and medical history were not provided.</p> <p><i>Reviewer Comment: Although this case had a positive dechallenge and rechallenge, it appears to be only in regard to recurrence of mouth and vaginal ulcers. It is also confounded by the lack of information regarding concurrent medical conditions, concomitant drugs and lab values for liver function test.</i></p>
3207995	9720087	1999	US	56-yr F	Other	Increased bilirubin level	<p>The patient had been using fluconazole oral tablets 150mg daily intermittently for 6 months to treat vaginal candida infection. She was also taking Macrobid 100mg BID for 4 months for a UTI. The patient developed an elevated bilirubin level (value unreported). Miconazole was listed as co-suspect drug because patient used monistat vaginal cream at some point during the period that she was not taking fluconazole. The patient concomitantly used estrogen vaginal ring, Premarin, Rocaltrol, Neurontin, Slow Mag and Claritin.</p> <p><i>Reviewer comment: This case is confounded by the prolonged use of oral fluconazole and nitrofurantoin. Both drugs have been associated with hepatotoxicity.</i></p>
3317853	B0068902	1999	Foreign	38-yr M	Death	Hepatic encephalopathy	<p>The patient had AIDS with previous hospitalization for hepatitis B & C, and cirrhosis. The patient was on lamivudine/zidovudine</p>

AERS Case #	MCN	Report Year	Location	Age/Gender	Outcome	Hepatic event type	Narrative
3679218	NSADSS 2001019936	2001	Foreign	38-yr F	Hosp	Acute hepatitis	<p>(Combivir) tablets. Concomitant drugs included domperidone, nevirapine, miconazole (unknown form), spironolactone and Micronase. The patient was hospitalized due to worsening condition. The patient developed rash suggestive of erythema multiforme. Miconazole was discontinued. The patient was diagnosed with Stevens-Johnson syndrome and died due to hepatic encephalopathy. Route of administration, indication and dose of miconazole were not provided.</p> <p><i>Reviewer comment: This case is confounded with patient's pre-existing liver condition and other medications known to be associated with hepatic adverse events such as nevirapine and Combivir. Also nevirapine has been associated with Steven-Johnson Syndrome.</i></p>
5783007	2004SE06156	2005	Foreign	63-yr F	Hosp	Neutropenia Anemia Thrombocytopenia	<p>The patient experienced acute hepatitis after having sexual intercourse with her husband who had applied miconazole cream to his penis. The patient had a similar previous hospitalization in 1991 after receiving Ornidazole and metronidazole orally, miconazole and clotrimazole vaginal tablets. Hepatic enzymes returned to normal in one month.</p> <p><i>Reviewer comment: This case is confounded with the previous hospitalization, the use of oral medications reported to be associated with hepatic adverse events (metronidazole and Ornidazole). However, this case was reported in the literature because it is supported by the positive dechallenge and rechallenge.</i></p>
5808605	K11-2005- 0016638	2005	US	56-yr F	Hosp	Coma, elevated liver enzymes	<p>The patient with history of thrombocytopenia purpura, developed normocytic anemia, normochromic anemia, and neutropenia while taking Cokenzen® (candesartan cilexetil/hydrochlorothiazide) for hypertension. The patient also experienced elevated AST/ALT to 72/102 IU (normal range unreported). The patient concomitantly used Daktarin® (miconazole nitrate ointment), zolpidem and clonazepam. Doses and indications were not provided.</p> <p><i>Reviewer comment: This case is confounded by the use of multiple systemic medications, and the lack of information of AST/ALT normal lab values for that specific site. Abnormal liver function tests and elevated liver enzymes have been reported with the use of Cokenzen®, zolpidem and clonazepam.</i></p>

AERS Case #	MCN	Report Year	Location	Age/Gender	Outcome	Hepatic event type	Narrative
							<p>albuterol, terbutaline wafarin, fentanyl, Rhinocort and ethanol.</p> <p><i>Reviewer comment: This case is profoundly confounded due to the very high alcohol level and positive drug screen indicating drug and alcohol abuse by the patient, and the use of other medications that have been associated with liver enzyme elevation.</i></p>

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/s/

Nagla Wahab
2/2/2006 12:12:20 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
2/3/2006 05:56:25 PM
DRUG SAFETY OFFICE REVIEWER



Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

January 30, 2006

155

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JAN 30 2006

CDER CDER

Stanka Kukich, MD, Acting Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation 3, HFD-540
5901-B Ammendale Road
Beltsville, MD 20700

NDA 21-026
Miconazole Nitrate 0.25% Ointment

Indication: Diaper Dermatitis
complicated by Candidiasis

Response to Draft Labeling Proposal

RECEIVED

FEB - 1 2006

ORIGINAL AMENDMENT

N 000-BL

Dear Dr. Kukich,

CDER White Oak DR1

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to the Revised Draft Labeling Proposal submitted on November 14, 2005 and the fax dated January 25, 2006 from the Agency regarding the Division's proposed changes to the Labeling for VUSION™ Ointment.

At this time, we submit herewith our responses to the January 25, 2006 fax. In general, we agree with the Division's proposal, except in areas as indicated below. We have enclosed with this submission both a red-lined and strike-through version and a clean version of our proposed response to the labeling. In the strike-through version, deleted text has a strike-through through it and new text is underlined. We have identified each proposed change by line number, and for ease of reference, we have also cross-referenced in parentheses and smaller font, the line number from the Agency's January 25, 2006 fax. Specific comments are delineated below.

We have agreed to all of the Agency's proposed revisions for the cartons and tubes, as outlined on pages 15-17 (Lines 461-552) except to bring them into agreement with the Package Insert change described in Line 2 (30) of the Physicians Package Insert. We moved the word "Ointment" so that it is located after the generic name, and removed the word as part of the generic name in order to avoid duplication. We hereby submit both printed copies and a CD containing PDF files of the revised artwork reflecting all of the Agency's proposed changes. We also refer to our submission of January 26, 2006, requesting the Agency's agreement to use the already printed VUSION tubes for the first batch of product distributed. All cartons will be revised to conform to the Agency's requested changes for this first batch.

b(4)

In a number of locations in the package insert the Division has included petrolatum and zinc oxide into the generic name along with miconazole nitrate. It is our experience that the function of those items listed in the generic name is usually defined in the body of the insert. This was done for the miconazole nitrate but not the petrolatum and zinc oxide. Assuming this was an oversight, we would recommend the description of "skin protectant" be added. You will note that we have not made this change in the attached labeling because we would like to discuss this further with you in a teleconference.

Line 1: (30)

Removed the word

b(4)

0106

Line 2: (30)	Moved the word "ointment" to the outside of the parentheses, changed the font size and added bolding	
Line 28: (57)	Corrected typographical error: 81.35 was changed to 813.5	
Line 88-89: (144-145)	Removed the words	b(4)
Lines 91-114: (146-161)	Rearranged paragraph order	
Line 142: (194)	Changed the word	to "health care provider"
Line 152: (204)	Changed the word	to "health care provider"
Line 207: (268)	Removed the word	from the table name. Changed order of Adverse Events according to FDA's request.
Line 252: (316)	Added "TM" in superscript to the end of VUSION	
Line 265-266: (329)	Added "For additional information, please call toll free at 1-866-440-5508 \	www.barriertherapeutics.com."
Line 276: (338)	Removed	b(4)
Line 278: (following 339)	Added the words "U.S. Patent No. 4,911,932"	
Line 279: (340)	Added "TM" in superscript to the end of VUSION and removed word	
Line 281: (342)	Moved the word "ointment" to the outside of the parentheses, changed the font size and added bolding	
Line 286: (347)	Changed the word	to "health care provider"
Line 288: (349)	Changed the word	to "health care provider" b(4)
Line 308: (369)	Changed the word	to "health care provider"
Line 310: (370)	Changed the word	to "health care provider"
Line 323: (384)	Changed the word	to "health care provider"
Line 340: (400)	Changed the word	to "health care provider"
Line 341: (401)	Changed the word	to "health care provider"

- Line 348: (407) Added missing bullet
- Line 349-350: (408-409) Right justified to correct formatting
- Line 360: (418) Changed the word to "health care provider" **b(4)**
- Line 380: (439) Changed the word to "health care provider" in two places
- Line 384: (442) Added the words
- Line 385: (443) Added the words
- Line 395: (following 452) Added the word "www.barriertherapeutics.com"
- Line 402: (459) Added the words "U. S. Patent No. 4,911,932"

We look forward to working with the Division on finalizing this labeling and would like to schedule a conference call to discuss it further at the Agency's earliest convenience.

This submission consists of 1 volume, including a CD containing both Word and PDF versions of the labeling, and is being submitted in duplicate with a signed FDA form 356h. Each CD has a label to confirm that it was checked on January 27, 2006 for viruses by Network Associates McAfee VirusScan Enterprise 8.0.0 and is deemed virus free. We understand that this submission and all information contained herein unless otherwise made public by Barrier Therapeutics, Inc., is CONFIDENTIAL. If you have any questions, please do not hesitate to contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,



For
Isabel B. Drzewiecki
Vice-President of Regulatory Affairs

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Barrier Therapeutics, Inc.

A Vision for Innovative Medicines

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DUPLICATE

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JAN 27 2006

CDR/CDER

JAN 30 2006

January 26, 2006

CDER White Oak DR1

Stanka Kukich, MD, Acting Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation 3, HFD-540
5901-B Ammendale road
Beltsville, MD 20700

NDA 21-026

Miconazole Nitrate 0.25% Ointment

**Indication: Diaper Dermatitis
complicated by Candidiasis**

General Correspondence

Dear Dr. Kukich,

NEW CORRESPONDENCE
N 000

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to the Revised Draft Labeling Proposal submitted on November 14, 2005 and the fax dated January 25, 2006 from the Agency regarding the Division's Proposed labeling for VUSION Ointment.

We acknowledge the Division's revisions for the container labels as noted on pages 15-17 (Lines 461-551) of the January 25, 2006 fax, and we intend to fully comply with all changes regarding the tube and carton labels. However, we have already printed launch quantities of the tubes (we realize at risk) and we have enclosed 6 of these tubes for your inspection. We believe that the actual finished printed tube is much more readable than the artwork that was submitted may have indicated. We respectfully request that the Agency allow Barrier to use this first batch of tubes that have already been manufactured, with the agreement that we will make all of the noted changes for subsequent batches. In addition, we will revise the carton text to agree with all your comments for this launch batch. This will mean that there will be slight differences between the tube and carton printing but this will only occur for this initial launch batch. We hope that this will be satisfactory for the Agency for this one time only occurrence. Thank you for your consideration of this matter.

This submission consists of 1 volume and is being submitted in duplicate with a signed FDA form 356h. We understand that this submission and all information contained herein unless otherwise made public by Barrier Therapeutics Inc. is CONFIDENTIAL. If you should have any questions, please contact me at idrzewiecki@barriertherapeutics.com or feel free to call directly at (609) 945-1247.

Sincerely,

Isabel Drzewiecki
Isabel B. Drzewiecki
Vice President Regulatory Affairs



Barrier Therapeutics, Inc.

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119

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NOV 15 2005

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November 14, 2005

Stanka Kukich, MD, Acting Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation 3, HFD-540
5901-B Ammendale road
Beltsville, MD 20700

**NDA 21-026
Miconazole Nitrate 0.25% Ointment**

**Indication: Diaper Dermatitis
complicated by Candidiasis**

**Amendment to Complete Response to
May 24, 2005 Not Approvable Letter
(Revised Draft Labeling Proposal)**

ORIGINAL AMENDMENT

N(BL)

Dear Dr. Kukich,

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to our amendment to this NDA of August 15, 2005, in which we provided a complete response to the non-approvable letter of May 24, 2005. We also refer to telephone requests on August 23, 2005, October 15, 2005, and November 8, 2005 from Ms. Millie Wright of your Division regarding the current proposed labeling.

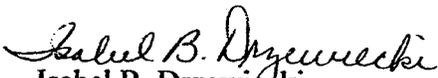
On August 25, 2005, we amended our Complete Response of August 15, 2005 to provide our proposed labeling for Miconazole Nitrate 0.25% Ointment. This proposal was originally submitted on May 17, 2005 in response to the Agency's comments on our original draft labeling. The labeling submitted on August 25, 2005 is identical in content to that contained in our May 17 submission. On October 24, 2005, we submitted revised draft labeling for the 5 g sample tube, 30 g sample tube, 30 g commercial tube, 5 g sample carton, 30 g sample carton, and 30 g commercial carton, as well as an updated draft Physician's Package Insert and Information for Patient Leaflet. The information contained in these labels and labeling is an exact duplicate of the information provided in our submission of May 17, 2005, except that it now reflects the trade name VUSION™.

In our November 8, 2005 teleconference, Ms. Wright requested that we submit all the labels and labeling for this product electronically in both Word and PDF formats. At this time, we submit herewith a CD containing the tube and carton labels and the Physician's Package Insert and Patient Leaflet in both word and PDF format. Please be advised that we could not provide the tube and carton labels in Word format that could be manipulated right in the text. We have therefore provided the tube and carton labels with white space after each panel where revised text can easily be presented. We trust this will be satisfactory for your needs.

It is our understanding that, since this is an amendment to previously submitted labeling, the Physician's Package Insert and patient Information Leaflet do not have to be in SPL format.

This submission consists of 1 volume, including a CD containing both Word and PDF versions of the labeling, and is being submitted in duplicate with a signed FDA form 356h. Each CD has a label to confirm that it was checked on November 14, 2005 for viruses by Network Associates McAfee VirusScan Enterprise 8.0.0 and is deemed virus free. We understand that this submission and all information contained herein unless otherwise made public by Barrier Therapeutics Inc. is CONFIDENTIAL. If you should have any questions, please contact me directly at (609) 945-1247 or at idezewiecki@barriertherapeutics.com.

Sincerely,


Isabel B. Drzewiecki
Vice President Regulatory Affairs

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Barrier Therapeutics, Inc.
A Vision for Innovative Medicine

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OCT 25 2005

CDR / CDER

October 24, 2005

310

Stanka Kukich, MD, Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
5901-B Ammendale Road
Beltsville, MD 20850

NDA 21-026
Miconazole Nitrate 0.25% Ointment

Indication: Diaper Dermatitis
complicated by Candidiasis

Revised Draft Labeling Proposal

ORIGINAL AMENDMENT

N(BL)

Dear Dr. Kukich,

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to our amendment to this NDA of November 24, 2004, in which we provided a complete response to the non-approvable letter of July 24, 2000. We also refer to the May 24, 2005 not approvable letter to our November 24, 2005 amendment and to our complete response to that not approvable letter on August 15, 2005. In addition, we refer to a telecon on October 13, 2005 with Ms. Millie Wright of your Division in which she requested that we submit revised draft labeling reflecting our new proposed tradename of VUSION™.

At this time, we submit herewith revised copies of the proposed labels for the 5 mg. sample tube, 30 mg. sample tube, 30 mg. commercial tube, 5 mg. sample carton, 30 mg sample carton, and 30 mg. commercial carton, as well as an updated draft Physician's Package Insert and Information for the Patient Leaflet. The information contained in the labels and in the Package Insert is an exact duplicate of the information provided in our submission of May 17, 2005, except that we have changed the name from Zimyca to Vusion. We have included four additional sets of this labeling information in the original copy of this submission.

We look forward to discussions with the Division on this labeling.

This submission consists of 1 volume and is being submitted in duplicate with a signed FDA form 356h. We understand that this submission and all information contained herein unless otherwise made public by Barrier Therapeutics Inc. is CONFIDENTIAL. If you should have any questions, please do not hesitate to contact me directly at idrzewiecki@barriertherapeutics.com or at (609) 945-1247.

Sincerely,

Isabel Drzewiecki
Isabel B. Drzewiecki



Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

October 18, 2005

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OCT 21 2005

CDR / CDER

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Office of Drug Evaluation, III HFD-540
5901-B Ammendale Road
Beltsville, MD 20850

NDA 21-026

**Miconazole Nitrate 0.25%, Zinc Oxide, 15%
and White Petrolatum 81.35% Ointment**

**Indication: Diaper Dermatitis Complicated
by Candidiasis**

**Protocol for Systemic Absorption Clinical
Study (Submission to IND 21,542)**

N-200(C)
NEW CORRESP

Dear Dr. Kukich,

Reference is made to our NDA 21-026 for Miconazole Nitrate 0.25%, zinc oxide, 15% and white petrolatum 81.35% Ointment, to the Not Approvable letter issued on May 24, 2005, and specifically to the End-of-Review Meeting on July 14, 2005, between representatives of your Division and Barrier Therapeutics. The purpose of the End-of-Review Meeting was to provide clarification for the basis of the deficiencies cited in the May 24, 2005 Not Approvable letter. One of the Agreements made at that meeting was that Barrier would conduct, as a post marketing commitment (Phase 4), a pharmacokinetic study, of the to be marketed product in infants with liver function testing. It was agreed that this would be included as part of our Complete Response to the Not Approvable letter.

This letter is to advise you that as requested by Millie Wright of your Division, we submitted a draft protocol entitled "An Open Label Study to Assess the Systemic Absorption and Safety of Topically Applied 0.25% Miconazole Nitrate Ointment in Infants with Moderate to Severe Diaper Dermatitis (Protocol No. BT0100-201-INT) to our IND 21,542 on October 18, 2005 for your review and comment. This draft protocol includes liver function testing. We look forward to your comments on this protocol.

We understand that this submission and all information contained herein unless otherwise made public by Barrier Therapeutics, Inc., is **CONFIDENTIAL**. If you have any questions and/or comments, please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,

Isabel B. Drzewiecki
Isabel B. Drzewiecki
Vice President, Regulatory Affairs

Encl: FDA 356h Form



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-026

Barrier Therapeutics, Inc.
Attention: Isabel Drzewiecki
Global Head, Regulatory Operations
600 College Road East
Suite 3200
Princeton, NJ 08540

Dear Ms. Drzewiecki:

We acknowledge receipt on August 16, 2005 of your August 15, 2005 resubmission to your new drug application for **Miconazole Nitrate, 0.25%**.

We consider this a complete, class 2 response to our May 24, 2005 action letter. Therefore, the user fee goal date is February 16, 2006.

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

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Mildred Wright
10/12/2005 08:22:48 AM
Signing for M.J. Kozma-Fornaro

FDA Fax Memorandum

Date: September 22, 2005

Subject: NDA 21-026/miconazole nitrate/amendment
Vusion proprietary name

Hi Isabel,

The Division of Medication Errors and Technical Support (DMETS) have completed their review of your proposed tradenames, _____ and Vusion. DMETS' recommendation and comments are as follows:

Recommendation:

DMETS does not recommend the use of the proprietary name _____. However, DMETS has no objections to the use of the proprietary name Vusion. In reviewing the proprietary name _____ the primary concerns related to look-alike and/or sound-alike confusion with _____

_____ may look similar to _____ when scripted. _____ contains _____ cream for the shortterm treatment of moderate pruritus in adults with eczematous dermatitis. Patients should apply a thin film four times daily for less than 8 days.

b(4)



b(4)



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Although the products differ in strength (5% compared to 0.25%) and formulation (cream compared to ointment), these are single-strength and both applied topically. To accurately dispense these products, the indication, notation of the strength and formulation are not needed on the order. In addition, both products share the dispensing quantity of thirty grams. They differ in frequency of dosing or directions for use (four times per day compared to with every diaper change), but for topical products it is not uncommon to see "use as directed" on the prescription. In addition, the products even share administration timing as [redacted] should be used for less than eight days and [redacted] should be used for 7 days. DMETS would be concerned if a child's prescription for [redacted] was incorrectly filled for [redacted] for which safety and efficacy has not been proven in children. Side effects [redacted] include drowsiness, headache, dizziness, and nausea with overdose symptoms of drowsiness to respiratory depression. The [redacted] package insert notes side effects of apnea and drowsiness in a nursing infant whose mother was taking [redacted]. The indication of use for [redacted] of diaper rash would be indicative of an innate irritation of the skin, which could be as severe as erosions of the skin. In light of this, the occlusive environment of the diaper and the increased absorption of an infant's skin due to irritation, DMETS is concerned with the possible outcomes if confusion occurs between the two names.

b(4)

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name, [redacted]. However, DMETS has no objections to the use of the proprietary name, Vusion from a safety perspective. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

b(4)

B. DMETS request submittal of the labels and labeling for review and comment, when available.

Isabel, if you have questions, please call.

Respectfully,
Millie

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/s/

Mildred Wright
9/26/2005 07:45:42 AM
CSO

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Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

August 25, 2005

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AUG 26 2005

N-000(BL)
ORIG AMENDMENT

MEGA / CDER

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

NDA 21-026
Miconazole Nitrate 0.25% Ointment
Indication: Diaper Dermatitis
complicated by Candidiasis
Amendment to Complete Response to
May 24, 2005 Not Approvable Letter

Dear Dr. Wilkin,

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to our amendment to this NDA of August 15, 2005, in which we provided a complete response to the non-approvable letter of May 24, 2005. We also refer to telephone request on August 23, 2005 from Ms. Millie Wright of your Division regarding the current proposed labeling.

At this time, we wish to amend our Complete Response of August 15, 2005 to provide our proposed labeling for Miconazole Nitrate 0.25% Ointment. This proposal was originally submitted on May 17, 2005 in response to the Agency's comments on our original draft labeling. Our currently proposed labeling is identical in content to that contained in our May 17 submission. For your ease of review, we are resubmitting it as part of this amendment.

We look forward to working with the Division to finalize this labeling in a timely manner.

This submission consists of 1 volume, including a CD containing both Word and pdf versions of the labeling, and is being submitted in duplicate with a signed FDA form 356h. Each CD has a label to confirm that it was checked on August 25, 2005 for viruses by Network Associates McAfee VirusScan Enterprise 8.0.0 and is deemed virus free. We are also enclosing 10 Desk Copies to be distributed with the 10 additional copies of the Complete Response of August 15, 2005 that are being sent separately. We understand that this submission and all information contained herein unless otherwise made public by Barrier Therapeutics Inc. is CONFIDENTIAL. If you should have any questions, please contact me directly at (609) 945-1247 or at idrzwiecki@barriertherapeutics.com.

Sincerely,

Isabel Drzewiecki
Isabel B. Drzewiecki
Global Head, Regulatory Operations

ORIGINAL



Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

August 15, 2005

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Jonathan Wilkin, MD, Director
 Division of Dermatologic and Dental Drug Products
 Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation V, HFD-540
 9201 Corporate Boulevard
 Rockville, MD 20850

ORIG AMENDMENT

N-000-(BZ)

NDA 21-026

Miconazole Nitrate 0.25%
 15% Zinc Oxide, 81.35% White
 Petrolatum Ointment

Indication: Diaper Dermatitis
 complicated by Candidiasis

Complete Response to
 May 24, 2005 Not Approvable Letter

Dear Dr. Wilkin:

Reference is made to New Drug Application 21-026 for Miconazole Nitrate 0.25% 15% Zinc Oxide, 81.35% White Petrolatum Ointment and specifically to the Division of Dermatologic and Dental Drug Products Action Letter dated May 24, 2005 and Information Request letter dated June 1, 2005.

Barrier Therapeutics, Inc. is submitting this complete response to FDA's May 24 not approvable letter regarding its ointment product (0.25% miconazole nitrate, 15% zinc oxide, 81.35% petrolatum) for treating diaper dermatitis complicated by candidiasis. Together with other data and information in the NDA, this complete response demonstrates that Barrier's product is safe and effective and that this NDA should be promptly approved.

The not approvable letter raised only one issue: the purported lack of sufficient information to characterize the systemic exposure to miconazole from the product, and, implicitly, the question of whether, without such information, the safety of the product had been demonstrated. In our May 20 and June 20 correspondence and at our meeting on July 14,¹ Barrier provided information demonstrating that the absorption levels demonstrated in the percutaneous absorption study of product containing petrolatum would not be meaningfully different from the levels using the to-be-marketed product (which was also used in the clinical trials in the NDA) containing petrolatum. Barrier also showed, based on the percutaneous absorption study, that the levels of miconazole systemically absorbed from topical administration of its product are in the range of non-detectable (less than 1 ng/mL) in 15 of 18 infants to less than 5 ng/mL in the other 3 infants, substantially below the levels FDA had

1. Copies of the two letters and Barrier's slides from the meeting are attached for your convenience. See Tabs 1, 2, 3.

previously found to be safe in approving NDAs for other miconazole products, including those administered intravenously, orally, and topically. (A 2% miconazole cream in the same percutaneous absorption study resulted in plasma levels of 5.2 – 7.4 ng/mL in 4 out of 5 subjects (the other had non-detectable levels), effectively demonstrating the ceiling for absorption from topical administration of miconazole in this population.)

At our meeting, you and Dr. Houn asked that Barrier provide additional information on the effects, if any, of miconazole on the liver, especially in infants. In this complete response, we provide the requested information, which shows that miconazole has no or negligible effects on the liver in patients ranging in age from infancy to adult, even at doses much higher and sustained for periods much longer than those associated with Barrier's product.² We also provide the requested safety update.

Background on Evaluating Hepatotoxicity

Drug-induced liver effects are generally detected by examining the liver (i.e., histopathology) or by reviewing liver function tests (i.e., changes in transaminase enzymes or other parameters). Two commonly measured transaminase (or "aminotransferase") enzymes are SGOT (also known as AST) and SGPT (also known as ALT), which are thought to leak from damaged liver cells, signaling injury.³ Other parameters of interest include alkaline phosphatase (AP) and bilirubin. Increasing AP levels are sometimes associated with drug-induced liver effects or obstructions, and increases in bilirubin levels also may signal liver effects.⁴

However, an increase in the concentration of one or more of these parameters does not necessarily signal liver damage. Such changes may signal an adaptive response to a drug, or may be shifts within an acceptable range of changes.⁵ Also, changes in SGOT or AP alone (without an increase in SGPT) are not determinative of liver injury because these enzymes are found in many parts of the body.⁶

2. In addition, Dr. Houn requested information on the characteristics of grades of petrolatum. See Tab 28.

3. Timothy J. Davern et al., Biochemical Liver Tests, 1227, in Sleisenger & Fordtran's Gastrointestinal and Liver Disease, Volume 2. "SGOT" is serum glutamic oxaloacetic transaminase ("AST" is aspartate aminotransferase). "SGPT" is serum glutamic pyruvic transaminase ("ALT" is alanine aminotransferase). See Tab 29.

4. Id. at 1228-30. See Tab 29.

5. Geoffrey C. Farrell, Liver Disease Caused by Drugs, Anesthetics, and Toxins, 1403 in Sleisenger & Fordtran's Gastrointestinal and Liver Disease, Volume 2 (Mark Feldman et al. eds., 7th Ed. 2002) (In general, liver injury is signaled by increases to more than twice the upper limit of normal for SGPT, AP, or bilirubin). See Tab 30.

6. Timothy J. Davern et al., Biochemical Liver Tests, 1227, 1229. See Tab 29.

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FDA has stated in guidance⁷ how biochemical parameters may be used to detect hepatotoxic signals. The guidance states that risk of severe hepatotoxicity is signaled by a set of findings: liver enzymes elevations of > 3x ULN (upper limit of normal), no significant evidence of obstruction (elevated AP), and a very small number of cases (even as few as one), accompanied by a rise in bilirubin to 2x ULN.⁸ Elevations of transaminase to > 3x ULN can by themselves signal a less severe hepatotoxic effect.⁹

- based Summary Basis of Approval

As discussed in more detail below, data from SBAs and the published literature demonstrate that even high doses of and long exposures to miconazole in animal and human (including neonate) studies show essentially no signals of hepatotoxicity, and none of serious hepatotoxicity. Increases in transaminase or AP levels were found in only a small number of subjects and were transient and generally mild; no increases in bilirubin were reported.

Animal Studies

FDA has previously reviewed animal liver data in the context of miconazole NDAs and the OTC review. The effect of miconazole on animal livers has been studied extensively in multiple species, via multiple routes of exposure, and with daily drug administration of up to 18 months. Liver studies in these animals included organ examinations and often tests for biochemical liver function parameters. High oral and IV doses of miconazole sometimes produced small changes in the liver (e.g., slight weight increases) and transaminase levels, but chronic topical applications of up to six months duration did not produce any reported changes (outside normal levels) to livers or biochemical parameters.

FDA commented on the issue of liver toxicity in its review of the first approved miconazole NDA, Monistat 7. The SBA for this drug notes that mild degenerative hepatic changes were observed in rats and dogs that received miconazole on a chronic basis, but that a daily oral dose of 10 mg/kg was a "long-term 'no-effect' level."¹⁰ Similar results were noted in subsequent reviews of both IV and oral dosing. The Pharmacology Review for Monistat IV notes that IV doses of miconazole up to 20 mg/kg/day in rabbits (6 days a week for 6 weeks) produced "generally unremarkable" serum levels¹¹ and no dose-related lesions.¹² A six-month study in

7. Review Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review (Feb. 2005) [hereinafter, Safety Guidance], available at <http://www.fda.gov/cder/guidance/3580fnl.pdf>. See Tab 31.

8. Safety Guidance, 29-30 (copy attached). See Tab 31.

9. Safety Guidance, 73 (copy attached). See Tab 31.

10. Monistat Vaginal Cream NDA 17-450, Summary Basis of Approval, Pharmacology, 2 (1974). See Tab 14.

11. The materials reviewed did not specify what parameters were measured. Terms such as "serum levels," "clinical chemistries," and "biochemical tests" sometimes appear in lieu of a specific list of parameters measured or tests performed. It seems probable, however, that measurements would have included those parameters relevant to liver function, because of interest in miconazole's effects on liver function.

rabbits with IV doses up to 20 mg/kg/day produced slight increases in SGOT and SGPT, and some fatty liver degeneration at 10 and 20 mg/kg/day.¹³ Chronic and subacute oral studies in rats and dogs stated that liver weight increases began to occur at 69 and 34.8 mg/kg miconazole nitrate, respectively, with very high doses producing elevated SGPT and AP serum levels in dogs.¹⁴ The FDA reviewer noted that these changes decreased over time, suggesting that the observed effects were reversible.¹⁵

No changes in the liver were observed following topical applications of 2% miconazole nitrate cream or 2% miconazole intravaginal suppositories. The SBA for Daktarin¹⁶ notes that following up to 2 gm/kg/day of 2% miconazole nitrate cream applied to rabbits for 6 months, gross and histopathological examinations of organs revealed no drug-related effects (other than to skin), and that there were no effects on organ weights or "blood chemistries."¹⁷ The OTC submission from Johnson & Johnson, which the OTC panel relied upon in determining that miconazole was safe, also summarizes a number of similar studies, ranging from 28 days to six months and using both rabbits and non-human primates, in which application of creams and suppositories produced no changes outside normal limits on livers or blood chemistries,¹⁸ some of which explicitly listed SGPT, SGOT, and AP among the tested parameters.¹⁹

12. Monistat IV NDA 18-040, Pharmacology Review, 2 (1977). See Tabs 19 and 20.

13. Id. at 3-4. See Tabs 19 and 20.

14. Id. at 8. See also Johnson & Johnson, Information Regarding Miconazole Nitrate Submitted to the Antimicrobial II OTC Panel Review: Submission 070204A, Vol. 1 [hereinafter J&J OTC 070204A], 17-21 (Stating similar results and conclusions from an 18-month study in rats and a one year study in dogs). See Tabs 19, 20 and 12.

15. Id. See Tabs 19, 20 and 12.

16. The product name at approval was Daktarin cream (also referred to as Mica-TIN cream). NDA 17-494, Summary Basis of Approval, 1 (this document is included as an attachment to our June 20 letter). The trade name for the product that is currently marketed under NDA 17-494 is Monistat-Derm. See Tab 16.

17. Daktarin Cream NDA 17-494, Summary Basis of Approval, 1; supra note 11 (regarding the term "blood chemistries"). See Tab 16.

18. Supra note 11.

19. J&J OTC 070204A, 14-15 (Three-month intravaginal study in rabbits using 2% miconazole suppositories. No change in liver weight was noted, and "clinical chemistry data were within normal limits and comparable to controls"); 16 (Three-month intravaginal study in monkeys using 2% miconazole suppositories. Organ weights in treatment group "were within normal limits and comparable to controls," and "clinical chemistry values" were within normal limits prior to and at termination of the study); 41 (Four week topical study in rabbits using cream (formula 001, % miconazole unspecified) up to 2g/kg/day with 6-7 hour daily exposure. Organ weight data within normal limits, and histopathologic examination revealed no drug-related lesions (organs not specified)); 41-42 (One month topical study in rabbits using 2% miconazole cream up to 1 ml/kg/day. No treatment-related changes were observed in SGPT, SGOT, or AP);

Taken together, the animal data show that high doses of miconazole administered by the routes that would cause the highest system exposure in the blood stream (IV and oral) may produce some transient, reversible changes in the liver, in particular an increase in organ weight which is associated with small increases in enzyme levels. Long term topical application of products with 8 times the concentration of miconazole nitrate used in Barrier's product (2% versus 0.25%) produced no changes outside normal limits.

Human Studies

The effects of miconazole on the human liver have been characterized in a number of studies, many of which FDA has previously considered in approving other miconazole drugs. In the vast majority of studies, no hepatotoxic effects were observed. Similar to animal models, high dose systemic exposures occasionally produced transient, reversible increases in transaminase and AP levels in a very small number of subjects. These increases were usually small, and were not accompanied by increases in bilirubin.

The SBA for Dakтарin summarizes a number of IV, oral, and topical miconazole studies in humans. Three studies were reported on IV use in nine patients (200 mg BID-TID for 7-10 days in three patients, 600 mg daily, BIW or TIW for 14 total infusions in six patients). In these studies, liver function tests (which were performed in three patients) showed no drug-related changes.²⁰ (IV doses of this amount would produce blood levels of miconazole ranging from hundreds to thousands of nanograms per milliliter,²¹ levels far exceeding those observed in the percutaneous study using the F100 formulation (15 of 18 with less than 1 ng/mL, and a maximum of 4 ng/mL), Barrier's conservative estimate of maximum levels that could be achieved with the F114 formulation (10.7 ng/mL), and the unrealistic estimate of complete absorption (65.6 ng/mL).²²)

In eight oral-dose clinical studies in which subjects received 250-3000 mg/day of miconazole for 2-9 weeks, liver function tests on 64 patients indicated no drug-related changes.²³ (Doses of

43 (Six month topical study in rabbits using 2% miconazole nitrate cream up to 2 mg/kg/day. Biochemical tests were performed periodically, and the report did not note any changes in liver enzymes); 47-48 (Three month intravaginal study in rabbits using 2% miconazole cream up to 1g/day. Biochemical tests performed included SGPT, SGOT, and AP. Some changes in biochemical parameters were noted, but were considered to be within normal limits for rabbits (the parameters that changed were not specified)). See Tab 12.

20. NDA 17-494, SBA, Clinical Safety Studies, 5. See Tab 16.

21. E.g., Barrier NDA 21-026, Report 989-012P, Section 6.0 (Children who received 7-10 mg/kg of miconazole intravenously had Cmax of 400-3600 ng/mL); Monitstat 1 Combination Pack NDA 21-308, Clinical Review, Human Pharmacokinetics and Pharmacodynamics, Pharmacokinetics (circa 2001) (plasma levels from IV infusions of miconazole ranged from 440 ng/mL to 6180 ng/mL). See Tab 21 and 32.

22. See the June 20 letter's discussion of systemic levels of miconazole. See Tab 2.

1000 mg/day produce plasma levels of about 500 - 1000 ng/mL,²⁴ again considerably higher than anything that could be produced by Barrier's product.)

The SBA also summarizes four topical studies using a 2% miconazole nitrate cream. Three of the four studies included tests for bilirubin, AP, SGOT and other parameters; one study used SGPT in place of SGOT. Results from the studies included occasional increases in SGOT and one slight increase in AP,²⁵ increases which are not necessarily specific to liver function (as discussed above). In the study where SGPT was monitored, an equal number of increases were observed in the placebo and treatment groups,²⁶ indicating no dose-related effect.

The NDA approval package for Monistat Soft Gel Vaginal Inserts includes a Phase 1 study that measured miconazole blood levels and various blood parameters during the study. During a four-day (1 dose) and six-day (2 dose) study miconazole blood levels were measured (achieving an average maximum concentrations of 10.6-10.7 and 12.0 ng/mL, respectively), and blood parameters including total bilirubin, AP, SGOT, and SGPT were measured prior to and after the study.²⁷ No significant changes in these parameters were noted.²⁸ The maximum levels of miconazole achieved were higher than those measured in the percutaneous absorption study of Barrier's product and roughly equivalent to the highest conservative estimate based on in vitro release calculations.

All the above data have previously been relied upon by FDA in determining that miconazole is safe. The literature is also replete with additional studies of miconazole's liver effects confirming FDA's conclusions, and adding a database of information on the effect of miconazole in infant livers.

23. NDA 17-494, SBA, Clinical Safety Studies, 4. See Tab 16.

24. E.g., Jorg E. Hoppe et al., Treatment of Oropharyngeal Candidiasis in Immunocompetent Infants: A Randomized Multicenter Study of Miconazole Gel vs. Nystatin Suspension, *Pediatr. Infect. Dis. J.*, 16:3, 288-93 (Mar. 1997) citing B. Roed-Petersen, Miconazole in the Treatment of Oral Candidosis, *Int. J. Oral. Surg.*, 7, 558-63 (1978) (prolonged administration of 500 mg as tablets twice a day resulted in 0.5-1.0 mcg/mL in serum). See Tab 6.

25. NDA 17-494, SBA, Clinical Safety Studies, 3. A study by Pugliese with applications of 2.5 grams to the back for 28 days noted increased SGOT in 2 of 10 patients. A study by Jolly with treatment BID for 28 days noted increased SGOT in 1 of 9 patients at days 28 and 56. A study by Kligman noted "slightly increased AP" in 1 of 13 patients (frequency and duration of treatment are not stated). The studies also appear in J&J OTC 070204A, 282-295. See Tab 16.

26. NDA 17-494, SBA, Clinical Safety Studies, 4. See Tab 16.

27. Monistat Soft Gel Vaginal Insert and Monistat External Vulvar Cream NDA 20-968, Clinical Pharmacology and Biopharmaceutics Review, 1-4 (June 1999); Medical Officer's Review, 83-91 (June 1999). See Tab 22.

28. NDA 20-968, Medical Officer's Review, 90 (Results from tests were "within normal limits or judged by an investigator to be not clinically significant"). See Tab 22.

Studies of IV miconazole's effects on the liver encompass over 150 patients ranging from neonatal to 80 years of age. Fischer noted that children with chronic mucocutaneous candidiasis who received IV doses of miconazole for over 15 months had "mild transient transaminase (SGOT and SGPT) elevations," but it appears that those patients also received clotrimazole (a known hepatotoxin) during their treatment.²⁹ Idemoto reported that in a study of 66 patients treated with high levels of miconazole, three had transaminase increases, two of which were ~ 3x baselines or lower, and all of which were transient.³⁰ Barton summarized case records of 121 patients, ranging from neonatal to 78 years of age, receiving IV miconazole treatment across the UK. Of the 121 patients, the records for 108 had serum biochemistry examinations,³¹ no significant drug-related changes, and no indications of hepatotoxicity were reported.³² Shehab noted that combined miconazole (IV) / ketoconazole (oral) therapy in 8 children, with miconazole administered daily for 2-6 months followed by reduced frequencies of administrations, produced no changes except for occasional increases in transaminase to less than two times normal levels.³³

Schaad reported results of a study testing the use of miconazole oral gel in 23 pediatric patients with an average age of approximately 5.5 weeks. Treatments with 100-200 mg/day of miconazole over an average of 8-12 days were performed. Levels of SGOT and SGPT in all patients up to 4 weeks of age (eight total) were obtained before and after therapy. None of the results indicated hepatotoxicity.³⁴

For topical applications, studies of over 700 patients using miconazole cream formulations generally failed to produce significant changes in liver function even after extended periods of use. For example, Shear states that application of a cream containing 2% miconazole nitrate for 12 weeks in 75 patients age 12-43 produced no clinically relevant changes in clinical chemistries.³⁵ And Larbi reported that a study of 23 patients that applied 2% miconazole cream

29. Thomas J. Fischer et al., Miconazole in the Treatment of Chronic Mucocutaneous Candidiasis: A Preliminary Report, J. Pediatr, 91(5), 815-19. Also, a marked elevation was noted in one patient during concomitant treatment with clotrimazole. See Tab 33.

30. H. Idemoto et al., Results of a Clinical Trial of Miconazole Against Deep-Seated Fungal Infections, 9, Table 15 (Translated from original published in Japan. J. Antibiot., 37(4):615, 638-39, 652, 658-61 (Apr. 1984)). See Tab 34.

31. Supra note 11.

32. G.J. Barton et al., Monitored Release of Intravenous Miconazole in the United Kingdom. A Report of the First 2 Years Experience, 28, 33, in The Role of Miconazole in the Treatment of Systemic Mycoses: Royal Society of Medicine International Congress and Symposium Series No. 45. See Tab 35.

33. Ziad M. Shehab et al., Imidazole Therapy of Coccidioidal Meningitis in Children, Pediatr. Infect. Dis. J. 7:40-44 (Jan. 1988). See Tab 36.

34. U. B. Schaad et al., Pilot Study Comparing Miconazole Gel and Nystatin Suspension in the Therapy of Oral Thrush, 5-6, 8, 15 (Translated from original published in Schweiz. Med. Wschr., 113(38); 1356-62 (1983)). See Tab 37.

to cutaneous leishmaniasis lesions twice daily for 30 days produced no difference between pre- and post-treatment levels of SGOT, SGPT, and AP.³⁶ Haneke reported some changes in a study of 396 patients that were enrolled to receive twice daily doses of 2% miconazole cream for 6 months; five patients had elevations of SGPT above 50 U/I, and one patient was withdrawn when SGPT levels rose above 80 U/I.³⁷

A table summarizing the literature Barrier reviewed, as well as copies of the articles which are not specifically cited in this document can be found in Table 1 for your review.

Conclusion

Miconazole has been shown to be safe in adults, children, and infants (as well as animal models) at systemic levels far exceeding those that would be produced by Barrier's product. It produces no or negligible effects on the liver, including infant livers, at doses far higher than those that would result from Barrier's product. It is safe for use in this product.

Other Issues

Safety Update

The not approvable letter requested a safety update as part of the complete response. Please be advised that we have no additional data from clinical or non-clinical studies, and that there have not been any significant changes or findings in the safety profile.

Responses to Items 1- 7 in Your June 1, 2005 Information Request Letter

For completeness of our response we also address the items listed in your Information Request letter, which you indicated do not impact the approvability of this NDA.

1. An acceptable Tradename is needed in order to market this drug safely.

We have submitted information supporting the safe use of the tradename Zimyca (NDA 21-026; February 16, 2005), which ultimately was not endorsed by DMETS. We respectfully disagree with DMETS' position regarding our initially proposed tradename, Zimyca, and realize that the final decision on approving a suitable trademark rests with the Division of Dermatological and Dental Drug Products. However, in order not to hold up marketing of this

35. Neil H. Shear et al., Benzoyl Peroxide-Miconazole Cream vs. Erythromycin Lotion in Patients with Moderate to Severe Acne Vulgaris, *Can. J. Derm.*, 4(2), 216-219; supra note 11. See Tab 38.

36. Emmanuel B. Larbi et al., A Randomized, Double-Blind, Clinical Trial of Topical Clotrimazole Versus Miconazole for Treatment of Cutaneous Leishmaniasis in the Eastern Province of Saudi Arabia, *Am. J. Trop. Med. Hyg.*, 52(2), 166-68 (1995). See Tab 39.

37. E. Haneke, Itraconazole in the Treatment of Onychomycosis: A Double Blind Comparison with Miconazole, *Dermatology*, 196, 323-29 (1998). See Tab 40.

product we suggested two alternative names (NDA 21-026; May 6, 2005). To date, we have not heard from either the Division or DMETS regarding our May 6, 2005 submission. In light of your commitment to try to expedite review of this complete response, we would greatly appreciate your assistance in accelerating the review and approval of our initially proposed tradename, Zimycan or one of the alternate tradenames proposed in the May 6, 2006 correspondence.

2. Continued discussion of labeling is needed as the current version of labeling has not been entirely agreed upon. In addition, labeling will need to incorporate any new systemic exposure information submitted.

We of course stand ready to discuss the labeling at your convenience. We believe the information submitted above, together with other information previously submitted, will allow the labeling discussions to go forward without the need for revision to provide information about hepatotoxicity.

3. Additional clinical studies are recommended, but not necessarily prior to approval.

As discussed at our July 14 meeting, Barrier agrees to do a post-approval (Phase IV) study evaluating in the same study both percutaneous absorption of miconazole from the approved product and changes in liver enzymes between baseline and one week. At this time, none of the other recommended studies seems appropriate or necessary. We would be pleased to discuss these issues with you.

4. Please provide a specification table for the miconazole nitrate drug substance

The specifications for miconazole nitrate drug substance are those of the current USP and a requirement for particle size. A tabular presentation of the specifications is presented below.

Test	Method	Acceptance Criteria
Infrared Absorption	USP <197K>	Matches standard
Ultraviolet Absorption	USP <197U>	Matches standard
Loss on Drying	USP <731>	NMT
Residue on Ignition	USP <281>	NMT
Chromatographic Purity	USP <621>	Similar R _f for standard and sample Individual spots NMT
Ordinary Impurities	USP <466>	Total spots NMT
Assay	USP Monograph	
Particle Size	Sieve	Minimum Minimum

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5. **The acceptance criterion for _____ in the regulatory specification should be based on actual data and not on the maximum amount that could be formed. No data have been provided to support the assumption that all the BHT present in petrolatum will react with miconazole nitrate.**

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At present, the regulatory specification _____ has been based upon the maximum amount that could be formed when BHT is present at the specification limit _____ in White Petrolatum USP. The levels that have been observed in the three registration stability batches and the one clinical batch manufactured thus far have ranged from _____ of the miconazole nitrate level. However, these batches have used only a few lots of petrolatum and there are inadequate data to establish the relationship between the level of BHT in the petrolatum and the resulting level of _____ in the drug product. Barrier commits to evaluate the BHT level in petrolatum and correlate those results to the level of _____ in the resulting batches of drug product. The BHT data from at least five lots of petrolatum and the _____ data from the resulting batches of drug product will be used to establish a data based acceptance criterion _____ in the drug product.

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6. **The drug product specification table should be modified to include all commitments, including the deletion _____ from the appearance acceptance criterion.**

Barrier commits to revise the drug product specification presented in 3.2.P.5 Table 1 of the NDA to include all commitments made during the review of this Application. Included will be the modified acceptance criteria for the Appearance parameter

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7. _____ **should be monitored in the drug product stability studies. Please provide a separate list of all items to be monitored in the stability studies.**

_____ has been monitored and reported for the accelerated and long-term stability studies of the three primary stability batches presented in 3.2.P.8.3 Table 1 of this NDA.

The parameters to be monitored during stability, and the testing schedule, for the three primary stability batches and for the first three post-approval batches are presented in 3.2.P.8 Table 2 of the NDA. A copy is presented below.

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Storage Condition ¹	Time Point (months)									
	0	1	3	6	9	12	18	24	36	48
25 ± 2°C/60 ± 5%RH	XY	X	X	X	X	X	X	XY	X	XY
30 ± 2°C/65 ± 5%RH ²	X	X	X	X	X	X	NT	NT	NT	NT
40 ± 2°C/75 ± 5%RH	X	X	X	X	NT	NT	NT	NT	NT	NT

1: Samples are packaged in 5-g, _____ tubes with _____ caps
 Samples are stored in both upright and horizontal positions. Horizontal samples are tested only if there is a significant change in the upright samples.

2: Intermediate condition samples are tested only if there is a significant change at 40°C/75%RH

X = Appearance of product and container closure
 Odor
 Assay miconazole nitrate
 Assay zinc oxide
 Impurities
 (Product from the cap, middle and crimp sections of the tubes are evaluated for assay and impurities for _____ samples. Composites are evaluated for 5-g tube samples.)

Y = Microbial Limits
 NT = Not tested

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The parameters to be monitored during stability and the testing schedule for the ongoing marketed product stability batches are presented in 3.2.P.8 Table 8 of the NDA. A copy is presented below.

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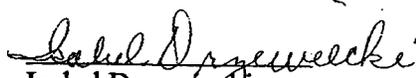
Storage Condition ¹	Time Point (months)					
	0	3	12	24	36	48
25 ± 2°C/60 ± 5% RH	XY	X	XY	XY	XY	XY
<p>1: Samples are packaged in 5-g, 30-g tubes with caps for the 30-g tubes.</p> <p>Samples are stored in upright positions.</p> <p>X = Appearance of product and container closure Odor Assay miconazole nitrate Assay zinc oxide Impurities (Product from the cap, middle and crimp sections of the tubes are evaluated for assay and impurities for 30-g samples. Composites are evaluated for 5-g tube samples.</p> <p>Y = Microbial Limits</p>						

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We appreciate your willingness to promptly review our complete response as discussed at our July 14, 2005 meeting.

This submission consists of 6 volumes and is being submitted in duplicate with a signed FDA form 356h. We understand that this submission and all information contained herein unless otherwise made public by Barrier Therapeutics Inc. is CONFIDENTIAL. If you should have any questions, please do not hesitate to contact me directly at (609) 945-1247.

Sincerely,


 Isabel Drzewiecki
 Global Head, Regulatory Operations

Enclosure: Form FDA 356h

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-026

Barrier Therapeutics, Inc.
Attention: Isabel Drzewiecki
Global Head, Regulatory Operation
600 College Road East, Suite 3200
Princeton, New Jersey 08540

Dear Ms. Drzewiecki:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for miconazole nitrate 0.25%, zinc oxide 15%, and white petrolatum ointment 81.35%.

We also refer to the teleconference between representatives of your firm and the FDA on July 14, 2005. The purpose of the teleconference was to provide clarification for the basis of the deficiencies cited in the May 24, 2005, Not Approvable letter for miconazole nitrate 0.25%, zinc oxide 15%, and white petrolatum ointment 81.35%.

The official minutes of that teleconference are enclosed.

If you have any questions, call Millie Wright, Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan Wilkin, M.D.

Director

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

Enclosure

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MEMORANDUM OF TELECON

DATE: July 14, 2005

Application: NDA 21-026

Sponsor: Barrier Therapeutic, Inc.

Topic: Sponsor's meeting package submitted June 20, 2005

Meeting ID: 15717

FDA Participants:

Office of Drug Evaluation III

Florence Houn, M.D., Office Director

Division of Pediatric Drug Development/HFD-960

Lisa Mathis, M.D. Acting Division Director

Division Dermatologic and Dental Drug Products/HFD-540

Jonathan Wilkin, M.D., Division Director

Brenda Carr, M.D., Medical Reviewer

Ramesh Sood, Ph.D., Chemistry Team Leader

Abi Adebowale, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer

Dennis Bashaw, Pharm. D., Clinical Pharmacology and Biopharmaceutics Team Leader

Millie Wright, RN, MSN, Project Manager

Melinda Harris-Bauerlien, Project Manager

Sponsor Participants:

Charles Nomides, Chief Operating Officer

Geert Cauwenbergh, PhD, CEO

Nancy Buc, Esq., Counsel for Barrier, Partner Buc and Beardsley

Stefan Ochalski, Director Regulatory Affairs

Mangaraju Gudipati, Ph.D., Head Global CMC

James Boiani, Associate Counsel for Barrier, Buc and Beardsley

Background

In response to the Agency's Not Approvable (NA) letter, issued May 24, 2005, Barrier requested a teleconference with the Agency to clarify the basis for the deficiencies listed in the May 24, 2005, NA letter.

Discussion

Ms. Buc opened the discussion with an overview of the available data to support their NDA. After Ms. Buc's opening comments, the discussion focused on the Sponsor's slides (See Attachments 1 and 2), which covered the different formulations, safety data, pediatric adverse events, and absorption.

Agreements Reach

1. The Sponsor will submit a complete response which should include the following:
 - a. data to address liver effects
 - b. draft protocol for a Phase 4 study which should include specific plans for safety surveillance
 - c. information in the complete response should be as relevant as possible to the age and population targeted.
2. The Division acknowledged that during the last review cycle draft labeling was shared with the Sponsor but noted that further labeling negotiations will be needed during the next review cycle.
3. When questioned about the time it would take to complete the review of the Sponsor's complete response, the Division stated that they would attempt to complete the review in less than the 6 months allowed by PDUFA.

Project Management

Comments shared today with the Sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the NDA might identify additional comments or informational requests.

Minutes Preparer/Mildred Wright, Regulatory Project Manager/HFD-540, DDDDP

Chair Concurrence/Jonathan Wilkin, M.D., Director/HFD-540/DDDDP

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15 Page(s) Withheld

b Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-026

Barrier Therapeutics, Inc.
Attention: Isabel Drzewiecki
Global Head, Regulatory Operations
600 College Road East, Suite 3200
Princeton, New Jersey 08540

Dear Ms. Drzewiecki:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum ointment.

We also refer to the action letter dated May 24, 2005.

Please respond to the following items in your resubmission:

1. An acceptable Tradename is needed in order to market this drug safely.
2. Continued discussion of labeling is needed as the current version of labeling has not been entirely agreed upon. In addition, labeling will need to incorporate any new systemic exposure information submitted.
3. Additional clinical studies are recommended, but not necessarily prior to approval. These studies are as follows:
 - a. The applicant should evaluate the safety and efficacy of their product in incontinent adults who have perineal dermatitis complicated by candidiasis.
 - b. The applicant should assess repeated use of their product for relapse in pediatric patients.
 - c. The applicant should conduct a prospective study to assess for the development of drug resistance for the first year of marketing (a literature survey would not be sufficient).
 - d. Please conduct efficacy and safety evaluations of their product for diaper dermatitis complicated by cutaneous candidiasis in the under 4 week old group.
4. Please provide a specification table for the miconazole nitrate drug substance.
5. The acceptance criterion for _____ in the regulatory specification should be based on actual data and not on the maximum amount that could be formed. No data have been provided to support the assumption that all the BHT present in petrolatum will react with miconazole nitrate.
6. The drug product specification table should be modified to include all commitments, including the deletion of _____ from the appearance acceptance criterion.
7. _____ should be monitored in the drug product stability studies. Please provide a separate list of all items to be monitored in the stability studies.

b(4)

b(4)

If you have any questions, please call Millie Wright, Project Manger, at 301-827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD-
540
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jonathan Wilkin
5/31/05 12:14:38 PM

MEMORANDUM OF TELECON

DATE: 5/24/05, 2:30 P.M.

APPLICATION NUMBER: NDA 21-026

DRUG PRODUCT: .025% miconazole nitrate ointment, 15% zinc oxide, and 81.35 white petrolatum ointment

BETWEEN:

Name: Isabel Drzewiecki, Gloabal Head, Regulatory Operations
Representing: Barrier Therapeutics, Inc.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
Jonathan Wilkin, M.D., Division Director
Melinda Harris-Bauerlien, M.S., Regulatory Project Manager

SUBJECT: NDA 21-026

The applicant informed the Agency that it received today's facsimile transmission of the Not Approvable Letter for this NDA application.

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

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/s/

Melinda Harris-Bauerlien
5/26/05 12:11:01 PM
CSO

Jonathan Wilkin
5/31/05 12:11:14 PM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-026

Barrier Therapeutics, Inc.
Attention: Isabel Drzewiecki
Global Head, Regulatory Operations
600 College Road East, Suite 3200
Princeton, New Jersey 08540

Dear Ms. Drzewiecki:

Please refer to your new drug application (NDA) dated November 24, 2004, received November 24, 2004, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for 0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum ointment.

We acknowledge receipt of your submissions dated December 13, 2004, January 5, February 15 and 16; March 10 and 15, April 14, 22 and 29, and May 3, 5, 6, 17, and 20, 2005.

The November 24, 2004, submission constituted a complete response to our July 24, 2000, action letter.

This new drug application provides for the use of 0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum ointment for the adjunctive treatment of diaper dermatitis only when complicated by candidiasis, as documented by microscopic evidence of pseudohyphae and/or budding yeasts, in immunocompetent pediatric patients four weeks old and older.

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiency is summarized as follows:

There is insufficient information to characterize the systemic exposure to miconazole from this product. Characterization of systemic exposure to miconazole is a component of the safety evaluation of the product.

Additional items which are not non-approval (NA) issues will be sent in a separate fax.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, please call Millie Wright, Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}
Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug
Products, HFD-540
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jonathan Wilkin
5/24/05 02:01:02 PM

Wright, Mildred

From: Peat, Raquel
Sent: Friday, May 20, 2005 12:21 PM
To: Wright, Mildred
CC: Harris-Bauerlien, Melinda
Subject: Re: Your 505(b)(2): NDA 21-026

Millie:
Your application was approved for clearance from IO, ORP and OCC. Happy Action! Raquel

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wright, Mildred <WrightM@cder.fda.gov>
To: Peat, Raquel <PeatR@cder.fda.gov>
CC: Harris-Bauerlien, Melinda <BauerlienM@cder.fda.gov>
Sent: Fri May 20 12:18:45 2005
Subject: RE: Your 505(b)(2): NDA 21-026

I will be on LV next week, if it doesn't come in today, please send to Melinda Harris-Bauerlien who will be covering for me. You have been so very helpful. It is greatly appreciated. Millie

-----Original Message-----
From: Peat, Raquel
Sent: Friday, May 20, 2005 11:29 AM
To: Wright, Mildred
Subject: Your 505(b)(2): NDA 21-026

Millie:
FYI: I am still waiting on clearance from OCC for approval of this product.

Raquel

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Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

DUPLICATE

RECEIVED

May 20, 2005

MAY 23 2005

MEGA / CDER

Jonathan Wilkin, MD, Director
 Division of Dermatologic and Dental Drug Products
 Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation V, HFD-540
 9201 Corporate Boulevard
 Rockville, MD 20850

ORIG AMENDMENT

N-000-(BC)

NDA 21-026

Miconazole Nitrate 0.25% Ointment

**Indication: Diaper Dermatitis
 complicated by candidiasis**

**Response to CMC Request for
 Information**

Dear Dr. Wilkin,

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to Barrier Therapeutics' amendment to the NDA of November 24, 2004, in which we provided a complete response to the non-approvable letter of July 24, 2000. Barrier Therapeutics would also like to refer to the FDA's facsimile dated May 19, 2005, where the Agency requested a response on the issues delineated below. For ease of review, in this correspondence, each Division question is repeated in its entirety, followed by a response from Barrier Therapeutics.

FDA Question 1:

You state the differences in the *in vitro* release rates between the drug product manufactured by Janssen and the drug product manufactured by DSM may be due to the particle size distribution of the zinc oxide. You also state that the data on the particle size distribution of zinc oxide are currently not available to you, and that you commit to gathering data on the batch-to-batch zinc oxide particle size reproducibility (3.2.P.2.3.5 "In-Vitro Studies", Vol. 2.1A, page 0000002). However, you did not include a particle size acceptance criterion in the specification of zinc oxide. The information provided in your Amendment dated April 22, 2005 contained particle size distribution of the zinc oxide drug substance (provided by the zinc oxide drug substance manufacturer). Please include a tentative particle size acceptance criterion (with the appropriate method) in the specification of zinc oxide. The acceptance criterion can be modified after the sufficient data has been accumulated. The analytical method should be validated.

May 20, 2005

Barrier Therapeutics Response

Barrier will include a requirement in the supplier's specification to determine the specific surface area of the zinc oxide. The particle size of the zinc oxide is such that it will be below the smallest of the U.S. Standard Sieves () that are used in mechanical sieve techniques. The assessment of the specific surface area is a preferred method to determine and insure the reproducibility of the fineness of the zinc oxide. Barrier will also include in the supplier's specification a requirement for determining the specific surface area using the compendial METHOD II-THE VOLUMETRIC METHOD of the USP Procedure <846> SPECIFIC SURFACE AREA. The acceptance criteria will be 4.5 – 5.5 m²/gram.

FDA Question 2:

You were informed that visual examination of the ointment for agglomerates is inadequate, and were requested to include a microscopic test to assure that no agglomerates are present, or alternately, to propose another test for homogeneity. Your response in the Amendment dated May 5, 2005, that the agglomerates are easily visible on a glass plate, is not acceptable. Please include a microscopic test to assure that no agglomerates are present, or alternately, propose another test for homogeneity.

Barrier Therapeutics Response

Barrier proposes to use a () gauge as the in-process control for the presence of agglomerates during the manufacturing process. A () gauge is a precision instrument that is used according to the test methodology () Such a method was evaluated early in the development of this formulation and it was concluded that any agglomerates detected by the () gauge were also visible when spread on a glass plate. Our choice of this methodology over microscopic methodology is based upon the fact that it is not subjective and can be accurately used on the manufacturing floor with minimal personnel training. Barrier commits to purchasing the equipment, evaluate the product and establish quantitative acceptance criteria.

b(4)

FDA Question 3:

You describe the appearance of the drug product as "White, homogeneous ointment ()". You were requested to describe in more detail what is meant by () and what causes the () Your explanation, that a () was only occasionally observed on the surface of a few tubes during stability studies, and that it is due to the trihydroxystearin being thixotropic and that it is unrelated to temperature, because it was not more prevalent at the higher temp (40 C), is inadequate. You also state that the separation has not been observed in clinical batches. Please remove () from the Appearance of the drug product in the drug product specification.

b(4)

May 20, 2005

Barrier Therapeutics Response

Barrier will remove product in the drug product specification. from the Appearance of the drug b(4)

FDA Question 4:

You stated that you do not intend to market the commitment should be revised accordingly so that the first three commercial and, thereafter, annual stability batches include the approved marketed sizes. The post marketing stability b(4)

Barrier Therapeutics Response

The post marketing stability commitment will be revised to indicate that Barrier will conduct stability studies on the first three commercial batches of any size included within the range bracketed by the primary stability studies. Those first three batches will be tested according to the protocol of the primary stability studies. We will also revise the commitment for each subsequent year to indicate that we will conduct stability studies for one batch of each tube size that is manufactured during that year. Those subsequent studies will be tested according to the post-approval stability protocol.

Barrier Therapeutics trusts that our responses are satisfactory.

This submission consists of 1 volume and is being submitted in duplicate with a signed FDA form 356h. We understand that this submission and all information contained herein unless otherwise made public by Barrier Therapeutics Inc. is CONFIDENTIAL. If you should have any questions, please do not hesitate to contact me directly at (609) 945-1208 or Isabel Drzewiecki, Global Head-Regulatory Operations at (609) 945-1247.

Sincerely,


STEPAN DRZEWIECKI
FR

Isabel B. Drzewiecki
Global Head, Regulatory Operations

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MEMORANDUM OF TELECON

DATE: May 19, 2005

Application: NDA 21-026, 0.25% miconazole nitrate ointment, 15% zinc oxide, and 81.35% white petrolatum ointment

Sponsor: Barrier Therapeutics, Inc.

Topic: Differences in the formulation used in the PK study and the to-be-marketed formulation.

FDA Participants:

Division Director, Division of Dermatologic & Dental Drug Products/HFD-540

Jonathan Wilkin, M.D., Division Director

Millie Wright, R.N., M.S.N., Project Manager

Office of Clinical Pharmacology and Biopharmaceutics, DPE III

Arzu Selen, Ph.D., Deputy Division Director

Dennis Bashaw, Pharm.D., Team Leader

Abimbola Adebawale, Ph.D., Reviewer

Division of New Drug Chemistry III, Office of New Drug Chemistry

Ramesh Sood, Ph.D., Team Leader

Saleh Turujiman, Ph.D., Reviewer

Sponsor Participants:

Stefan Ochalski, Director-Regulatory Affairs

Mangaraju Gudipati, Ph. D- Global Head, CMC

Charles Nomides-COO

Vera van de Velde, Ph. D-Director-Pharmacokinetics

Mat Nunes, Consultant to Barrier-CMC

Background

The chemistry team discovered that the formulation used in the pharmacokinetics (PK) study was not the same as the to-be-marketed formulation. The formulation differed in the composition of the petrolatum. The change in the composition of the petrolatum raised a concern as, in this formulation; petrolatum is both a "structure forming ingredient" as defined in SUPAC-SS, and an active ingredient (skin protectant). It is unknown to what degree the change in petrolatum will have on the bioavailability of the miconazole component of the to-be-marketed formulation. The t-con was scheduled to discuss the review team findings and request input from the Sponsor..

Discussion

Dr. Wilkin began the discussion by noting that the chemistry team discovered only in the last 24 hours that there is a difference in the composition of the petrolatum, contained in the formulation used in the PK study and the composition of the petrolatum in the formulation used in the clinical trial. In addition it was noted that in vitro testing done by the sponsor was unable to demonstrate equivalence between the two formulations, thus raising a safety concern as we do not know what the human systemic exposure is with the to-be marketed formulation. This finding of a safety concern this late in the review cycle could lead to a less than positive action by the Division on this application. The telecon was held with the Sponsor to inform them of this finding and to encourage them to provide us with an explanation to allay the Division's concerns.

The Sponsor acknowledged that they were aware of the compositional difference and the failed in vitro testing but noted that the petrolatum in both formulations still met the USP requirements.

The Agency indicated that while it is necessary to meet USP requirements, they represent a minimum standard. In their product, as a result of their formulation change a change in the in vitro release was noted. Adherence to the USP monograph alone cannot suffice in light of this observed difference. Ultimately a change in petrolatum may affect the in vivo bioavailability and may affect the "deployability" of the product, both of which could alter the pattern of use and absorption. The Agency again stressed that the information that is needed is an assessment of the degree of systemic exposure or information that would allow us to address this issue in another manner, and inquired if the Sponsor could provide that to the NDA?

The Sponsor replied that in the to-be-marketed formulation, they haven't done systemic exposure study in infants. Their perspective is that miconazole is not rapidly absorbed; therefore they felt the studies presented were adequate. If it is not adequate, they asked what they need to do. Also, they asked if the PK data could be obtained in a Phase 4 study.

Dr. Wilkin stated that before the Division could agree that the study could be conducted as a Phase 4 study, that the sponsor needed to supply the Division with compelling data about the systemic absorption that would give us a level of comfort in allowing a Phase 4 study. The Sponsor was informed that due to the approaching PDUFA date, this information needed to be submitted to the Division by close of business, May 20, 2005.

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Signature, minutes preparer

Chair concurrence (or designated signatory)

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/s/

Melinda Harris-Bauerlien
5/24/05 09:33:34 AM
CSO

Jonathan Wilkin
5/24/05 10:36:03 AM
MEDICAL OFFICER

FDA Fax Memorandum

Date: May 19, 2005

Subject: NDA 21-026/miconazole nitrate/amendment
CMC information request

Hi Stefan,

The chemistry reviewer has the following additional information requests:

1. You state the differences in the *in vitro* release rates between the drug product manufactured by Janssen and the drug product manufactured by DSM may be due to the particle size distribution of the zinc oxide. You also state that the data on the particle size distribution of zinc oxide are currently not available to you, and that you commit to gathering data on the batch-to-batch zinc oxide particle size reproducibility (3.2.P.2.3.5 "In-Vitro Studies", Vol. 2.1A, page 0000002). However, you did not include a particle size acceptance criterion in the specification of zinc oxide. The information provided in your Amendment dated April 22, 2005 contained particle size distribution of the zinc oxide drug substance (provided by the zinc oxide drug substance manufacturer). Please include a tentative particle size acceptance criterion (with the appropriate method) in the specification of zinc oxide. The acceptance criterion can be modified after the sufficient data has been accumulated. The analytical method should be validated.
2. You were informed that visual examination of the ointment for agglomerates is inadequate, and were requested to include a microscopic test to assure that no agglomerates are present, or alternately, to propose another test for homogeneity. Your response in the Amendment dated May 5, 2005, that the agglomerates are easily visible on a glass plate, is not acceptable. Please include a microscopic test to assure that no agglomerates are present, or alternately, propose another test for homogeneity.
3. You describe the appearance of the drug product as "White, homogeneous ointment". You were requested to describe in more detail what is meant by "homogeneous", and what causes the "white" appearance. Your explanation, that a "white" appearance was only occasionally observed on the surface of a few tubes during stability studies, and that it is due to the trihydroxystearin being thixotropic and that it is unrelated to temperature, because it was not more prevalent at the higher temp (40 C), is inadequate. You also state that the "white" appearance has not been observed in clinical batches. Please remove "white" from the Appearance of the drug product in the drug product specification.

b(4)

4. You stated that you do not intend to market the . The post marketing stability commitment should be revised accordingly so that the first three commercial and, thereafter, annual stability batches include the approved marketed sizes.

b(4)

In order to facilitate an action on this application, we will need your responses to the above information requests by close of business, Friday, May 20, 2005.

If you have questions, please call.

Respectfully,
Millie

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/s/

Mildred Wright
5/19/05 09:33:05 AM
CSO

Barrier Therapeutics, Inc.*A Vision for Innovative Medicine*

May 17, 2005

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MAY 20 2005

MEGA / CDER

Jonathan Wilkin, MD, Director
 Division of Dermatologic and Dental Drug Products
 Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation V, HFD-540
 9201 Corporate Boulevard
 Rockville, MD 20850

N-000(2)
 ORIG AMENDMENT

NDA 21-026

Miconazole Nitrate 0.25% Ointment

Indication: Diaper Dermatitis
 complicated by Candidiasis

Response to Draft Labeling Proposal

Dear Dr. Wilkin,

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to our amendment to this NDA of November 24, 2004, in which we provided a complete response to the non-approvable letter of July 24, 2000. We also refer to an email transmission of May 13, 2005 from Ms. Millie Wright of your Division where the Division's draft labeling was provided.

At this time, we submit herewith our responses to the May 13, 2005 email. In general, we agree with the Division's proposal, except in areas as indicated below. Enclosed with this submission is a strikethrough and clean versions of our response and proposed labeling. In the strikethrough version, deleted text has a double strikethrough through it and new text is highlighted. Specific comments are delineated below:

- Line 2: Added Ointment after TRADENAME for consistency and clarity.
- Line 3: Corrected concentration amount of petrolatum.
- Line 57: Added Ointment after TRADENAME for consistency and clarity.
- Line 59: Changed “,” to a “.” after dermatitis. Changed “...236 of whom were included...” to “...236 of 330 infants were included...” for clarity.
- Line 64: Capitalized Ointment after TRADENAME for consistency and clarity.
- Line 66: Removed “,” after Study 1.
- Line 71: Capitalized Ointment after TRADENAME for consistency and clarity.
- Line 72: Deleted a period after Table 1.

Line 75: In table, added Ointment after TRADENAME for consistency and clarity.

Line 85-86: Deleted proposed text. Barrier Therapeutics had submitted to the Division the requested microbiology data on April 29, 2005. These data show that development of resistance is not a factor with the use of TRADENAME Ointment.

Line 88: Replaced text in Line 85-86,

b(4)

Line 90: Deleted the formerly proposed tradename, ZYMICAN.

Line 91: Added the tradename placeholder TRADENAME and capitalized ointment.

Line 92: Changed Candida to *C. albicans*.

b(4)

Line 101: Deleted

Line 102-105: As per the Division's recommendation, Barrier Therapeutics has amended former

Line 109-116: Reformatted for clarity.

Line 118-121: Deleted text. Barrier Therapeutics believes that the proposed text, although appropriate, does not belong in the Indication and Usage section. The proposed text is of the cautionary tone and we believe it is best suited to be in the Precautions section.

Line 126: Deleted,

b(4)

Line 128: Deleted,

Line 130-132: Deleted text. This text is already repeated in the FDA proposed Precautions section, where it is most appropriate.

Line 141: Deleted “,” after irritation.

Line 145: Deleted from the body of the labeling.

Line 147: Added Ointment after TRADENAME for consistency and clarity.

Line 148: Changed ‘ to 4 weeks. This is for clarity and consistency with FDA proposed verbiage in Line 112.

b(4)

Line 151: Added Ointment after TRADENAME for consistency and clarity.

Line 152: Added Ointment after TRADENAME for consistency and clarity.

Line 153: Added "adult" to clarify that the proposed statement is related to adult patients.

b(4)

Line 154-155: Deleted

This statement is repeated in Line 157-160.

Line 157-160: This section was moved from Line 118-121. Barrier Therapeutics believes that the proposed text is best suited to be in the Precautions section.

Line 159-160: Added for clarification.

Line 169: Deleted This precaution is repeated in
Line 171.

Line 193-194: Rephrased for clarity.

Line 197-198: Added Barrier Therapeutics believes that the proposed text better conveys to the prescribing physician the stated of drug-drug interaction studies conducted in the pediatric population.

b(4)

Line 201: Added Ointment after TRADENAME for consistency and clarity.

Line 204: Added Ointment after TRADENAME for consistency and clarity.

Line 206: Added nitrate after Miconazole for consistency and clarity.

Line 209: Added nitrate after Miconazole for consistency and clarity.

Line 214-221: Rephrased section for clarity.

Line 223-224: Added cautionary statement for use of product by pregnant women. This is for consistency with language used in Line 229-230 for nursing mothers.

Line 228: Added Ointment after TRADENAME for consistency and clarity.

Line 233: Changed to 4 weeks. This is for clarity and consistency with FDA proposed verbiage in Line 112.

b(4)

Line 234: Changed to 4 weeks. This is for clarity and consistency with FDA proposed verbiage in Line 112.

Line 238: Added Ointment after TRADENAME for consistency and clarity.

Line 258: Changed

Line: 284-288: Deleted proposed text. Barrier Therapeutics believes that this text has effectively been stated in the Precautions section, where it is best appropriate. The proposed text does not effectively convey appropriate information related to the Dosage and Administration of the product.

Line 307-311: Added a description of the product and appropriate NDC Numbers.

Line 311: Deleted the configuration.

b(4)

Line 328: Added phone number.

Line 332: Added Ointment after TRADENAME for consistency and clarity.

Line 334: Corrected concentration amount of petrolatum.

Line 363: Added "...on..." after Ointment.

Line 407: Clarified statement by adding "...child's..." after your.

Line 413: Deleted Barrier Therapeutics believes that the storage instructions to the patient should be relevant to TRADENAME Ointment only.

b(4)

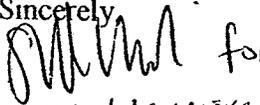
Line 443: Deleted This is the first printing of this labeling.

Line 444: Deleted

We look forward to working with the Division on finalizing this labeling. We would also be very appreciative if we could reach a resolution on the product trade name prior to the Action Date.

This submission consists of 1 volume and is being submitted in duplicate with a signed FDA form 356h. We understand that this submission and all information contained herein unless otherwise made public by Barrier Therapeutics Inc. is CONFIDENTIAL. If you should have any questions, please do not hesitate to contact me directly at (609) 945-1208 or Isabel Drzewiecki, Global Head-Regulatory Operations at (609) 945-1247.

Sincerely,

 for
STEFAN OCHALSKI

Isabel B. Drzewiecki
Global Head, Regulatory Operations



Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

May 6, 2005

u9

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MAY 09 2005

MEGA / CDER

N-000000
NEW CORRESP

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug
Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

NDA 21-026
Miconazole Nitrate 0.25% Ointment
Indication: Diaper Dermatitis
complicated by candidiasis
Request for New Trade Name

Dear Dr. Wilkin,

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to our amendment to this NDA of November 24, 2004, in which we provided a complete response to the non-approvable letter of July 24, 2000. We also refer to a facsimile transmission of May 5, 2005 from Ms. Millie Wright of your Division advising us that The Division of Medication Errors and Technical Support (DMETS) does not recommend our use of the trade name ZIMYCAN™ which had been chosen for this product.

Based on this recommendation, Barrier Therapeutics, Inc. has selected the following two proposed trademark names for the nonproprietary name miconazole nitrate. The preferred trade name _____ and the alternate name is VUSION. We have attached draft package inserts (Attachments 1 and 2) containing the new proposed Trade Names. b(4)

Since the PDUFA date for this application is May 24, 2005, we would greatly appreciate anything that can be done to expedite the review of these names. Thank you for your consideration of this matter.

We trust that we have satisfactorily responded to your May 5, 2005 fax. This product is very important to Barrier and we are available to work with you should you have any questions and/or comments regarding this submission. Please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,

Isabel Drzewiecki
Isabel B. Drzewiecki

Global Head, Regulatory Operations

Enclosure: Form FDA 356h

u5



Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

May 5, 2005

N-000(BC)

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MAY 06 2005 ORIG AMENDME

MEGA / CDER

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

NDA 21-026
Miconazole Nitrate 0.25% Ointment

Indication: Diaper Dermatitis complicated by candidiasis

Response to Request for Chemistry, Manufacturing and Control Information

Dear Dr. Wilkin,

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to our amendment to this NDA of November 24, 2004, in which we provided a complete response to the non-approvable letter of July 24, 2000. We also refer to facsimile transmission of April 25, 2005 from Ms. Millie Wright of your Division requesting additional Chemistry, Manufacturing, and Control Information.

At this time, we submit herewith our responses to the fax of April 25. We have included your questions in bold face type followed by our responses.

- 1. Please submit a certificate of analysis of miconazole nitrate manufactured at the Noramco site in the U.S.A. Please also provide a chromatographic comparison (impurity profile) for miconazole nitrate from each site (to ascertain that there are no differences in the drug substance quality from the two sites).**

We have attached a certificate of analysis for miconazole nitrate manufactured at the Noramco site in the U.S.A. (Attachment 1). We have also provided an impurity profile comparison for miconazole nitrate from each site. (Attachment 2).

- 2. The visual examination of the ointment for agglomerates is inadequate. Please include a microscopic test to assure that no agglomerates are present. Alternately, another test for homogeneity may be proposed.**

This is an in-process test that is used to insure the adequacy of homogenization during the manufacturing process. During early work at J&J a Gage was used for this assessment and it was found that any agglomerates that were found were also easily seen by the current method of spreading the product on a glass plate. We submit that the current method has been found to meet the objective of insuring adequate dispersion.

b(4)

ORIGINAL

3. All applications (e.g. NDAs, INDs) requesting Agency action require the submission of an environmental assessment or a claim of categorical exclusion [21 CFR 25.15(a) and 21 CFR 314.101(d)(4)]. Please submit an environmental assessment or a claim of categorical exclusion.

An environmental assessment report is included in Attachment 3 to this letter.

4. Please provide a UV/VIS spectrum of the drug product.

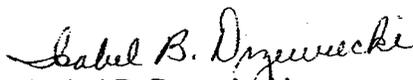
A report containing a UV/VIS spectrum of the Miconazole Nitrate, USP 0.25% Ointment is included in Attachment 4.

5. The acceptance criterion for the appearance in the Specification of the drug product is described as follows: **White, homogeneous ointment**. Please describe in more detail what is meant by **White, homogeneous ointment** and what causes the **White, homogeneous ointment** Was the **White, homogeneous ointment** observed in the clinical batches? b(4)

A **White, homogeneous ointment** has only been occasionally observed on the surface of a few tubes observed during stability studies. It is believed to be due to a small amount of syneresis that is related to the presence of the thixotropic agent trihydroxystearin. Since it has not been found to be more prevalent in the 40°C/75% RH samples, it is not believed to be a temperature related phenomenon. It has not been observed in the clinical batches.

We trust that we have satisfactorily responded to the requests made in the April 25, 2005 fax. This product is very important to Barrier and we are available to work with you should you have any questions and/or comments regarding this submission. Please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,


Isabel B. Drzewiecki
Global Head, Regulatory Operations

Enclosure: Form FDA 356h

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Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

May 3, 2005

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MAY 04 2005

N-000(BC)

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ORIG AMENDMENT

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

NDA 21-026
Miconazole Nitrate 0.25% Ointment
Indication: Diaper Dermatitis complicated by candidiasis
Response to Request for Chemistry, Manufacturing and Control Information

Dear Dr. Wilkin,

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to our amendment to this NDA of November 24, 2004, in which we provided a complete response to the non-approvable letter of July 24, 2000. We also refer to facsimile transmission of April 12, 2005 from Ms. Millie Wright of your Division requesting additional Chemistry, Manufacturing, and Control Information and our response to that request of April 22, 2005. In our April 22, 2005 response, we advised you that the information requested in Item 2 of that fax on the test for extractables from the tube's lining was in the process of being conducted by applying the "PHYSIOCHEMICAL TESTS—PLASTICS" portion of USP <661> to the tube lining. We also advised you that we expected the results shortly and would submit them for your review.

We have now received the results of the extractables test and they are appended to this letter. In one study _____ was used as the extracting solvent using a modification (only interior used to calculate surface area) to the "PHYSIOCHEMICAL TESTS - PLASTICS" portion of USP <661>. Since the drug product formulation is non-aqueous, a second study was conducted using _____ as the extracting solvent. Again, only the inner surface area was used and because of the non-aqueous nature of the extracting solvent, the Heavy Metals and the Buffering Capacity tests of USP <661> were not possible. Detailed reports of both studies are contained in Attachment 1 and Attachment 2 to this letter.

We trust that we have now satisfactorily responded to all of the requests made in the April 12, 2005 fax. This product is very important to Barrier and we are available to work with you should you have any questions and/or comments regarding this submission. Please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,

Isabel B. Drzewiecki
Isabel B. Drzewiecki
Global Head, Regulatory Operations

ORIGINAL

ORIGINAL

REGULATORY AFFAIRS DEPARTMENT

56

Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

April 29, 2005

N-090(B1)

ORIG AMENDMENT

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MAY 02 2005

MEGA / CDER

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

NDA 21-026
Miconazole Nitrate 0.25% Ointment

Indication: Diaper Dermatitis
complicated by candidiasis

Response to Request for Microbiology
Information

Dear Dr. Wilkin,

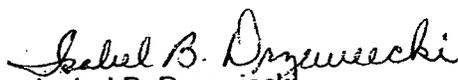
Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to our amendment to this NDA of November 24, 2004, in which we provided a complete response to the non-approvable letter of July 24, 2000. We also refer to a facsimile transmission of April 12, 2005 from Ms. Millie Wright of your Division requesting additional Microbiology Information.

At this time, we submit herewith our responses to the fax of April 12, 2005. In that transmission you requested that we provide miconazole nitrate MIC data for isolates of *C.albicans* or other *Candida* species obtained from clinical and therapeutic failures at test of cure (day 14) for both the miconazole nitrate and vehicle treatment groups. You also requested that we provide the MIC results after 24 hours and 48 hours of incubation.

Attached hereto you will find the requested information. The MIC values in the attached document were run on frozen samples of parallel isolates taken from subjects who were therapeutic failures which provided n=37 subjects on 0.25% miconazole nitrate and n=24 vehicle control subjects. The only species found in the isolates were *Candida albicans* or *Candida tropicalis*.

We trust that we have satisfactorily responded to this request made in your April 12, 2005 fax. This product is very important to Barrier and we are available to work with you should you have any questions and/or comments regarding this submission. Please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,


Isabel B. Drzewiecki
Global Head, Regulatory Operations

Enclosure: Form FDA 356h

IBD/ma

Trihydroxystearin meets the test requirements of the National Formulary monograph for Hydrogenated Castor Oil; however, it is not _____ during the manufacturing process as indicated in the Description of NF 23.

b(4)

Information Request #5

Is formula F100 identical to formula F114? If formula NP0426 is the same as formula NP0425, why do they have different formula numbers? How do these two formulas, NP0426 and NP0425, relate to formulas F100 and F114?

During development of Miconazole Nitrate Ointment 0.25% w/w, the product was manufactured at several different facilities as discussed in 3.2.P.2.3 **Manufacturing Process Development**. The formulations contained within this Application are summarized in 3.2.P.2 **Table 3 Compositions of Miconazole Nitrate Ointment Formulations**. Formula F100 differs from F114 only in the grade of White Petrolatum USP that is used. F100 uses _____ Petrolatum while F114 uses _____ Petrolatum. Both are sourced from _____ and both meet the requirements of the USP monograph for White Petrolatum. The specific consistency (180-210) of _____ Petrolatum that is used in F114 has been chosen for this NDA. All clinical studies were conducted using F114.

b(4)

Formulas NP0425 and NP0426 are the DSM designations for the formula identified at Janssen Pharmaceutica as F114. NP0425 is the designation for a _____ batch size and NP0426 designates a batch size of _____

b(4)

Information Request #6

Please note that the primary stability data on the _____ tube are not directly applicable to the _____ tube, and could not be used in lieu of a primary stability study on the _____ tubes. Contrary to your assertion in 3.2.P.8.1.2.1 "Stability Batches", the difference of size between two tubes is not considered insignificant by the Agency. You have provided no stability data on the _____ tube.

We will continue and complete our primary stability studies in 5 gram and _____ tubes.

b(4)

Information Request #7

Your proposal to use the results of a study of the 3 production batches manufactured at Janssen as supportive stability data is acceptable, but it cannot be used instead of primary stability data to determine the expiration date. Only primary stability data (and appropriate statistical analysis, if provided) may be used to determine shelf life.

We agree that only the primary stability data from batches manufactured at DSM will be used to determine the expiration date of Miconazole Nitrate 0.25% Ointment. These are identified in 3.2.P.8.1 Table 1 Batch Information for Primary Stability Batches Manufactured at DSM. The available results for these batches are presented in 3.2.P.8.3 Tables 5 – 15.

Information Request #8

Are there any CMC changes in the current NDA submission from those provided in the original submission by Johnson and Johnson? Please provide a tabulated list and details of such changes, if any.

Please be advised that at the Agency's request on March 3, 2004 we submitted an amendment (Serial No. 046) to our IND 21,542 for this product. It was a completely revised and updated Chemistry, Manufacturing and Controls section in the current CTD format. This was done at the request of the Supervisory Chemist at that time so that the reviewing chemists would have a completely updated document and not have to refer back to the original submission made by Johnson and Johnson. See the minutes of a Telecon that was held on August 28, 2003 regarding this and other CM&C issues. These minutes can be found in Attachment 1 to this letter. We have also attached a tabulated list and summary of changes that were made between our IND Amendment of March 3, 2004 and our NDA Amendment of November 24, 2004 (Attachment 2).

Information Request #9

Please state which batches/formulas were used in the pre-clinical trials and which batches/formulas were used in the clinical trials. Please specify if there are any differences between batches/formulas.

There are two pre-clinical studies in this Application that use Miconazole Nitrate 0.25% w/w Ointment.

Study No.	Formula	Batch	Study Type
7336/10841.57	610-58	279-883	Primary Dermal Irritation in albino rabbit
7336/10841.56B	610-58	279-883	Ocular Irritation in the albino rabbit

The batches, with formula numbers, that were used in the clinical studies are presented in 3.2.P.2 Table 4 Batches of Miconazole Nitrate Ointment used in Clinical Studies.

Formula No.:		610-58	610-73	F114	F100
Study No.	Study Type	Batch Number			
10833/10842.33	Phase 3	279-883			
12966.37A	Phase 3		899-760		
12966.37B	Phase 3		899-760		
12966.37C	Pharmaco-kinetic				88B19/957
BT100 USA/001	Phase 3			02K13/172	

The composition of each formulation is presented in 3.2.P.2 Table 3 Compositions of Miconazole Nitrate Ointment Formulations. The only difference in the formulations is that for Formula 610-58, one of the components of **b(4)** was removed. Otherwise, all of these formulations are identical in composition.

Should you have any questions and/or comments regarding this submission, please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,


Isabel B. Drzewiecki
Global Head, Regulatory Operations

Enclosure: Form FDA 356h

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