

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-946

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

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

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

NDA NUMBER

NDA 021-946

NAME OF APPLICANT / NDA HOLDER

Barrier Therapeutics, Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)

Ketoconazole USP 2% Topical Gel

ACTIVE INGREDIENT(S)

Ketoconazole USP

STRENGTH(S)

20 mg/g

DOSAGE FORM

Topical

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

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

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

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

1. GENERAL

a. United States Patent Number

b. Issue Date of Patent

c. Expiration Date of Patent

d. Name of Patent Owner

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

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

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

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration

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

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

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

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

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

6. Declaration Certification

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

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

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



9/16/05

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

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Barrier Therapeutics

Address
600 College Road East
Suite 3200

City/State
Princeton, NJ

ZIP Code
08540

Telephone Number
609-945-1247

FAX Number (if available)
609-945-1216

E-Mail Address (if available)
idrzewiecki@barriertherapeutics.com

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

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

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

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EXCLUSIVITY SUMMARY

NDA # 21-946

SUPPL # n/a

HFD # 540

Trade Name XOLEGEL Gel, 2%

Generic Name ketoconazole, USP

Applicant Name Barrier Therapeutics

Approval Date, If Known 7/28/06

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

Clinical data submitted to show safety and effectiveness of ketoconazole USP 2% Topical Gel alone versus vehicle. In addition, a pharmacokinetic study was submitted on the percutaneous absorption of ketoconazole USP 2% Topical Gel which monitored the exposure of active ingredient under maximal use conditions in subjects.

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:

N/A

d) Did the applicant request exclusivity?

YES NO

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

3 years

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

#(s).

NDA#	18-533	Nizoral (ketoconazole)
NDA#	19-084	Nizoral (keotconazole) Cream
NDA#	19-576	Nizoral (keotconazole) Shampoo
	19-648	Nizoral (ketoconazole) Cream
	19-927	Nizoral (ketoconazole) Shampoo
	20-310	Nizoral A-D (ketoconazole) Shampoo

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# N/A

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

Study # BT1400N01-300-USA

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1

YES

NO

Investigation #2

YES

NO

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

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

Study # BT1400N01-300-USA

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 67,820

YES

!

!

! NO

! Explain:

Investigation #2

IND #

YES

!

!

! NO

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not

identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ! NO
Explain: ! Explain:

Investigation #2 !
!
YES ! NO
Explain: ! 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: Margo Owens
Title: Regulatory Project Manager
Date: 8/30/06

Name of Office/Division Director signing form: Stanka Kukich, M.D.
Office of Drug Evaluation III
Division of Dermatology and Dental Products

Title: Deputy Division Director

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

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/s/

Stanka Kukich

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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-946 Supplement Type (e.g. SE5): n/s Supplement Number:

Stamp Date: September 28, 2005 Action Date: July 28, 2006

HFD 540 Trade and generic names/dosage form: TRADENAME (ketoconazole, USP) Gel, 2%

Applicant: Barrier Therapeutics Therapeutic Class: 3

Indication(s) previously approved:

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

Number of indications for this application(s): 1

Indication #1: Treatment of seborrheic dermatitis

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

Yes: Please proceed to Section A.

XNo: 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. <u>0</u>	yr. <u>0</u>	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. <u><12</u>	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. 0 yr. 12 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. <18 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}

Margo Owens
Regulatory Project Manager

cc: NDA 21-946
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)

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/s/

Jill Lindstrom
7/28/2006 01:02:10 PM

Stanka Kukich
7/28/2006 01:32:05 PM

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: August 3, 2005

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FDA Facsimile Memorandum

Date: June 13, 2006
To: Isabel Drzewiecki
Global Head, Regulatory Operations
Barrier Therapeutics
From: Margo Owens, Project Manager
Subject: NDA 21-946 Ketoconazole Gel, 2%

Ms. Drzewiecki,

The Chemistry, Manufacturing and Controls Reviewer has the following informational request for your NDA 21-946 Ketoconazole Gel, 2%.

CMC Reviewer's Request for Information:

The finished product should be revised as follows:

From: "Sebazole (Ketoconazole USP 2%)"

To: Tradename (ketoconazole, USP) Gel, 2 %

Should the applicant agree to the above labeling request, please submit a formal commitment that the following revision is acceptable.

Please call if you have questions.

Margo Owens
Project Manager

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/s/

Margo Owens
6/13/2006 03:18:15 PM
CSO

MEMORANDUM OF TELECON

DATE: Friday, May 5, 2006

APPLICATION NUMBER: NDA 21-946

BETWEEN:

Name: James B. Davis, Isabel Drzewiecki and Mat Nunes
Phone: V: 609-945-1277 F: 609-945-1216
Representing: Barrier Therapeutics

AND

Name: Office of New Drug Quality Assessment:
Ernest G Pappas, Review Chemist,
Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality

SUBJECT: Clarification of CMC Deficiencies

This teleconference occurred on Friday, May 5, 2006, to discuss and clarify the FDA's CMC comments outlined in the facsimile dated April 27, 2006, which pertain to NDA 21-946, Sebazole Topical Gel.

{See appended electronic signature page}

Ernest G. Pappas
Review Chemist
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Scott Goldie
5/10/2006 09:46:59 AM
PROJECT MANAGER FOR QUALITY

Ernest G. Pappas
5/10/2006 10:29:51 AM
CHEMIST

Moo-Jhong Rhee
5/10/2006 03:41:39 PM
CHEMIST
Chief, Branch III

FDA Facsimile Memorandum

Date: May 8, 2006
To: Isabel Drzewiecki
Global Head, Regulatory Operations
Barrier Therapeutics
From: Margo Owens, Project Manager
Subject: NDA 21-946 Ketoconazole Gel, 2%

Ms. Drzewiecki,

The Pharmacology/Toxicology Reviewer has the following comment regarding your NDA 21-946 Ketoconazole Gel, 2%.

Pharmacology/Toxicology Comment:

It is the Division's understanding that Barrier Therapeutics, Inc. will conduct a dermal carcinogenicity study on their ketoconazole (2%) product, if it receives FDA approval. In advance of a decision on this NDA, please send the Division a timeline of the expected dates for your phase 4 commitments. This timeline should include dates for the expected study start as well as an expected date for submission of the final study report.

Please call if you have questions.

Margo Owens
Project Manager

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/s/

Margo Owens
5/8/2006 10:34:58 AM
CSO

FDA Facsimile Memorandum

Date: May 5, 2006
To: Isabel Drzewiecki
Global Head, Regulatory Operations
Barrier Therapeutics
From: Margo Owens, Project Manager
Subject: NDA 21-946 Ketoconazole Gel, 2%

Ms. Drzewiecki,

The Pharmacology/Toxicology Reviewer has the following informational request for your NDA 21-946 Ketoconazole Gel, 2%.

Please call if you have questions.

Margo Owens
Project Manager

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/s/

Margo Owens
5/5/2006 02:10:19 PM
CSO

FDA Facsimile Memorandum

Date: May 19, 2006
To: Isabel Drzewiecki
Global Head, Regulatory Operations
Barrier Therapeutics
From: Margo Owens, Project Manager
Subject: NDA 21-946 Ketoconazole Gel, 2%

Ms. Drzewiecki,

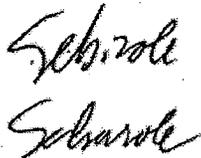
The Division of Medication Error and Technical Support (DMETS) in the Office of Drug Safety has completed review of your two proposed tradenames, Sebazole and _____ for NDA 21-946 ketoconazole Gel, 2% and has asked that the following comments be conveyed to you.

DMETS Comments:

DMETS does not recommend the use of the proprietary names Sebazole and _____. In reviewing the proprietary name Sebazole, the primary concerns related to look-alike and/or sound-alike confusion between Sebazole and Sebizole, Sebazole (veterinary product), Spectazole, or Ketoazole. In reviewing the proprietary name _____ the primary concerns related to sound-alike confusion between _____ and Sebizole or Sebazole.

A. Sebazole Name Confusion

1. Sebizole may sound similar to Sebazole when spoken and look similar when scripted. In fact, one participant of the Rx Studies interpreted a verbal order for Sebazole as "Sebizole". Sebizole is ketoconazole shampoo, formulated to inhibit the yeast that forms dandruff. Sebizole is recommended for twice weekly use. Sebizole and Sebazole owe sound-alike and look-alike similarities to shared letters, differing only in the middle syllable ("i" vs "a"). Not only may the short vowel sounds represented by the "i" and "a" sound similar, but they may also look alike, especially if the dot on the "i" lacks prominence or the "a" is not closed at the top when scripted in cursive handwriting (see writing below).



The image shows two lines of handwritten cursive text. The top line is "Sebizole" and the bottom line is "Sebazole". Both are written in a similar cursive style, with the 'i' in Sebizole and the 'a' in Sebazole being particularly similar in appearance, especially when the dot on the 'i' is not prominent or the 'a' is not fully closed at the top.

In addition to phonetic and orthographic similarities, Sebizole and Sebazole share product similarities including, route of administration (topical), strength (2%), active ingredient (ketoconazole), dosage form (viscous liquid), indications of use (both may be used for skin conditions), and health care provider populations (dermatologists), respectively. Sebizole and Sebazole differ with regard to dosing regimen. However, because of the overall shared product characteristics and strong sound-alike/look-alike properties, DMETS believes that there is potential for confusion with these products.

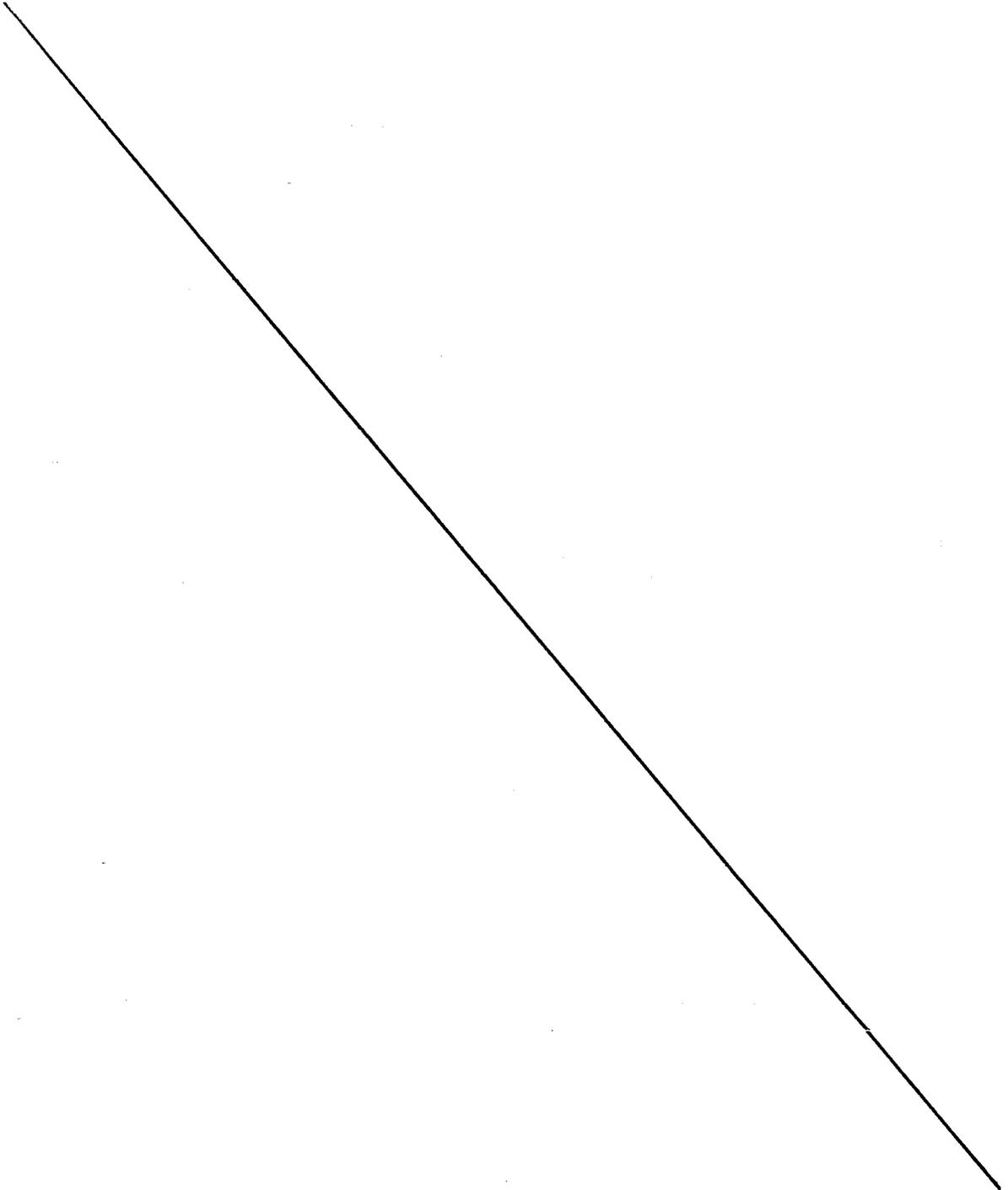
2. DMETS identified the proposed proprietary name Sebazole as the same name used for a veterinary product used as a medicated shampoo, formulated for seborrheic dermatitis use on pets. It contains the active ingredients, econazole nitrate, sulphur, sodium salicylate and chloroxylenol. The salicylic acid in Sebazole causes the tissue cells to swell and soften thereby losing the dry cells and the other active ingredients have fungicidal and antibacterial properties. The shampoo comes in a 250 mL squeeze bottle (see image below).



Along with identical look-alike and sound-alike name properties, Sebazole and Sebazole (veterinary use) have many overlapping product characteristics including, route of administration (topical), dosage form (viscous liquid), dosing regimen (once daily), and indication for use (seborrheic dermatitis). However, the products contain different active ingredients and different strengths. The differences in strength may not be a distinguishing factor since both are available in a single strength. Thus, the product strength does not need to be present in order to process and dispense a prescription. DMETS envisions a scenario where a consumer receives a prescription for Sebazole for their pet and has it filled at the local pharmacy for the proposed product. Also, someone seeking information on Sebazole may inadvertently discover information about the wrong product. Overall, DMETS believes there is potential for these products to be confused.

3. Spectazole may sound similar to Sebazole when spoken and look similar when scripted. Spectazole is econazole nitrate cream indicated for patients with tinea pedis, tinea cruris, tinea corporis, and tinea versicolor, as well as patients

(both may be used once-a-day), indications of use (both may be used for seborrheic dermatitis), and health care provider populations (dermatologists), respectively. Overall, DMETS believes that there is potential for confusion with these products.



suffering from cutaneous candidiasis. Spectazole is recommended for once daily use in the tinea infections and for twice daily use in cutaneous candidiasis. Spectazole and Sebazole names, each having three syllables, owe sound-alike properties to shared letters, "S", "e", and "azole". However, the first syllable of each name should help to differentiate the names "Spec" vs. "Seb." The shared letters "S", "e", and "azole" also contribute to the look-alike properties of the name pair, although the "p" and "t" in Spectazole and "b" in Sebazole may serve to differentiate the names orthographically (see writing sample below).

In addition to phonetic and orthographic similarities, Spectazole and Sebazole share product similarities including, route of administration (topical), dosage form (both are semisolids), dosing regimen (both may be used once-a-day), similar indications (both are used for skin conditions), and health care provider populations (dermatologists), respectively. Spectazole and Sebazole also have differences including strength (1% vs. 2%), however, strength differences may not serve to differentiate the products since each of these single strength products may be ordered without a strength. Overall, DMETS believes that there is potential for confusion with these products.

4. Ketozole may sound similar to Sebazole when spoken and look similar when scripted. Ketozole is a proprietary name for ketoconazole topical cream indicated for cutaneous candidiasis, tinea corporis, tinea cruris, and tinea versicolor, as well as for seborrheic dermatitis. Ketozole is recommended for once daily use in the candidiasis and tinea infections and for twice daily use in seborrheic dermatitis. Ketozole and Sebazole names, each having three syllables, owe sound-alike properties to shared letters, "e", and "azole". The first syllable are phonetically different "Ket" and "Seb." The shared letters "e", and "azole" also contribute to the look-alike properties of the name pair, although the "K" in Ketozole and "S" in Sebazole may serve to differentiate the names orthographically (see writing sample below).

In addition to phonetic and orthographic similarities, Ketozole and Sebazole share product similarities including, route of administration (topical), dosage form (both are semisolids), strength (2%), active ingredient (ketoconazole), dosing regimen

NDA 21-946

Please call if you have questions.

Margo Owens
Project Manager

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/s/

Margo Owens
5/19/2006 03:01:07 PM
CSO

MEMORANDUM

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

DATE: April 27, 2006

TO: Stanka Kukich, M.D., Acting Director
Division of Dermatology and Dental Products

VIA: Maria M. Anderson
Regulatory Health Project Manager
Division of Dermatology and Dental Products

FROM: Catherine Miller, M.T.(ASCP)
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Acting Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCs Review of Patient Labeling for Sebazole Gel
(ketoconazole USP 2% Gel), NDA 21-946

The attached patient labeling (PPI) represents our revisions to the draft PPI submitted with the New Drug Application for Sebazole Gel (ketoconazole USP 2% Gel), NDA 21-946. We have put this PPI in the in the patient-friendly format that we are recommending for all patient information, although this format is not required for voluntary PPIs. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on draft labeling submitted on September 28, 2005. Patient information should always be consistent with the prescribing information. All future relevant changes to the product labeling (PI) should also be reflected in the PPI.

Comments and Recommendations:

2 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-

1/1

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/s/

Toni Piazza Hepp
4/27/2006 10:59:55 AM
DRUG SAFETY OFFICE REVIEWER
Authored by: Catherine Miller

FDA Facsimile Memorandum

Date: February 28, 2006
To: Isabel Drzewiecki
Global Head, Regulatory Operations
Barrier Therapeutics
From: Margo Owens, Project Manager
Subject: NDA 21-946 Ketoconazole Gel, 2%

Ms. Drzewiecki,

The Pharmacology/Toxicology Reviewer has the following response to your December 21, 2005 Information Update for NDA 21-946 Ketoconazole Gel, 2%.

Pharmacology/Toxicology Response to Information Update (12-21-05)

The Division has received your Information Update and finds the decision to delay initiating the dermal carcinogenicity study acceptable. Please submit a timeline indicating the expected dates for the study start and final report submission, as soon as this information becomes available.

Respectfully,

Margo Owens
Project Manager

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/s/

Margo Owens
2/28/2006 11:19:40 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE
COVERSHEET

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

1. APPLICANT'S NAME AND ADDRESS

BARRIER THERAPEUTICS INC
Isabel Drzewiecki
600 College Road East
Princeton NJ 08540
US

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

NDA 21-946

2. TELEPHONE NUMBER

609-945-1200 1247

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

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

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME

To Be Determined (Ketoconazole USP 2% Topical Gel)

6. USER FEE I.D. NUMBER

PD3006125

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

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

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

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

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

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

Public reporting burden for this collection of information is estimated to average 30 minutes 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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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

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

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

Isabel B. Drzewiecki

TITLE *Global Head, Regulatory Operations*

DATE

September 9, 2005

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION

\$672,000.00

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-946	Efficacy Supplement Type SE-	Supplement Number n/a
Drug: Xolegel (ketoconazole, USP) Gel, 2%		Applicant: Barrier Therapeutics
RPM: Margo Owens		HFD-540 Phone # 301-796-2110
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority 		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<ul style="list-style-type: none"> • Chem class (NDAs only) 		3
<ul style="list-style-type: none"> • Other (e.g., orphan, OTC) 		
❖ User Fee Goal Dates		July 28, 2006
Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee 		<input checked="" type="checkbox"/> Paid UF ID number PD3006125
<ul style="list-style-type: none"> • User Fee waiver 		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
<ul style="list-style-type: none"> • User Fee exception 		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

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

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? () Yes () No

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

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? () Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

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

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ () No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	RPM - 4/4/06

General Information

Actions	
<ul style="list-style-type: none"> Proposed action 	(X) AP () TA () AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	N/A
<ul style="list-style-type: none"> Status of advertising (approvals only) 	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	(X) Yes () Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	July 18, 2006
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	July 14, 2006
<ul style="list-style-type: none"> Original applicant-proposed labeling 	Sept. 28, 2005
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) 	DDMAC – 5/4/06 DMETS – 5/16/06; 7/21/06 DSRCS – 4/27/06 Labeling faxes – 7/13/06; 7/18/06 Labeling mtg minutes – 7/28/06
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	N/A
Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	7/24/06
<ul style="list-style-type: none"> Applicant proposed 	7/14/06; 7/24/06
<ul style="list-style-type: none"> Reviews 	DDMAC – 5/4/06; DMETS 5/16/06; 7/21/06
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	2/28/06; 5/8/06
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	- Dec. 21, 2005 letter from Applicant requesting Phase 4 - Agency reply – Feb. 28, 2006 - May 8, 2006 fax from Agency requesting timeline of Phase 4 studies - May 12, 2006 letter from applicant providing timeline
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	Feb. 23, 2004
<ul style="list-style-type: none"> Pre-NDA meeting (indicate date) 	Jan. 13, 2005
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date; approvals only) 	
<ul style="list-style-type: none"> Other 	

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Medical Team Leader 7/28/06 Biostatistics Team Leader 7/26/06
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	7/27/2006
❖ Microbiology (efficacy) review(s) (indicate date for each review)	5/22/06
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Clinical Review 7/27/06; pg. 64
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	7/28/06
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	5/22/06
❖ Biopharmaceutical review(s) (indicate date for each review)	5/8/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	N/A
• Clinical studies	
• Bioequivalence studies	
CMC Information	
CMC review(s) (indicate date for each review)	7/14/06
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	7/14/06 – CMC review (pg. 76)
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	7/14/06 – CMC review (pg. 76)
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	7/14/06 – CMC review (pg. 58)
❖ Facilities inspection (provide EER report)	Date completed: 12/14/05 (X) Acceptable () Withhold recommendation
❖ Methods validation	(X) Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	5/26/06 - NDA 12/21/05 (carc SPA) - IND 67,820
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	5/18/04
❖ CAC/ECAC report	12/2/05

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-946

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA:	21-946
Brand Name:	Sebazole
Generic Name:	Ketoconazole
Dosage form and Strength:	2% Gel
Route of administration:	Topical
Indication:	Seborrheic Dermatitis
Sponsor:	Barrier Therapeutics, Inc.
Type of submission:	Original
Clinical Division:	Dermatology and Dental Drug Products
OCPB Division:	DCP III
Priority:	Standard
Submission date:	09/28/05
OCPB Consult date:	10/28/05
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Edward D. Bashaw, Pharm. D.

I. Executive Summary

Ketoconazole is a broad-spectrum antifungal agent and has been approved previously for seborrheic dermatitis. Nizarol® is currently available as a 2% ketoconazole cream for topical use, with BID application to the affected area for 4 weeks or until clinical clearing.

NDA 21-946 submitted on 09/28/05 is for Sebazole (ketoconazole) 2% topical gel contains. It contains no sodium sulfite in order to eliminate the risk associated with the use of sodium sulfite. The proposed dosing regimen is to apply topically to the affected area once daily for 2 weeks.

In addition to a pivotal and two supportive Phase III clinical trials, a Phase II study was conducted to investigate the percutaneous absorption and pharmacokinetics (PK) of Sebazole 2% topical gel in 10 male and 8 female adult patients with severe seborrheic dermatitis. Sebazole 2% gel was applied QD for 2 weeks to the affected area (dosed based on % of body surface area, BSA).

The results of the Phase II study showed that the absorption of ketoconazole from Sebazole 2% topical gel was generally low, however, large intersubject variation was found. The reported means (\pm standard deviation, SD) of 18 peak plasma levels (C_{max}) were 1.35 ± 3.18 ng/mL (Day

7) and 0.80 ± 1.22 ng/mL (Day 14) and that for reported mean AUC_{0-24} were 20.8 ± 44.7 ng-hr/mL (Day 7) and 15.6 ± 26.4 ng-hr/mL (Day 14), respectively.

A. Recommendations:

From the view point of the Office of Clinical Pharmacology (OCP), NDA 21-946 is acceptable provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to the proposed language in the package insert. Please see the labeling comments (page 10) and Appendix 1 for details.

B. Phase IV Commitments:

None

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04/07/06

Tien-Mien Chen, Ph.D.
Division of Clinical Pharmacology III

Team Leader

Edward D. Bashaw, Pharm. D. _____

II. Table of Contents

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IV. QBR	4
V. Detailed Labeling Recommendations	10
VI. Appendices	10

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Sebazole (ketoconazole) 2% topical gel (NDA 21-946) contains no sodium sulfite in order to eliminate the risk associated with the use of sodium sulfite. The proposed dosing regimen is to apply topically to the affected area once daily for 2 weeks.

In this NDA, as part of the standard development program for a topical product, four Phase I studies were conducted to investigate the phototoxicity, photoallergy, skin contact sensitization potential (Repeated Insult Patch Test), and cumulative irritation. No PK data was generated from these Phase I studies. Therefore, they were not reviewed here.

One Phase II study was conducted to investigate the percutaneous absorption of Sebazole 2% topical gel in 18 male and female adult patients with severe seborrheic dermatitis. Sebazole 2% gel was applied QD for 2 weeks to the affected area (dose on % of body surface area, BSA). In addition, a pivotal Phase III clinical trial (BT1400N01-300-USA) plus two supportive Phase III trials were also conducted. The above Phase II and the pivotal Phase III used the to-be-marketed (TBM) formulation.

The results of the Phase II study (BT1400N01-303-USA) showed that the percutaneous absorption of ketoconazole from Sebazole 2% topical gel was low but detectable. The reported means (\pm SD) of 18 peak plasma levels (C_{max}) were 1.35 ± 3.18 ng/mL (Day 7) and 0.80 ± 1.22 ng/mL (Day 14) and that for reported mean AUC_{0-24} were 20.8 ± 44.7 ng-hr/mL (Day 7) and 15.6 ± 26.4 ng-hr/mL (Day 14), respectively. One patient (No. 28) had the highest C_{max} (13.9 ng/mL) and AUC_{0-24} (197 ng-hr/mL) values. This patient also received the highest dose (46.3 gm) and had the largest affected BSA of 14 %. When excluding patient No. 28, the reported means of 17 C_{max} values were 0.609 ng/mL (Day 7) and 0.534 ng/mL (Day 14) and the reported mean AUC_{0-24} values were 10.5 ng-hr/mL (Day 7) and 9.63 ng-hr/mL (Day 14), respectively. A definite dose-response relationship between the systemic exposure of ketoconazole and affected % BSA, however, was not found which could be due to the small number of patients enrolled.

In this Phase II study, after application of Sebazole 2% Gel for 2 weeks, the mean affected area was reported to decrease from $3.8 \pm 3.6\%$ (baseline) to $3.1 \pm 3.9\%$ (Day 7), and then to $2.2 \pm 3.7\%$ (Day 15).

IV. Question Based Review

A. General Attributes

Ketoconazole is a broad-spectrum antifungal agent. *In vitro* studies suggest that ketoconazole impairs the synthesis of ergosterol, which is a vital component of fungal cell membranes. It is postulated that the therapeutic effect of ketoconazole in seborrheic dermatitis is due to the reduction of *Malassezia furfur* (also known as *Pityrosporum ovale*), but this has not been proven. Ketoconazole is currently approved for seborrheic dermatitis as a 2% cream for topical use, e.g., Nizoral, with BID application to the affected area for 4 weeks or until clinical clearing.

Submitted under NDA 21-946 on 09/28/05 was Sebazole (ketoconazole) 2% topical gel. This contains no sodium sulfite in order to eliminate the risk associated with the use of sodium sulfite. The proposed dosing regimen is to apply topically to the affected area once daily for 2 weeks.

B. General Clinical Pharmacology

In this NDA, the percutaneous absorption of Sebazole 2% topical gel was investigated in a Phase II study. It was a multiple-center, open-label, non-controlled study in 18 male and female adult patients with severe seborrheic dermatitis. Sebazole 2% gel was applied QD for 2 weeks to the affected area (dosed based on % of BSA). In addition, a pivotal Phase III clinical trial plus two supportive Phase III trials were also conducted.

Q. Was the absorption of Ketoconazole from Sebazole 2% topical gel significant in patients after 14-day application?

A. The percutaneous absorption of ketoconazole from Sebazole 2% topical gel was low. The results of the Phase II study (BT1400N01-303-USA) showed that mean (\pm SD) values of 18 peak plasma levels (C_{max}) were 1.35 ± 3.18 ng/mL (Day 7) and 0.80 ± 1.22 ng/mL (Day 14) and those for mean AUC_{0-24} were 20.8 ± 44.7 ng-hr/mL (Day 7) and 15.6 ± 26.4 ng-hr/mL (Day 14), respectively.

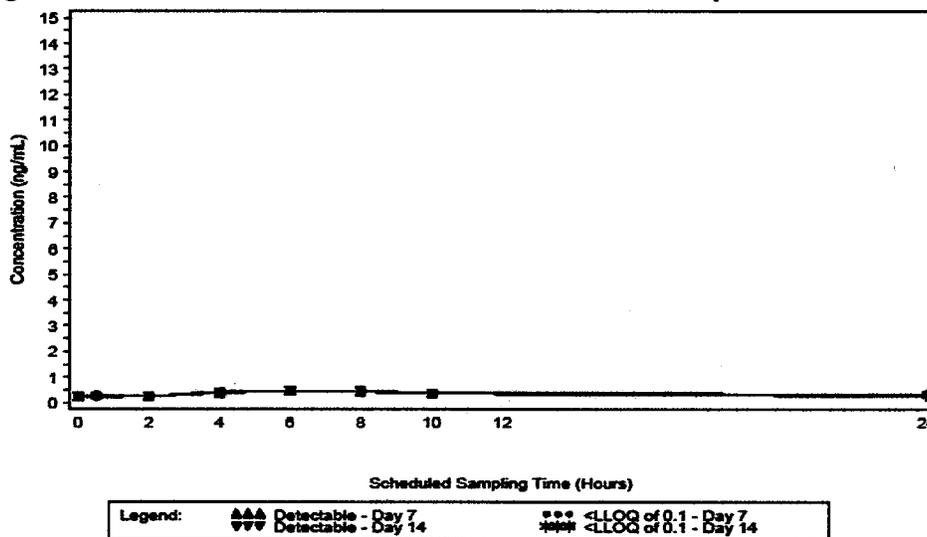
The results obtained from the Phase II absorption study are shown below:

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Table 1. Mean PK Parameters Ketoconazole obtained at Days 7 and 14

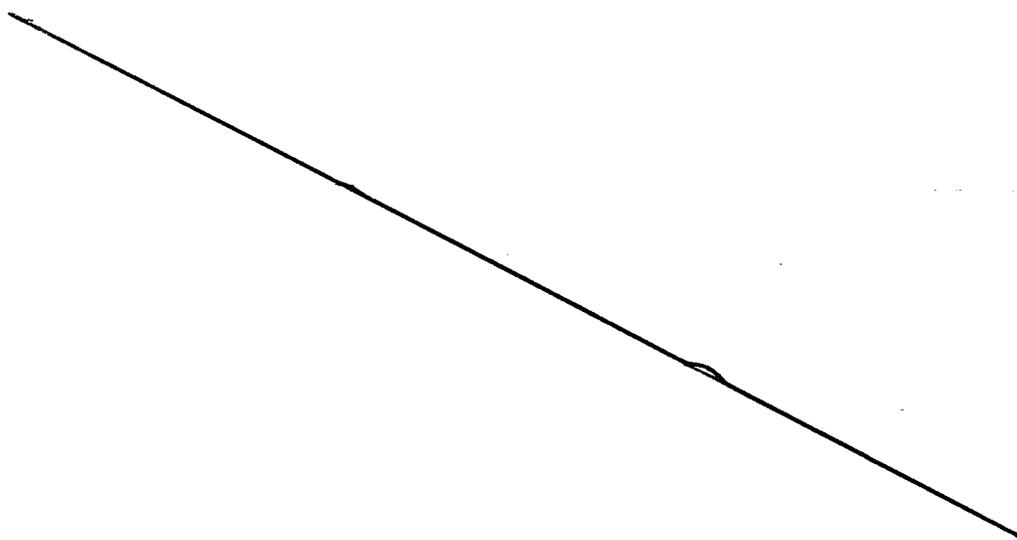
Mean (\pm SD) PK Parameters	Day 7 (range)	Day 14 (range)
C_{max} (ng/mL)	1.35 \pm 3.18 (<0.1 – 13.9)	0.80 \pm 1.22 (<0.1 – 5.36)
T_{max} (hr)	7.88 (2.0 - 24.7)	7.00 (3.8 - 24.0)
AUC (ng-hr/mL)	20.8 \pm 44.7 (<2.4 – 197)	15.6 \pm 26.4 (<2.4 – 117)

Figure 1. PK Profiles of Ketoconazole obtained at Days 7 and 14



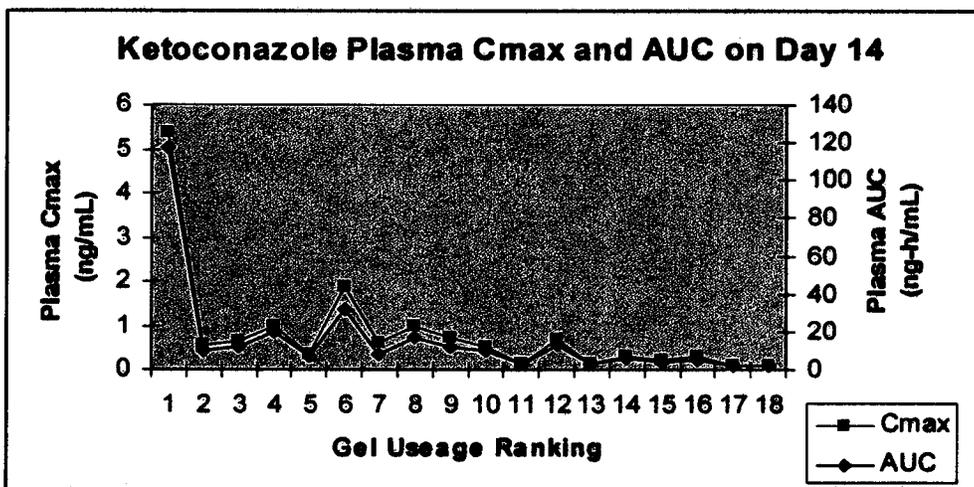
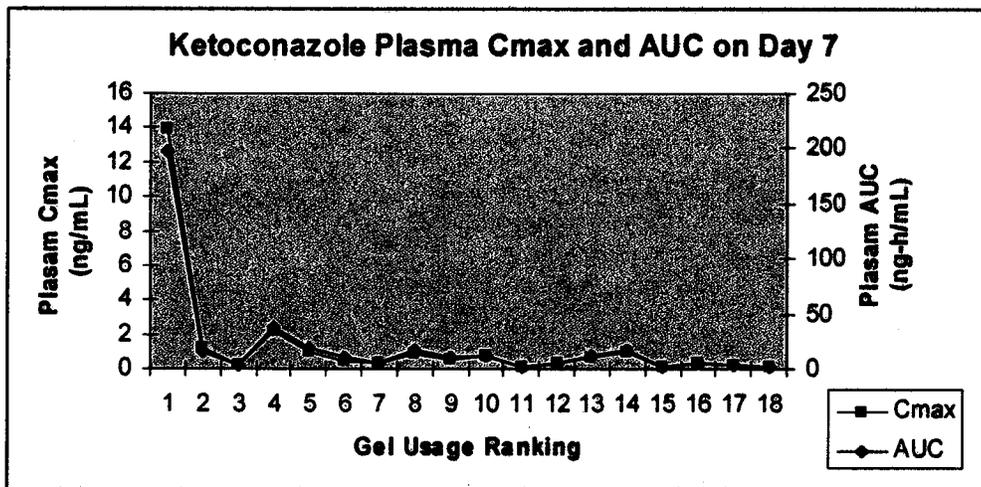
One patient (No. 28) had the highest C_{max} (13.9 ng/mL) and AUC_{0-24} (197 ng-hr/mL) values on Day 7 since this patient received the highest gel dose (46.3 gm) due a largest affected BSA of 14 % (Figure 2 below).

Figure 2. The Plasma PK Data Obtained from Patient # 28



When excluding patient No. 28, the reported mean values of C_{max} (n=17) were 0.609 ng/mL (Day 7) and 0.534 ng/mL (Day 14) and those for means of AUC_{0-24} (n=17) were 10.5 ng-hr/mL (Day 7) and 9.63 ng-hr/mL (Day 14), respectively.

A trend between the systemic exposure (C_{max} and AUC_{0-24}) of ketoconazole and the amount (grams) of gel used on Days 7 and 14 (by the descending ranking of usage from 1 to 17) was analyzed for dose-exposure relationship, however, the above relationship was not found (shown below) which could be partly due to a small number of patients enrolled.



In this Phase II study, after application of Sebazole 2% Gel for 2 weeks, the mean affected area (% BSA) was reported to decrease from $3.8 \pm 3.6\%$ (baseline) to $3.1 \pm 3.9\%$ (Day 7), to $2.2 \pm 3.7\%$ (Day 15) which is consistent with the lower systemic exposure from Day 7 to Day 14.

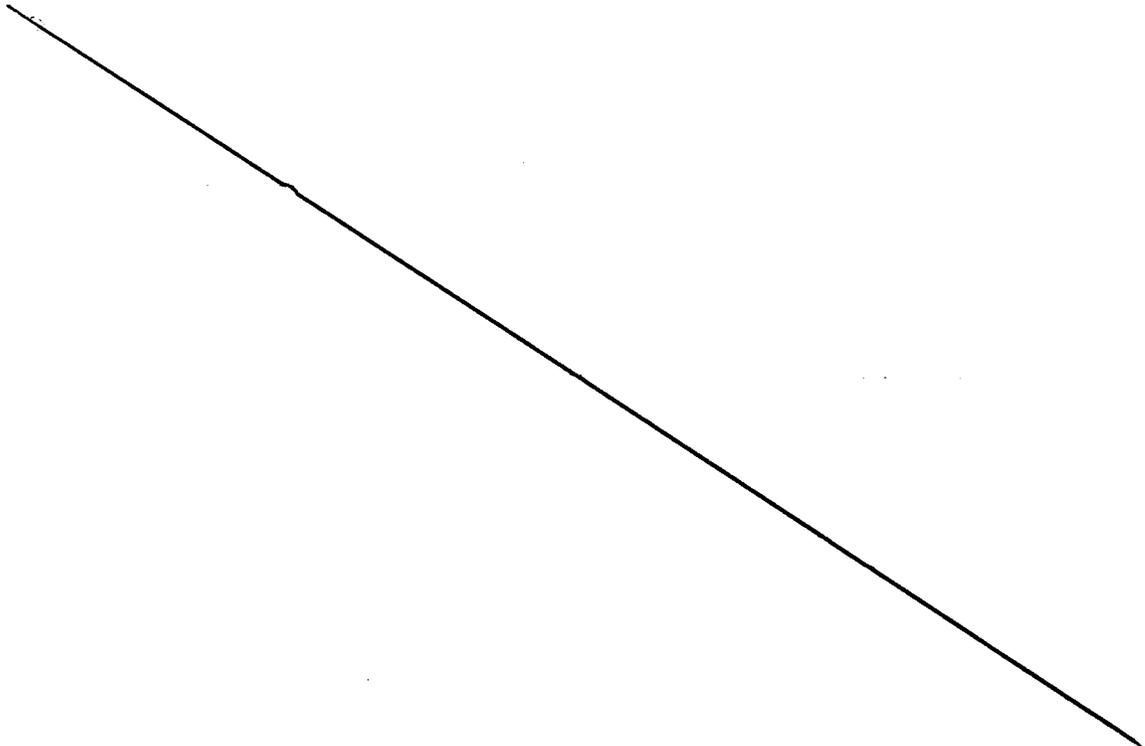
- C. Intrinsic Factors: Not studied
- D. Extrinsic Factors: Not studied
- E. General Biopharmaceutics:

The TBM formulation of Sebazole 2% topical gel has been tested clinically and the composition of Sebazole is shown below:

Drug name:	Ketoconazole USP 2% topical gel (formula BTX-1)
Active ingredient:	Ketoconazole USP 2%
Other ingredients:	Alcohol ——— USP ascorbic acid; butylated hydroxytoluene; citric acid, monohydrate; D&C Yellow No. 10; FD&C Yellow No. 6; glycerin; hydroxypropyl cellulose; polyethylene glycol 400; PPG-15 stearyl ether; propylene glycol.

F. Analytical Section

An LC-MS/MS method was employed which had been used and validated previously. It was reviewed and found acceptable.



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Trade Secret / Confidential

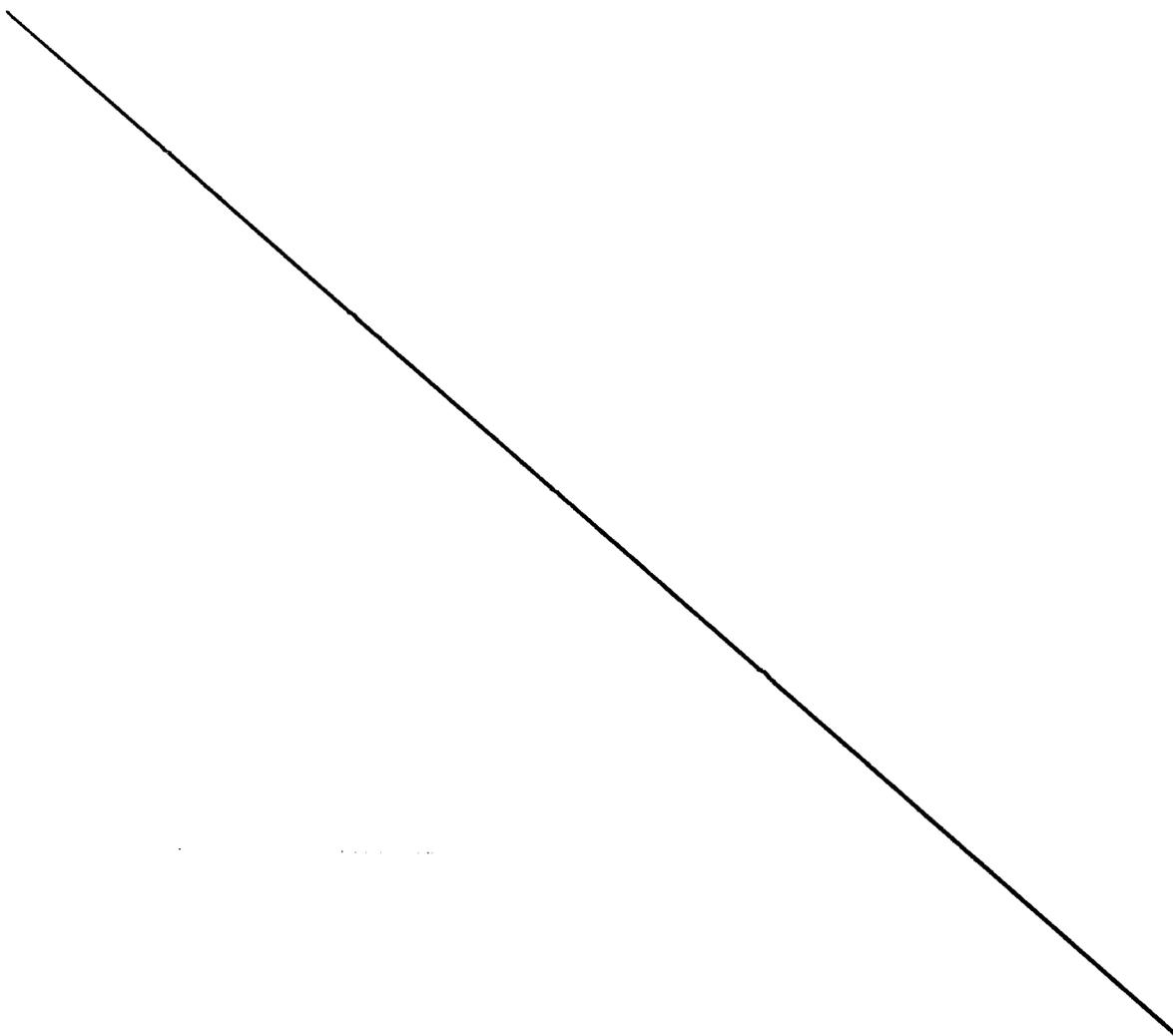
Draft Labeling

Deliberative Process

Withheld Track Number: Clin Pharm/Bio-

1/2

V. Detailed Labeling Recommendations



VI. Appendices

1. Proposed Package Insert (Original and Patient Leaflet)
2. Individual Study Review
3. OCPB Filing/Review Form

**NDA 21-946 for
Sebazole (Ketoconazole) 2% Topical Gel**

Appendix 1

**Sponsor's Proposed Package Insert
(September, 05 Version)**

10 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Clin Pharm/Bio-

2/2

**NDA 21-946 for
Sebazole (Ketoconazole) 2% Topical Gel**

Appendix 2

Synopsis of Phase II Absorption Study

2 SYNOPSIS

Name of Sponsor: Barrier Therapeutics	<i>(For National Authority Use only)</i>
Name of Finished Product: Ketoconazole USP 2% Topical Gel	
Name of Active Ingredient: Ketoconazole USP 2%	
Title of Study: An Open-Label Study to Evaluate the Systemic Absorption of Ketoconazole in Subjects Applying Ketoconazole USP 2% Topical Gel for the Treatment of Seborrheic Dermatitis	
Investigators:	
Study center(s):	
Publication (reference): None	
Study period: March 29, 2005 to June 1, 2005	Phase of development: II
Objectives: The primary objective of this study was to evaluate the systemic absorption of ketoconazole in subjects applying ketoconazole USP 2% topical gel for the treatment of seborrheic dermatitis.	
Methodology: This was a multi-center, open label, non-controlled study of the systemic absorption of ketoconazole in subjects applying ketoconazole USP 2% topical gel for the treatment of seborrheic dermatitis. All subjects were to apply ketoconazole USP 2% topical gel once daily (QD) for 14 days.	
Number of subjects (planned and analyzed): Eighteen subjects were enrolled in and completed this study at four study sites.	
Diagnosis and main criteria for inclusion: Male and female subjects 12 years of age or older with seborrheic dermatitis who had an Investigator's Global Assessment (IGA) score of 4 (severe) and met the inclusion/exclusion criteria were eligible to be enrolled in this study. Male subjects had to have seborrheic dermatitis on the sternum.	

<p>Name of Sponsor: Barrier Therapeutics</p> <p>Name of Finished Product: Ketoconazole USP 2% Topical Gel</p> <p>Name of Active Ingredient: Ketoconazole USP 2%</p>
<p>Test product: Ketoconazole USP 2% Topical Gel, Batch Number UEBM-C of Formula BTX-1</p> <p>Dose and mode of administration: Topically applied gel to affected areas</p>
<p>Duration of treatment: 14 days</p>
<p>Reference therapy, dose and mode of administration, batch number: None</p>
<p>Evaluations:</p> <p>Efficacy: Body surface area (BSA) of seborrheic dermatitis.</p> <p>Safety: Adverse events Clinical laboratory tests Ketoconazole plasma concentrations.</p>
<p>Statistical methods:</p> <p>All statistical processing was performed using SAS® unless otherwise stated. No hypothesis testing was performed.</p> <p>Age, gender, race, body weight and height were summarized with frequency counts and percentages or means, standard deviation, and range, as appropriate. Additionally, individual subject demography was presented.</p> <p>Means, standard deviation, minimum and maximum of the % BSA was presented for each visit.</p> <p>Adverse events (AEs) were classified according to the Medical Dictionary of Regulatory Affairs (MedDRA) dictionary. The same AE recorded by a subject at different visits counted as one event for that subject, and the strongest intensity and relationship to treatment was utilized. All reported AEs were summarized by the number and percentage of subjects reporting AEs, system organ class, preferred term, intensity, and relationship to study medication.</p> <p>For routine clinical laboratory tests, descriptive statistics (mean, standard deviation, median and range for continuous measures and frequency distributions for categorical measures) were presented by visit. Additionally, shift tables that showed the number of subjects with results that were low, normal, or high at Visit 1 versus post-Visit 1 were tabulated.</p> <p>Plasma concentrations of ketoconazole were determined by LC-MS/MS, with a lower limit of quantification of 0.1 ng/mL. The following pharmacokinetic parameters were determined after 7 and 14 days of treatment: concentration minimum (C_{min}); concentration maximum (C_{max}); time to C_{max} (T_{max}); area under the plasma concentration-time curve from 0 – 24 hour after dosing (AUC).</p> <p>Descriptive statistics (median, minimum and maximum) were presented for the ketoconazole plasma concentrations and the pharmacokinetic parameters.</p>

Name of Sponsor: Barrier Therapeutics

Name of Finished Product: Ketoconazole USP 2% Topical Gel

Name of Active Ingredient: Ketoconazole USP 2%

SUMMARY-CONCLUSIONS

Pharmacokinetic Results:

The area under the curve (0-24 hours) (AUC_T), Concentration minimum (C_{min}), Time to concentration maximum (T_{max}), Concentration maximum (C_{max}) were calculated for each subject with quantifiable plasma concentrations for Days 7-8 and Days 14-15. Median, minimum and maximum values were calculated for each of the parameters. The pharmacokinetic parameters are summarized in the following table.

	<u>Days 7-8</u>	<u>Days 14-15</u>
C_{min} (ng/mL)		
N	18	18
Median	0.22	0.21
Range	<LLOQ to 2.97	<LLOQ to 2.06
C_{max} (ng/mL)		
N	18	18
Median	0.52	0.52
Range	<LLOQ to 13.94	<LLOQ to 5.36
T_{max} (h)		
N	16	16
Median	7.88	7.00
Range	2.00 to 24.68	3.78 to 24.00
AUC_T (ng·h/mL)		
N	18	18
Median	10.08	8.88
Range	<2.40 to 196.83	<2.40 to 117.80

Adverse Events:

Only one subject experienced an adverse event, "Facial swelling (both cheeks) Tx area," which was rated as "Mild" in intensity and the relationship to study drug was indicated as "Probable." Treatment was neither discontinued nor interrupted. No serious adverse events were reported.

Laboratory Evaluations:

Of the 109 abnormal laboratory evaluations, two were indicated as "Clinically Relevant" but neither was reported as an adverse event. The Serum Glucose level for subject 03-23 was high (235 mg/dL with reference range of 70-115 mg/dL), however, the subject has diabetes. The Triglycerides level for subject 02-10 was high (809 mg/dL with reference range of 44-249 mg/dL) on Visit 2 and indicated as "Clinically Relevant." However, justified by the normal triglycerides levels at the visits before and after the abnormal value, a comment on the next lab report stated the abnormal value was deemed to have been an error.

CONCLUSION:

In this study in patients with severe seborrheic dermatitis, absorption of ketoconazole was limited. Median trough and peak plasma concentrations fluctuated between 0.22 and 0.52 ng/mL on Day 7 and between 0.21 and 0.52 ng/mL on Day 14. In 17 out of the 18 subjects, the highest observed plasma concentration of ketoconazole was 2.2 ng/mL. In one subject, ketoconazole absorption was somewhat more pronounced, with peak plasma levels of 13.9 ng/mL on Day 7 and 5.36 ng/mL on Day 14. This subject had the highest BSA and the amount of ketoconazole gel used by this subject was much higher than that used by the other subjects.

Date of report: August 9, 2005

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On Original

**NDA 21-946 for
Sebazole (Ketoconazole) 2% Topical Gel**

Appendix 3

OCPB Filing/Review Form

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APPEARS THIS WAY ON ORIGINAL

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

/s/

Tien-Mien Chen
5/3/2006 03:40:59 PM
BIOPHARMACEUTICS

Dennis Bashaw
5/4/2006 09:51:55 AM
BIOPHARMACEUTICS

John P. Hunt
5/8/2006 12:42:57 PM
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-946

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO 22, MAIL STOP 4447)**

DATE RECEIVED: August 8, 2005	DESIRED COMPLETION DATE: July 16, 2006	OSE REVIEW #: 05-0209-2
DATE OF DOCUMENT: April 25, 2005	PDUFA DATE: July 28, 2006	

TO: Susan J. Walker, MD
Director, Division of Dermatology and Dental Products
HFD-540

THROUGH: Alina Mahmud, R.Ph., M.S., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Kimberly Pedersen, R.Ph., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: Xolegel (Ketoconazole USP Topical Gel) 2%	SPONSOR: Barrier Therapeutics, Inc.
NDA#: 21-946	

RECOMMENDATIONS:

- DMETS has no objections to the use of the proprietary name Xolegel provided that only one name _____ or Xolegel is approved. This decision is based on the available product information on _____ is currently under review in the investigational new drug (IND) phase. DMETS will inform the review division responsible for _____ and this decision can be revisited upon submission of the _____
- DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product. Additionally please note the recommendation from CDER Labeling and Nomenclature Committee regarding the proper designation of the established name in Section III.
- DDMAC finds the proprietary names Xolegel acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

*** This review contains proprietary and confidential information that should not be released to the public.***

**Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
WO 22, MAIL STOP 4447
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 21, 2006
NDA #: 21-946
NAME OF DRUG: Xolegel
(Ketoconazole USP Topical Gel) 2%
NDA SPONSOR: Barrier Therapeutics, Inc

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

I. INTRODUCTION

This consult was written in response to a request from the Division of Dermatology and Dental Products (HFD-540) for assessment of the proprietary name "Xolegel", regarding potential name confusion with other proprietary or established drug names. Container label, insert and carton labeling were provided for review and comment. This is the third proprietary name review for this application. DMETS previously reviewed and did not recommend the proposed names of Sebazole and _____ (ODS Consult 05-0209, _____ in August 2005 due to potential confusion with Sebizole, veterinary product Sebazole, Spectazole, and Ketozole.

PRODUCT INFORMATION

Xolegel contains 2% ketoconazole in an anhydrous gel indicated for topical treatment of seborrheic dermatitis. The sponsor make claims that the proposed _____
_____ Xolegel is to be applied once daily to the affected area(s) for two weeks and will be available in 15 gram and 2 gram (sample) tubes.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{i,ii} as well as several FDA databases^{iii,iv} for existing drug names which sound-alike or look-alike to Xolegel to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and

ⁱ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

ⁱⁱ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, Missouri.

ⁱⁱⁱ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

^{iv} Phonetic and Orthographic Computer Analysis (POCA)

Trademark Office's Text and Image Database was also conducted^v. The SAEGIS^{vi} Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Xolegel. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff with representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary names Xolegel acceptable from a promotional perspective.
2. The Expert Panel identified ten names as having the potential for confusion with Xolegel. Independent investigation identified an additional seven names as having the potential for confusion with Xolegel. These products along with the available dosage forms and usual dosage are listed in Table 1 (see below and page 4).

Table 1: Potential Look-Alike Names Identified for Xolegel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Xolegel	Ketaconazole Topical Gel, 2%	Apply once daily to the affected area for 2 weeks	N/A
Xylogel® Foreign products	Xylometazolini Hydrochloridum Nasal Gel, 0.05% and 0.1% (treatment of rhinitis symptoms) (Poland) Natural Teething Oral Gel, 5% Xylitol (Philippines) Lignocaine HCl 2% (Pakistan)		LA/SA
Solugel (4 and 8)	Benzoyl Peroxide Gel 4% and 8% (Argentina, Brazil, Canada, Chile, Dominican Republic, Honduras, Mexico, Nicaragua, Guatemala, Panama, and El Salvador)	Apply once or twice daily to affected areas.	LA/SA
Colazal	Balsalazide Disodium Capsules, 750 mg	3 capsules three times daily for 8 weeks (up to 12 weeks)	LA
Choledyl SA	Oxtriphylline, Extended Release Tablet 400 mg and 600 mg	400 mg to 600 mg every 12 hours	SA

^v www location <http://www.uspto.gov/tmdb/index.html>.

^{vi} Data provided by Thomson & Thomson's SAEGISTM Online service, available at www.thomson-thomson.com

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Xolegel	Ketoconazole Topical Gel, 2%	Apply once daily to the affected area for 2 weeks	N/A
Salagen	Pilocarpine Hydrochloride Tablet 5 mg and 7.5 mg	5 mg two to four times daily	SA
Renagel	Sevelamer Hydrochloride Tablet 400 mg and 800 mg	800 mg to 1600 mg three times daily with each meal	LA
Xolair	Omalizumab Lyophilized Powder for Injection, 75 mg and 150 mg	150 to 375 mg subcutaneous every 2 to 4 weeks	LA/SA
Zoladex	Goserelin Acetate Implant 3.6 mg and 10.8 mg	Subcutaneously every 28 days	SA
Xylitol	Five carbon sugar alcohol as a sweetener	N/A	LA/SA
Solage	Mequinol and Tretinoin, 2%/0.01% Topical Solution	Apply twice daily, at least 8 hours apart.	LA/SA
Ketozole (now marketed as Ketoconazole in US by Taro)	Ketoconazole Topical Cream, 2%	Apply to affected area daily.	LA
Ketazol	Ketoconazole Tablet, 200 mg Foreign, Ketoconazole in multiple countries (Thailand, South Africa, Dubai, Bahrain, Algeria, Mesopotamia, Jordan, Lebanon, Libia, Oman, Qatar, Saudi Arabia, Sudan, Yemen)	200 mg to 400 mg daily	LA
Torisel***	Temsirolimus Intravenous 25 mg vial (protect from light)	25 mg weekly	SA
Zelapar	Selegiline HCl Orally Disintegrating Tablet, 1.25 mg Carton of 6 pouches (60 tablets)	1.25 mg once daily for at least 6 weeks, may be increased to 2.5 mg	LA
Divigel***	Estradiol Gel, 0.1% Single-dose foil packets 0.25 grams, 0.5 grams and 1 grams in boxes of 30		LA/SA
Xilapen	Omeprazole 20 mg (Dominican Republic), 14 capsule package	Unable to locate- US dosing 20 mg daily.	LA

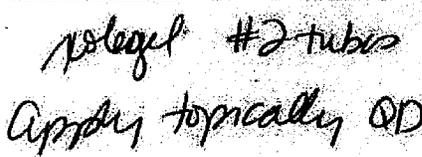
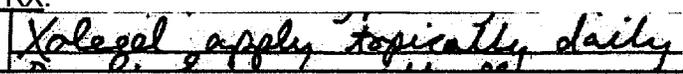
*Frequently used, not all-inclusive.
**LA (look-alike)/SA (sound-alike).
***Name pending approval. Not FOI releasable.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Xolegel with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). The exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and an outpatient prescription were written, each consisting of a combination of marketed and unapproved drug products with a prescription for Xolegel (see page 5). These prescriptions

were optically scanned and one prescription was delivered to a random sample of participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail and sent to a random sample of participating health professionals for their interpretation and review. After receiving either written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> 	<p><u>Xolegel</u> <u>Dispense number two tubes</u> <u>Apply Topically Daily</u></p>
<p><u>Inpatient RX:</u></p> 	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Xolegel, the primary concerns identified relating to confusion with Xolegel are Xylogel, Solugel, Colazol, Choledyl SA, Salagen, Renagel, Xolair, Zoladex, Xylitol, Solage, Ketozone, Torisel***, Zelapar, ——— Divigel***, and Xilapen.

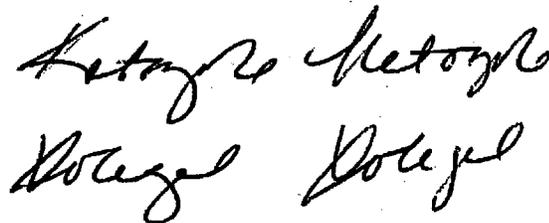
The names Colazol, Choledyl SA, Salagen, Renagel, Xolair, Zoladex, Xylitol, Solage, Torisel***, and Zelapar will not be reviewed further due to a lack of convincing look and sound-alike similarities in addition to numerous differentiating product characteristics such as product strength, indication for use, route of administration, and/or dosage form. Additionally, the proprietary names, Xylogel and Xilapen, are foreign products with limited areas of marketing (Poland, Philippines, Pakistan, and Dominican Republic). They also have differentiating product characteristics and thus, will not be considered further in this review.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predictive as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Xolegel.

*** This review contains proprietary and confidential information that should not be released to the public.

2. Ketozone was identified as a name with similar appearance to Xolegel when scripted. Ketozone is a proprietary name for ketoconazole topical cream indicated for cutaneous candidiasis, tinea corporis, tinea cruris, and tinea versicolor, as well as for seborrheic dermatitis. Ketozone is recommended for once daily use in the candidiasis and tinea infections and for twice daily use in seborrheic dermatitis.

The orthographic similarities stem from the leading letters (K vs. X) that may look similar depending upon how they are scripted. Moreover, the names share a central upstroke (“t” and “l”), subsequent downstroke (“z” and “g”) and concluding upstroke of “L.”



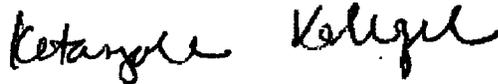
The image shows two lines of handwritten text in cursive. The first line contains the words "Ketozone" and "Ketozone" written side-by-side. The second line contains the words "Xolegel" and "Xolegel" written side-by-side. The handwriting is fluid and cursive, illustrating the orthographic similarities mentioned in the text.

In addition to orthographic similarities, Ketozone and Xolegel share product similarities including, route of administration (topical), dosage form (both are semisolids), strength (2%), active ingredient (ketoconazole), dosing regimen (both may be used daily), indication of use (both may be used for seborrheic dermatitis), and health care provider populations (dermatologists), respectively. However, Taro pharmaceuticals confirmed that this product was never launched with the **branded generic name of “Ketozone.”** Thus, this information appears to be limited to FDA associated websites; and not readily available in standard references or popular webpages such as <http://www.Walgreens.com> and <http://www.Drugstore.com>. Due to **the likely limited familiarity with the name “Ketozone”, the limited possibility for the numerous scripting anomalies to occur, and the lack of access in standard references (i.e. Facts and**

Comparisons and Clinical pharmacology), DMETS believes the potential for confusion between these two names to be minimal. Moreover, the potential for harm is nominal due to the identical active ingredient and route of administration.

3. Ketazole was identified as a name with similar appearance to Xolegel when scripted. Ketazole is a foreign proprietary name for ketoconazole oral tablets indicated for varied fungal infections. Ketazole is recommended at 200 mg to 400 mg once daily for 5 days to one year depending on the diagnosis. This branded product is marketed in Thailand, South Africa, Dubai, Bahrain, Algeria, Mesopotamia, Jordan, Lebanon, Libia, Oman, Qatar, Saudi Arabia, Sudan, and Yemen.

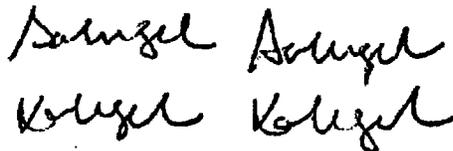
The orthographic similarities stem from the leading letters (K vs. X) that may look similar depending upon they are scripted. The names share a **central upstroke (“t” and “l”)**, **subsequent downstroke (“Z” and “G”)** and **concluding upstroke of “L.”**

Handwritten cursive script of the words 'Ketazole' and 'Xolegel' side-by-side. The letters are fluid and connected, showing the orthographic similarities mentioned in the text.

The drug products share indications (topical fungal infections), active ingredient (ketoconazole), and dosing frequency (daily). Although the names have similar length, upstrokes, and downstrokes (see above), the products differ in route of administration (oral compared to topical), strength (200 mg compared to 2%), and dosage form (tablets compared to gel). Moreover, DMETS can not see the potential for great confusion in light of the limited distribution.

4. Solugel was identified as a name with similar appearance and sound to Xolegel when scripted and spoken. Solugel is a proprietary name for an over-the-counter benzoyl peroxide product marketed in Argentina, Brazil, Canada, Chile, Dominican Republic, Honduras, Mexico, Nicaragua, Guatemala, Panama, and El Salvador. Solugel is indicated for the control of acne vulgaris through desquamation, keratolysis, free fatty acid reduction/drying, and antibacterial action. Solugel is packaged in tubes of 45 grams with a recommended usage of once to twice daily. Due to current United States drug importation issues that directly involve South America, Mexico, and Canada, DMETS will review this drug name due to the potential for actual confusion.

The orthographic similarities stem from the “olugel” and “olegel” that appear identical when scripted. However, the leading “S” and “X” should differentiate the two names, depending on how they are scripted. Phonetically, the names share three syllables and the concluding “gel.” However, the potential pronunciation of “Söl” and “Zöl” and the “y^{oo}” sound in Solugel may differentiate the two names in speech. Moreover, DMETS questions how often prescription orders are called-in to Canada from the United States.

Handwritten cursive script of the words 'Solugel' and 'Xolegel' side-by-side on the first line, and 'Kolegel' and 'Kolegel' side-by-side on the second line. This illustrates the orthographic similarities between the names.

The products share the following product characteristics: route of administration (topical), dosage form (gel), dosing regimen (daily), and health care provider populations (dermatologists). They differ in strength (4 and 8% compared to 2%), prescription status (over-the-counter compared to prescription), and indication of use (acne compared to seborrheic dermatitis). Due to the differing strengths and prescription status, DMETS believes the likelihood of this to occur is limited.

5. Divigel*** was identified as a name with similar appearance and sound to Xolegel when scripted and spoken. Divigel is the proposed proprietary name for the 1% estradiol gel indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause. The recommended dosage _____ to be applied topically on the skin of either the right or left upper thigh on alternate days. The product is packaged in single-dose foil packets of 0.25 grams, 0.5 grams, and 1 gram in boxes of thirty.

Orthographically, the beginning letters (D vs. X) have a limited potential for similarity depending upon how they are scripted. An additional potential similarity is the central "L" of Xolegel that may resemble a "V" if not written with a prominent upstroke. The strongest orthographic overlap is the concluding "gel." Phonetically, the names share a three syllable count and the concluding "gel." In the voice study, one participant interpreted the name as "Dilligel." Despite this finding, DMETS believes the leading "dīv" and "zō" plus the distinct "v" of Divigel will likely differentiate the names.

Handwritten cursive script comparing the words "Divigel" and "Xolegel". The letters are written in a fluid, connected style, with the 'D' in Divigel and 'X' in Xolegel being particularly prominent.

Divigel and Xolegel share product similarities including, route of administration (topical), dosage form (gel), and dosing regimen (once daily). They share single-strength status (1% and 2%) which means the strength does not need to be indicated on the prescription for accurate order completion. However, they differ in indication (symptoms of menopause compared to seborrheic dermatitis), packaging configuration, and likely provider populations (gynecologist compared to dermatologists). Due to the limited likelihood of orthographic and phonetic confusion, DMETS believes the possibility for confusion to be minimal.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

DMETS continues to recommend the changes as requested in the previous consult (consult number 05-0209 and 05-0209-1), which are reprinted for simplicity. Upon further review of the Xolegel container labels, carton and insert labeling, DMETS has the following additional label and labeling comments.

A. GENERAL COMMENT

DMETS consulted the CDER Labeling and Nomenclature Committee (LNC) regarding the proper designation of the established name and requests that the established name of your drug product be revised: _____

The LNC also recommended that the following statement appear on labels and labeling following the established name:

For topical use only.

B. CARTON AND CONTAINER LABELS

*** This review contains proprietary and confidential information that should not be released to the public.

1 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Appendix A: Prescription Study Results for Xolegel

Inpatient	Outpatient	Verbal
Xolegel	Xolegel	Zologel
Xoegel	xolegel	Villagel
Xalegal	XOLEGEL	Dillagel
Xolegel	Xolegel	Vilagel
Xolegel	Xolegel	Vilagel
Xolegel	Xolegel	Zologel
Xolegel	Xolegel	Velagel or Velogel
Xalegel	Xolegel	Velagel
Xolegel	Xolegel	Zologel
Xolegal	Rolegel	
Xolegel	Xolegel	
Xolegel	Xolegel	
Xolegel	Xolegal	
Xolegel	Xologel	
Xalegel	Xolegel	
Xolegel	Xolegel	
	Xologel	
	xolegel	
	Vilagel	

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