CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-385

ADMINISTRATIVE DOCUMENTS

NDA Section 13: Patent Information

The Section 13 Patent Information for Sertaconazole Nitrate Cream, 2% New Drug Application is found on the following page.

Patent Information

Applicant hereby submits the following patent information under 21 CFR §314.53(b) and (c) relevant to patents that claim the drug or a method of using the drug that is the subject of this new drug application 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:

United States Patent No. 5,135,943. This patent expires August 4, 2009 and is assigned to Ferrer International SA. Ferrer's United States agent authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the act and §§314.52 and 314.95 is Birch, Stewart, Kolasch & Birch, LLP.

The undersigned declares that United States Patent No. 5,135,943 covers the formulation, composition, and/or method of use of sertaconazole. This product is the subject of this application for which approval is being sought:

By: _____

Name: Shelly Monteleone

Title: Associate Patent Counsel

EXCLUSIVITY SUMMARY for NDA # 21-385 SUPPL #
Trade Name _____
Generic Name sertaconzaole nitrate cream, 2%
Applicant Name Mylan Pharmaceuticals, Inc. **HFD-** 540
Approval Date 12/10/03

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

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

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

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

      YES /_X_/ NO /___/

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

      _____

      _____

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

      _____

      _____

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

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

5 years.

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

YES /___/ NO /_X_/

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

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

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

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

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

YES /___/ NO /_X_/

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

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

1. Single active ingredient product.

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

YES /___/ NO /_X_/

Investigation #1, Study # #SER-960602 - IND 50,726 - Mylan
Investigation #2, Study # #SER-960603 - IND 50,726 - Mylan

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 /__/ N/A

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

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

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

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

YES /___/ NO /___/

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

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

YES /___/ NO /___/

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

_____

_____

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

YES /___/ 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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

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

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

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

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

Investigation #1

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

_____ _____

_____ _____

Investigation #2

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

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

(S1)

Signature of Preparer
Title: PM

5/29/02
Date

(S1)

Signature of [illegible]ctor

5/29/02
Date

II.2. is N/A

Reviewed and reconfirmed.

(S1)

cc:
Archival NDA 21-385
HFD-540/Division File
HFD-540/Cross
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

NDA Number:	021385	**Trade Name:**	SERTACONAZOLE NITRATE CREAM 2%
Supplement Number:	000	**Generic Name:**	SERTACONAZOLE NITRATE CREAM 2%
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	
Original NDA Action Date:	9/28/01		

Indication # 1

Comments (if any): A Pediatric Waiver is granted for pediatric patients ages 0 to 12 years of age on the basis that interdigital tinea pedis is not widely seen in this population.

Ranges for This Indication

Lower Range	Upper Range	Status	Date
0 years	12 years	Waived	
Comments: Too few affected children for the indication of interdigital tinea pedis.			
12 years	Adult	Completed	

This page was last edited on 5/29/02

LSI

Signature

5/29/02

Date

LSI

LSI

LSI

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

Although the Pediatric Rule is no longer in effect a Pediatric Page should be filled out as if it were still in effect to document what the Division would have done under the Rule. Therefore, if the Division would have deferred and/or waived specific age ranges for the application under review, this information should be captured on this Pediatric Page. Furthermore, if any pediatric studies were completed for this application, then that information should be captured as well.

NDA/BLA #: 21-385 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: 10/10/03 Action Date: 12/10/03

HFD 540 Trade and generic names/dosage form: ERTACZO™ (sertaconazole) Cream, 2%

Applicant: Mylan Pharmaceuticals, Inc Therapeutic Class: 1

Indication(s) previously approved: None

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

Number of indications for this application(s): 1

Indication: topical treatment of immunocompetent patients with interdigital tinea pedis in patients 12 years of age and older caused by *Trichophyton* rubrum and Trichophyton mentagrophytes and Epidermophyton floccosum

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

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

Section A: Fully Waived Studies – N/A

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. 0	Tanner Stage	
Max	kg	mo.	yr. 12	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
- [X] Too few children with disease to study

- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: too few children with disease to study #5

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 N/A

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.** 12 (17) **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.** Adult **Tanner Stage**____

Comments:

A Pediatric Waiver is granted for pediatric patients ages 0 to 12 years on the basis that interdigital tinea pedis is not widely seen in this population. Safety data for 17 year olds and older subjects are sufficient to extrapolate safety and down to age 12. Tinea pedis interdigital efficacy would apply to all ages.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-385
HFD-960/ Grace Carmouze
(revised 10-14-03)

LST 12/9/03

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

Attachment A

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

Indication #2: _____

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

- ☐ **Yes: Please proceed to Section A.**

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

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

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg____ mo.____ yr.____ Tanner Stage____.
Max____ kg____ mo.____ yr.____ Tanner Stage____.

Reason(s) for deferral:

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

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

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

ction 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 complet[illegible]

¡See app

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Grace Carmouze
(revised 10-14-03)

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

The Section 16 Debarment Certification for Sertaconazole Nitrate Cream, 2% New Drug Application is found on the following page.

APPEARS THIS WAY
ON ORIGINAL

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

September 28, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD 540
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
ATTENTION: Central Document Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: SERTACONAZOLE NITRATE CREAM, 2%
NDA #21-385

Dear Dr. Wilkin:

Pursuant to 21 CFR 314.50(k) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 335a(k)), as amended by the Generic Drug Enforcement Act of 1992, Mylan hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Act in connection with the application for the referenced product.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

Interdisciplinary Summary of NDA 21-385
ERTACZO (sertaconazole nitrate) Cream, 2%

December 9, 2003

ERTACZO (sertaconazole nitrate) Cream, 2% is a topical antifungal drug product indicated for the treatment of interdigital tinea pedis in immunocompetent patients 12 years of age and older, caused by *Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum*. The original NDA submission had an Approvable action given on July 26, 2002. As noted in the previous Clinical Team Leader Summary Memorandum for this NDA dated, July 24, 2002, the Applicant had not supported the addition of the [redacted], in the original proposed formulation. The formulation used in the clinical studies did not have this ingredient. As per the CMC review, application of the SUPAC logic indicated the need for additional information prior to approval. With the current submission, the Applicant addresses this concern by asking for approval of the original formulation that does not contain [redacted].

In addition, various review disciplines were involved in the review of this document. This review is a summary review regarding certain critical issues that remain outstanding since the Approvable action of July 26, 2002.

Chemistry

Sertaconazole nitrate, a salt of sertaconazole, is a new molecular entity in the United States (although previously and currently marketed in other countries in other formulations). The drug product contains 1.75% (17.5 mg per gram) dispersion of the sertaconazole or 2% (20 mg per gram) sertaconazole nitrate in an oil-in-water cream base. The product is packaged in blind-end aluminum tubes [redacted] capped with a white [redacted] cap with a piecing tip and is proposed to be available in 2 g sample, 15 g and 30 g tube sizes. Manufacturing facility inspections were judged to be acceptable by the Office of Compliance on November 5, 2003.

The Chemistry Reviewer, Dr. Steve Hathaway, concluded that the recommendation for this application should be Approval. This was concurred by the Chemistry Team Leader.

Pharmacology/Toxicology

The Pharmacology/Toxicology review team recommends the following postmarketing study commitment which was accepted by the Applicant:

Commitment/Study Description: Conduct a dermal carcinogenicity study.
Protocol Submission by March 10, 2004.
Study start by December 10, 2004.
Final report submission by December 10, 2007.

This study request is appropriate for the NME that does not have dermal carcinogenicity data, but will be used in a recurring chronic condition on the skin.

The Pharmacology/Toxicology review team concluded that the recommendation for this application should be Approval.

Biopharmaceutics

The Biopharmaceutics data regarding systemic exposure did not include patients treated that had maximal involvement with interdigital tinea pedis. However, the data that the Sponsor submitted was accepted due to previous regulatory advice which represents an out-dated evaluation paradigm (i.e. application to broader areas of relatively intact skin might suffice as a substitute for small areas of potentially macerated skin). Further, the Sponsor did provide small numbers of patients (5) with intergitial tinea pedis. To this effect, the following was recommended to be conveyed as part of this action:

"With regards to the pharmacokinetic data, for this and future NDA's, we encourage you to conduct future in vivo bioavailability trials under maximum use conditions in patients with the desired indication. In general, such studies should enroll a sufficient number of subjects generally > 15) to assure the proper characterization of circulating drug levels where feasible. The use of pooled data from mixed indications, although allowed in the past, does not represent current thinking in this area."

The previous approvable action included a recommendation for a post-marketing commitment for a Biopharmaceutics study. However, in the Addendum to the second Biopharmaceutics Review dated December 9, 2003, it was indicated that the data and the administrative record were reconsidered and it was determined that "the Sponsor had fulfilled the *in vivo* bioavailability requirement under 21 CFR 320 and the post-marketing commitment requirement for a new study...is removed."

The Biopharmaceutics review team concluded that the recommendation for this application should be Approval.

Clinical Microbiology

The July, 2002 Approvable letter contained a post-marketing commitment requirement for susceptibility tests.

The Clinical Microbiology review team participated in the final labeling of the product, during labeling negotiations with the Sponsor, it was determined that data from the suggested post-marketing commitment would not lead to any labeling change as *in vitro* microbiological studies would need to be supported by *in vivo* clinical data. Thus, the post-marketing commitment requests that originated from clinical microbiology were taken off the table. Additionally, the following was recommended in discussion with the Clinical Microbiology Team Leader to be included in the letter regarding future evaluations for this indication with modification by the Clinical Team on December 9, 2003:

"For this and future NDAs, we ask that you perform clinical studies that establish a correlation between clinical and microbiological outcomes. These studies should include in vitro susceptibility evaluations of the relevant fungal pathogens isolated from a sufficient number of patients enrolled. The *in vitro* susceptibility studies must demonstrate the fungicidal activity of the test drug against all relevant pathogens for the

requested indications. While data from animal models may help evaluate the equivalent human clinical dose, and pre-clinical in vitro susceptibility results may demonstrate the spectrum of activity of the test drug against selected fungal strains, the in vitro susceptibility to the test drug of the causative pathogens isolated from the target site in patients enrolled in clinical trials helps confirm microbiological and clinical efficacy."

The application was deemed acceptable for Approval by the Clinical Microbiology team, with the label as modified and attached in the Clinical Review dated December 9, 2003, during the labeling discussions with the Sponsor.

Clinical & Biostatistics

The sertaconazole application is consistent with previous topical antifungal products with regard to relative efficacy in treating interdigital tinea pedis. The rates of cure are low, but statistically and numerically better than vehicle. The safety evaluation, including provocative dermal safety testing, revealed no serious side effects or major non-serious side effect that would be of undue concern. Other topical antifungal products were approved in such a setting. Two examples discussed during this review were Lamisil Cream and Mentax Cream (both are now OTC for the treatment of interdigital tinea pedis).

Due to the competitive marketplace for these products, Applicants appear to be attempting to demonstrate statistical superiority vs. vehicle rather than looking to seek maximization of clinical effect (i.e., achieving the most efficacy and still maintaining a very low safety concern).

The Clinical and Biostatistical teams recommendations for this product are the same: Approval. However, advice given for future products should encourage evaluation for greatest efficacy achievable in the setting of minimal safety concern.

Markham C. Luke, M.D., Ph.D.
Dermatology Lead Medical Officer

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

/s/

Markham Luke
12/9/03 06:27:48 PM
MEDICAL OFFICER
TL Interdisciplinary Summary Review as per MAPP 6020.8.

Jonathan Wilkin
12/9/03 06:31:12 PM
MEDICAL OFFICER

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 5/24/02	**DUE DATE: 6/30/02**	**ODS CONSULT #:** 02-0109

TO: Jonathan Wilkin, MD
Director, Division of Dermatologic and Dental Drug Products
HFD-540

THROUGH: Frank Cross
Project Manager
HFD-540

PRODUCT NAME: —— (Primary name) **Ertaczo™** (Alternate name) (Sertraconazole Nitrate) Cream, 2% **NDA#: 21-385**	**NDA SPONSOR: Mylan Pharmaceuticals, Inc.**

SAFETY EVALUATOR: Charlie Hoppes, RPh, MPH

SUMMARY: In response to a consult from the Division of Dermatologic and Dental Drug Products (HFD-540), he Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary names —— and "Ertaczo™" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:
DMETS does not recommend the use of proposed proprietary name, ——. However, DMETS has no objections to the use of the proprietary name, Ertaczo™. In addition, DMETS recommends implementation of the labeling revision outlined in section IV of this review to minimize potential errors with the use of this product. This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 10, 2002

NDA# 21-385

NAME OF DRUG: [redacted] or **Ertaczo™** (Sertaconazole Nitrate) Cream, 2%

NDA HOLDER: Mylan Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult is written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540) for an assessment of the proposed proprietary names [redacted] and Ertaczo. Although the container labels and carton labeling, and package insert labeling were reviewed for possible interventions in minimizing medication errors, this labeling did not bear either of the proposed proprietary names.

PRODUCT INFORMATION

[redacted] and Ertaczo are the proposed proprietary names for Sertaconazole Nitrate Cream. Sertaconazole Nitrate Cream is indicated for [redacted] The recommended dosage is a twice a day application to the affected areas for 4 weeks. This product will be supplied in 15 g and 30 g tubes.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to [redacted] and Ertaczo 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 Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 00-02, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

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 for each name, 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 names [redacted] and Ertaczo. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and 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. The Expert Panel identified eight proprietary names that were thought to have the potential for confusion with [redacted] These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage. In addition, the Expert Panel identified four proprietary names that were thought to have the potential for confusion with Ertaczo. These products are listed in Table 2 (see page 4), along with the dosage forms available and usual dosage.

2. DDMAC did not have concerns about either name with regard to promotional claims.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

[redacted]

Table 2: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Ertaczo	**Sertaconazole Nitrate Cream, 2%**	**Apply twice a day**	
Estrace	Estradiol Tablets, USP Estradiol Vaginal Cream, USP, 0.01%	Tablets: 0.5 to 2 mg once daily OR 1 to 10 mg three times daily. Vaginal Cream: 1 to 4 g daily initially then 1 g one to three times a week for maintenance.	LA
Entac***	An expectorant***	***	LA
Taxol	Paclitaxel Injection	135 mg/m^2 or 175 mg/m^2 intravenously over 3 hours every 3 weeks.	SA
Tazorac	Tazarotene Topical Gel 0.05% and 0.1%	Apply once a day, in the evening, to psoriatic lesions.	SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike) ***This product is no longer marketed.			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Six separate studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of —— and Ertaczo with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 108 —— , and 108 (Ertaczo) health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescriptions for —— (see page 5) and Ertaczo (see page 6). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

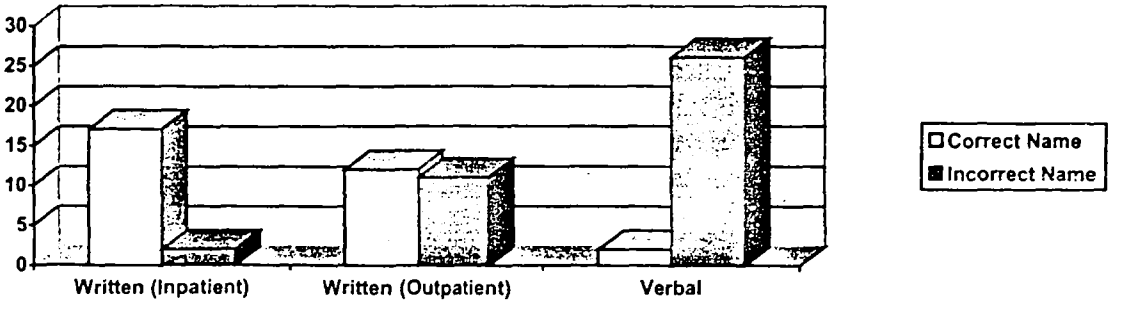
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION

2. Results:

The results for — are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	36	19 (53%)	17 (89%)	2 (11%)
Written Outpatient	33	23 (70%)	12 (52%)	11 (48%)
Verbal	39	28 (72%)	2 (7%)	26 (93%)
Total	108	70 (65%)	31 (44%)	39 (56%)



Among participants in the written prescription studies, 13 of 42 respondents (31%) interpreted the name incorrectly. The interpretations were

Among participants in the verbal prescription studies, 26 of 28 (93%) interpreted the name incorrectly. Most incorrect name interpretations were

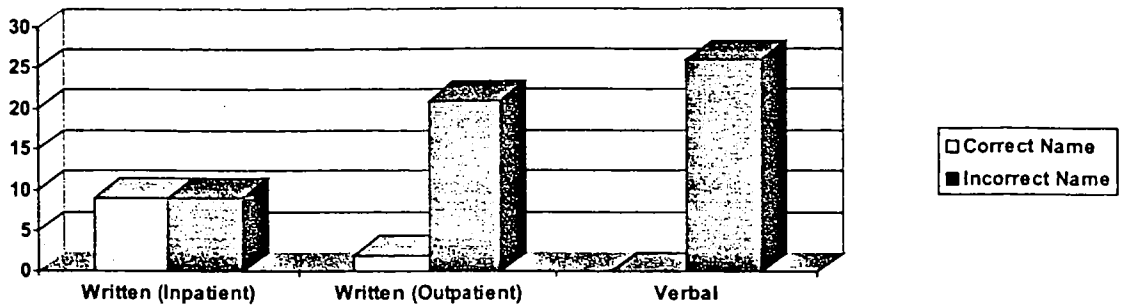
ERTACZO

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Ertaczo Sig: qd dx #1	Continue Ertaczo for 5 more days.
Inpatient RX : Continue Ertaczo for 5 more days	

The results for Ertaczo are summarized in Table II.

Table II

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%) "Ertaczo"	Incorrectly Interpreted (%)
Written Inpatient	36	18 (50%)	9 (50%)	9 (50%)
Written Outpatient	33	23 (70%)	2 (9%)	21 (91%)
Verbal	39	26 (67%)	0 (0%)	26 (100%)
Total	108	67 (62%)	11 (16%)	56 (84%)



Among participants in the written prescription studies, 30 of 41 respondents (73%) interpreted the name incorrectly. The interpretations were misspelled variations of "Ertaczo". Incorrect interpretations of written prescriptions included: *Ertaczer* (10 occurrences), *Enacza, Ertazet, Ertacz, Ertacza, Entazar, Ertaczes, Ertaczec* (2 occurrences), *Emaczo, Emaczer* (2 occurrences), *Ertac 20 mg, Ertac* (2 occurrences), *Entac, Estac 20, Entaczo,* and *Ertac 20* (3 occurrences).

Among participants in the verbal prescription studies, 26 of 26 (100%) interpreted the name incorrectly. Most incorrect name interpretations were phonetic variations of "Ertaczo". Incorrect interpretations of the verbal prescription included: *Vertaxil, Urtaxo, Urtaxil, Protaxil, Vertexo, Ertaxo* (10 occurrences), *Ortaxo* (2 occurrences), *Urtaxol* (2 occurrences), *Ertaxil, Ertaxil, Vertaxo, Ertaxol, Ortaxol, Ertaxel,* and *Ertaxil.*

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proposed proprietary name [redacted] the primary concerns raised related to look-alike, sound-alike confusion with names already in the U.S. marketplace. The products considered to have potential for name confusion with [redacted] The products considered to have the potential for name confusion with Ertaczo were Estrace, Entac, Taxol, and Tazorac. Although the product "Entac" was identified by the Expert Panel as having potential for confusion with Ertaczo, no evidence was found that this product is still being marketed. Of the above products, those considered to have the ***greatest*** potential for name confusion with **Ertaczo** were Estrace and Taxol.

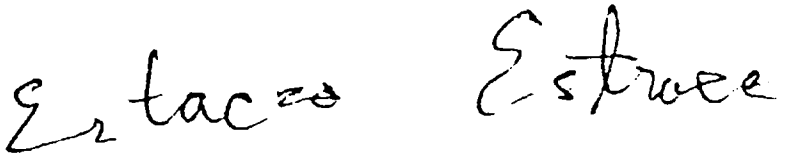
[redacted]

2 Page(s) Withheld

ERTACZO

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Ertaczo can be confused with Estrace, Taxol, or Tazorac. The majority of interpretations from the written and verbal prescription studies were phonetic/misspelled interpretations of the drug name Ertaczo. The letters "zo" in the inpatient written prescription for Ertaczo were interpreted as the number 20 by five of the 18 respondents. Another three respondents left the letters "zo" off altogether without indicating the number 20 ("ertac" and "entac"). One participant provided the name Entac, which was the name of a marketed drug product. However, Entac is no longer marketed because it contained the ingredient, phenylpropanolamine. The names thought to have the greatest potential for confusion are discussed below.

Estrace is a proprietary name for Estradiol Tablets, USP and Estradiol Vaginal Cream, USP, 0.01%. Estrace Tablets are indicated for the treatment of moderate-to-severe vasomotor symptoms associated with menopause; vulval and vaginal atrophy; hypoestrogenism due to hypogonadism, castration, or primary ovarian failure; breast cancer (for palliation only) in appropriately selected women and men with metastatic disease; advanced androgen-dependent prostate carcinoma (for palliation only); osteoporosis prevention. Estrace Vaginal Cream is indicated for the treatment of urogenital symptoms associated with postmenopausal atrophy of the vagina or the lower urinary tract. The recommended dosage of Estrace Tablets is 0.5 to 2 mg once daily OR 1 to 10 mg three times daily. The recommended dosage for Estrace Vaginal Cream is 1 to 4 g daily initially then 1 g one to three times a week for maintenance. *Estrace* and *Ertaczo* may look similar when written (see writing sample below). The names share the letters "E", "t", "r", "a" and "c". However, the "r" appears in a different position in each name and the "z" in Ertaczo is distinctive. The two drug products have differences. Estrace is available as a tablet for oral administration or a cream for vaginal administration while Ertaczo is a cream for topical administration. The strength of Estrace Vaginal Cream is 0.01% and it is given once a day while Ertaczo has a strength of 2% and it is administered twice a day. Although it is possible for the names to be confused, especially if Estrace Cream is written without a strength or the descriptor "Vaginal Cream", the risk of dispensing the wrong medication should be low based on differences such as route of administration, dosing intervals and a lack of convincing look alike similarities between the names.

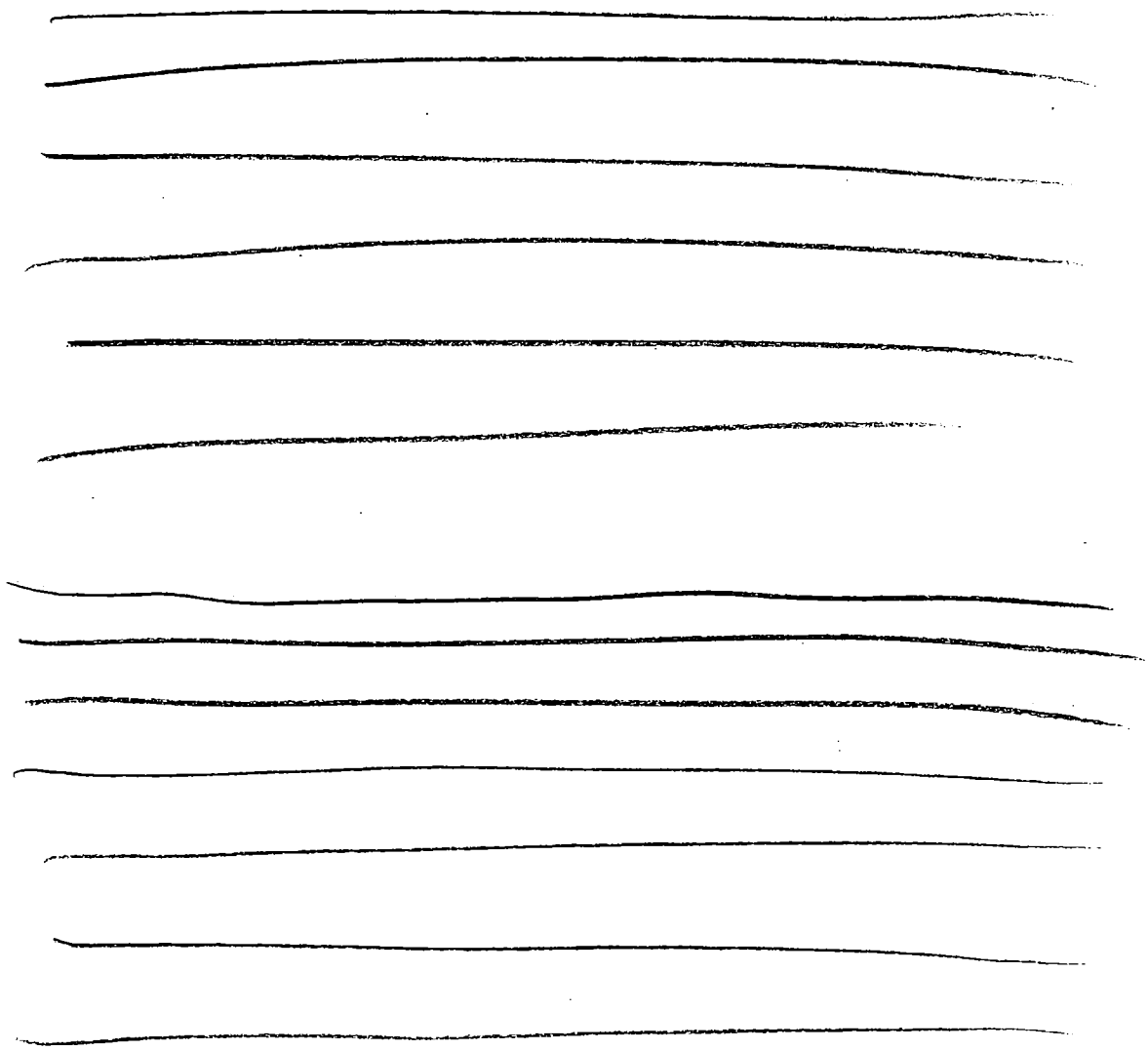


Taxol is the proprietary name of Paclitaxel Injection. Taxol is indicated for ovarian cancer, breast cancer, non-small cell lung cancer and as a second-line treatment in AIDS-related Kaposi's sarcoma. The usual dosage is 135 mg/m ^{2} or 175 mg/m ^{2} intravenously over 3 hours every 3 weeks. *Taxol* and *Ertaczo* may sound similar when spoken. The name Taxol sounds very much like the "taczo" portion of the proposed proprietary name, Ertaczo. In fact, responses from the verbal prescription study included, *urtaxol, ertaxol,* and *ortaxol.* However, the leading "Er" of

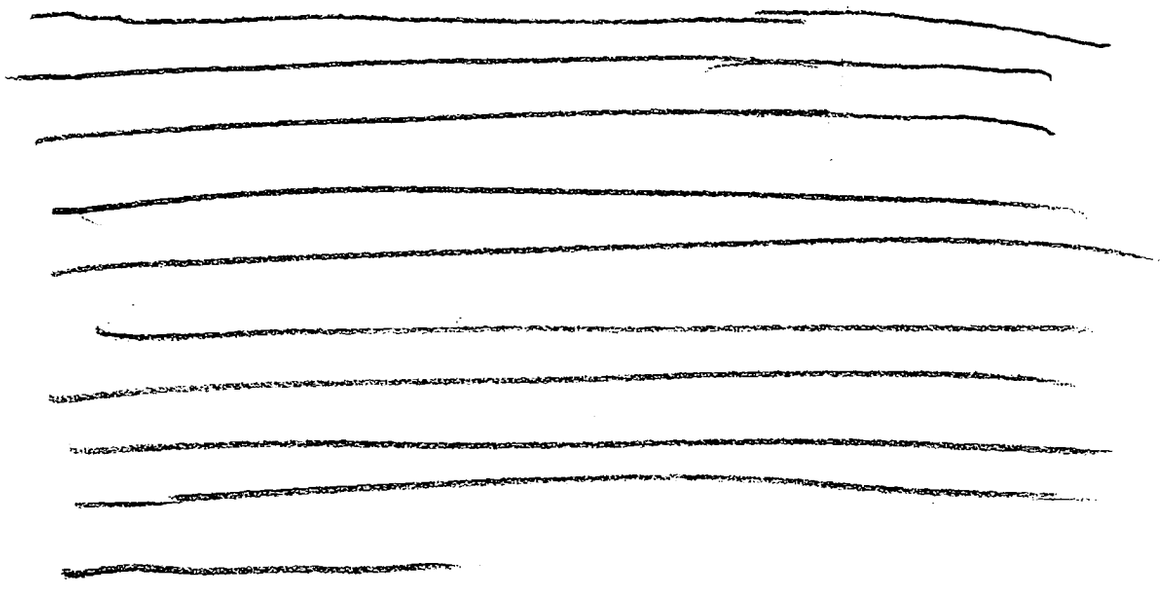
Ertaczo, helps to distinguish these names by adding an additional syllable to the beginning of the name. The two drug products also have differences. Taxol is available in an injection dosage form while Ertaczo is a cream for topical administration. The strength of Taxol is 6 mg/mL and it is administered in a single intravenous dose every 3 weeks based on the patient's body weight. In contrast, Ertaczo has a strength of 2% and is administered twice a day. Taxol is administered under controlled circumstances including special preparation of the injection and pre-medication of the patient. Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on the differences between the medications including differences in route of administration dosage forms, strengths, dosing intervals and the special conditions under which Taxol is administered.

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proposed proprietary name —— However, DMETS has no objections to the use of the proprietary name Ertaczo. The names thought to have the greatest potential for confusion with ← are discussed below.



* A good reference for phonetic terminology can be found at: http://www.unil.ch/ling/phonetique/api-eng.html



IV. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of — Ertaczo, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified one area of possible improvement, which might minimize potential user error.

GENERAL COMMENT

You may simplify and increase the prominence of the route of administration appearing on labels and labeling by deleting the

V. 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 Ertaczo.

B. DMETS recommends the above labeling revision that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

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 Sammie Beam, project manager, at 301-827-3242.

Charlie Hoppes, RPh, MPH
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Charles Hoppes
7/2/02 11:14:19 AM
PHARMACIST

Alina Mahmud
7/3/02 07:20:26 AM
PHARMACIST

Carol Holquist
7/3/02 12:58:53 PM
PHARMACIST

Jerry Phillips
7/3/02 02:26:22 PM
DIRECTOR

Office of Drug Safety

Memo

To: Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
HFD-540

From: Denise Toyer, Pharm.D.
Team Leader, Division of Medication Errors and Technical Support, HFD-420

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support, HFD-420

CC: Frank Cross
Project Manager
HFD-540

Date: November 25, 2003

Re: ODS Consult 02-0109-1; Ertaczo 2% [Sertaconazole Nitrate Cream] NDA 21-385

This memorandum is in response to the November 12, 2003 request from your Division for a re-review of the proprietary name, Ertaczo. Additionally, revised container labels, carton and package insert labeling were submitted for review and comment.

In our consult, dated June 10, 2002 (ODS consult # 02-0109), DMETS did not have any objections to the use of the proprietary name Ertaczo. Since this initial Ertaczo proprietary name review, DMETS has not identified any additional proprietary or established names that have the potential for confusion with Ertaczo. DDMAC did not have concerns about the proposed name, Ertaczo, with regard to promotional claims.

In the review of the container labels, carton and insert labeling of —— DMETS focused on safety issues relating to possible medication errors. DMETS recommends that the information presented in the Precautions, Information for Patients Subsection is reprinted at the end of the package insert labeling in accordance with CFR 201.57(f)(2).

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name and it's associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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

/s/

Denise Toyer
11/25/03 01:33:45 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/25/03 02:06:33 PM
DRUG SAFETY OFFICE REVIEWER

5 Page(s) Withheld

Teleconference Date: December 8, 2003 Time: 1415 Location: N229

NDA 21-385, ERTACZO™ (sertaconazole nitrate) Cream, 2%

Treatment of Interdigital Tinea pedis

Applicant: Mylan Pharmaceuticals, Inc.

Purpose of Teleconference: Discussion of Labeling – Clinical Pharmacology: Pharmacokinetics Sub-Section

Meeting Chair: Dennis Bashaw, Pharm.D.

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

FDA Attendees, titles and offices:

Dennis Bashaw, Pharm.D., Biopharmaceutics Team Leader, DPE-III, HFD-880
Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

Andrea B. Miller, R.Ph., Esq., Executive Director, Regulatory Affairs

Biopharmaceutics:

Agency:

In the Agency's November 25, 2003, draft labeling for the Package Insert for ERTACZO™ Cream, 2%, the Applicant revised the Pharmacokinetics Sub-section of the Clinical Pharmacology Section of the Applicant's Package Insert submitted December 5, 2003, "In a multiple dose pharmacokinetic study [redacted] interdigital tinea pedis (range of diseased area, 42 – 140 cm^2; mean, 93 cm^2) [redacted] ERTACZO™ Cream, 2%, was topically applied every 12 hours for a total of 13 doses to the diseased skin (0.5 grams sertaconazole nitrate per 100 cm^2)."

The Applicant should remove the [redacted] as it implies that the Agency is [redacted]

Applicant:

The Applicant conceded that the inclusion of the [redacted] was an oversight on their part and committed to its removal. A revised Package Insert will be submitted to the Agency later today, December 8, 2003.

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

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

/s/

Dennis Bashaw
12/8/03 03:21:05 PM

Clinical Team Leader Summary Memorandum for NDA 21-385
Ertaczo (sertaconazole nitrate) Cream 2%

Date of Memo: July 24, 2002

Drug Formulation Issues for Drug Product

It was noted and discussed at the pre-NDA meeting (Meeting ID #6259), October 18, 2000 that the Applicant would need to support the addition of the [redacted] to its final formulation as the formulation studied in clinical Phase 3 studies did not contain this ingredient.

The Medical Officer Review (signed May 30, 2002) confirmed that the formulation used for clinical studies did not contain the [redacted]. However, the Applicant has added this to its proposed formulation. It was felt by the review team that the Applicant could either market the [redacted] free formulation or conduct a vehicle-controlled bioequivalence study using clinical endpoints (as per 21 CFR 320.24(b)(4)) to compare both the [redacted] containing and [redacted] free formulations. The Biopharmaceutics reviewer in a review addendum (signed May 30, 2002) also agreed with this assessment.

In a teleconference with Agency on May 31, 2002, the Applicant asked several questions regarding the Agency's position on the addition of [redacted] to the proposed to-be-marketed formulation. The Applicant was informed that SUPAC logic for [redacted] does not apply as [redacted] and that [redacted] is not an impurity, but deliberately added to the batch so it does not qualify for Agency guidelines for impurities. The Applicant stated they would consider seeking approval for the formulation without [redacted] The Agency pointed out that additional information was needed for such an approval, which was not provided in the original NDA submission (see also Chemistry Review, dated July 24, 2002).

In a follow-up teleconference on July 16, 2002, the Agency discussed with the Applicant its two options for reaching an Approval in CMC. The Applicant informed the Agency that it planned to seek approval of the [redacted] free formulation of Ertaczo Cream, 2%.

The final recommendations for reaching an Approval are outlined below for Option 1 – [redacted] free formulation and Option 2 – [redacted] containing formulation. In any resubmission, the Applicant should unambiguously identify the formulation chosen.

Option 1 –

In order to market the [redacted] free formulation of the sertaconazole nitrate cream, the Applicant would have to submit the following:

A) Chemistry CMC -

1. A revised master batch manufacturing procedure, deleting the [redacted] from the formulation.
2. A revised finished drug product specification which omits the [redacted] the recommended change to the specification for Related Substances, noted in item 2. above, would also apply to the formulation without [redacted]
3. Revisions to the carton, container, and package insert labeling to remove the reference to [redacted] in the list of ingredients.
4. Revised qualitative and quantitative statements of composition.

5. The supporting stability data submitted in the NDA would be considered as the primary data, and the data derived from [redacted] containing lots would be considered supporting lots.
6. The "Description" test acceptance criterion for drug product is listed as [redacted]. This should be revised to declare the actual observation, i.e., [redacted] This is required to allow detection of changes during storage. The corresponding method [redacted] should be revised accordingly.

B) Pharmacology/Toxicology -
A dermal carcinogenicity study is needed that may be satisfied as a post-marketing commitment. This requirement derives from the proposed indication, in which chronic repeated use is anticipated. (ICH S1A, "For pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed.")

C) Biopharmaceutics –
This deficiency may be satisfied as a post-marketing commitment:

[redacted]

D) Clinical Microbiology –
The following deficiencies may be satisfied as a post-marketing commitment:

[redacted]

E) Clinical –
The Applicant should submit draft labeling revised in accordance with the enclosed labeling (text for the package insert, patient package insert, immediate container and carton labels). Further discussions regarding the labeling may be necessary.

Option II –

In order to market the [redacted]-containing formulation of the sertaconazole nitrate cream, the Applicant would have to submit the following:

[redacted]

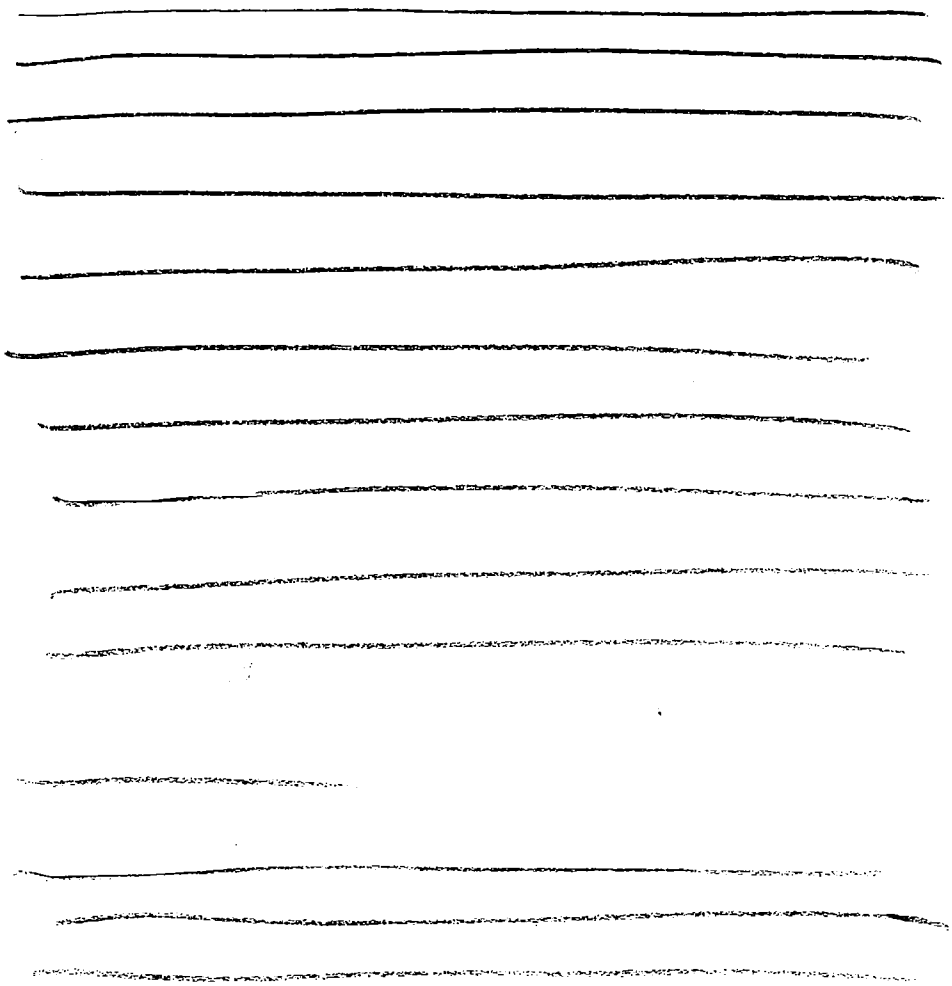
2. The drug product regulatory and stability specifications contain a [redacted] which does not conform to the recommendation in ICH Q3B, Impurities in New Drug Products.
Since [redacted] impurities above the identification threshold of 0.2% (assuming a maximum daily dose of 100 mg of sertaconazole nitrate) have been identified as [redacted] the specification should be revised to specify these impurities individually, as well as to include an acceptance criterion of [redacted] for any unspecified impurity. The recommended section is shown here:

Test	Acceptance Criterion	Procedure
[redacted]		
Impurity [redacted]	NMT [redacted]	
Impurity [redacted]	NMT [redacted]	
Impurity [redacted]	NMT [redacted]	
Any Individual Unspecified Impurity		
Total	NMT [redacted]	
	NMT [redacted]	

* To be determined upon further review of data.

[redacted]

1 Page(s) Withheld



Clinical Team Leader Summary

Thus, in summary, this application is Approvable, provided the Applicant agrees to one of the two Options described above.

Clinical Team Leader, Dermatology
Markham C. Luke, M.D., Ph.D.

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

/s/

Markham Luke
7/24/02 02:38:06 PM
MEDICAL OFFICER
TL Summary Memorandum

Jonathan Wilkin
7/24/02 02:58:19 PM
MEDICAL OFFICER

Teleconference Date: May 31, 2002 Time: 1030 Location: N225

NDA 21-385, sertaconazole nitrate cream, 2%

Treatment of Interdigital Tinea pedis

Applicant: Mylan Pharmaceuticals, Inc.

Purpose of Teleconference: Discussion of Formulation Issues – Deletion of BHA

Meeting Chair: Wilson DeCamp, Ph.D.

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

FDA Attendees, titles and offices:

Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830
Steve Hathaway, Ph.D., Chemistry Reviewer, DNDCIII, HFD-830
Joe Porres, M.D., Medical Officer, DDDDP, HFD-540
Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

Andrea B. Miller, R.Ph., Esq., Director, Regulatory Affairs
Frank Sisto, Executive Vice President, Regulatory Affairs, Mylan Pharmaceuticals, Inc,
Dan Snyder, Ph.D., Director, Analytical Laboratories
Walt Owens, Ph.D., Vice President, Chemistry
John O'Donnell, Ph.D., Chief Scientific Officer

Chemistry, Manufacturing, and Controls:

The purpose of this teleconference was for discussion of questions the Applicant had regarding the formulation change. The specific items were provided in an electronic mail dated May 30, 2002. The questions were as follows:

1. Applicant's Question 1: "Why isn't the addition of [redacted], treated as a [redacted] change that does not require clinical data under SUPAC-[redacted]

Agency:

[redacted] is not an [redacted] Therefore, this logic from SUPAC [redacted] doesn't apply. A change of this type clearly falls under Level 3 changes to components and composition.

2. Applicant's Question 2: "We would like to further discuss the potential or lack thereof that the addition of such a [redacted] could have on the formulation. The current Agency guidances do not require a sponsor to qualify impurities that appear in formulations at levels higher than the [redacted] level."

Agency:

[redacted] is not an impurity, but an ingredient which is deliberately added to the batch. Therefore, SUPAC doesn't apply.

3. Applicant's Question 3: "If we were to seek approval for the formulation without [redacted] Mylan still would be requesting that DPT be approved as the contract manufacturing site. Does the Agency concur that this approach would be acceptable?"

Agency:

Yes.

4. Applicant's Question 4: "What documentation would the Agency require to support the approval of the formulation without [redacted] manufactured by DPT? Would this information be required pre- or post approval?"

Agency:

At a minimum, the following items are needed before approval of the NDA would be considered:

a. revised master batch manufacturing procedure deleting the [redacted] from the formulation

b. revised finished drug product specifications

c. revisions to the carton, container, and package insert labeling to remove the reference to [redacted]

d. revised qualitative and quantitative statements of composition.

e. the NDA should be amended to remove references to [redacted] where the NDA refers to the to-be-marketed formulation

f. the supporting stability data submitted in the NDA would be considered as the primary data.

Applicant:

The Applicant agreed to make the requested submissions within the next 3 weeks.

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory):_____

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

/s/

Frank Cross
7/24/02 01:27:27 PM
CSO

Steve Hathaway
7/25/02 07:33:02 AM
CHEMIST

Wilson H. DeCamp
7/25/02 03:23:30 PM
CHEMIST
concur

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-385	Efficacy Supplement Type SE-	Supplement Number	
Drug: ERTACZO™ (sertaconazole nitrate) Cream, 2%		Applicant: Mylan Pharmaceuticals, Inc.	
RPM: Cross		HFD-540	Phone # 301-827-2020
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A	

❖ Application Classifications:	
• Review priority S	(X) Standard ( ) Priority
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	12/10/03
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid 9/24/01
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	5/30/02
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified 21 CFR 314.53(b)(c)
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(I)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(I)(1) ( ) (ii) ( ) (iii) N/A
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified N/A

❖ Exclusivity (approvals only)	
• Exclusivity summary	Yes
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE – 7/26/02
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes **(X)** Not applicable
• 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)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Yes
• Most recent applicant-proposed labeling	Yes
• Original applicant-proposed labeling	Yes
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	ODS Review: 7/3/02, 11/25/03 DDMAC Review: 11/18/03
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Yes
• Applicant proposed	Yes
• Reviews	CMC Review: 7/19/02, 11/25/03
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Yes
• Documentation of discussions and/or agreements relating to post-marketing commitments	Yes
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	Yes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	Yes (6/23/97)
• Pre-NDA meeting (indicate date)	Yes (10/18/00)
• Pre-Approval Safety Conference (indicate date; approvals only)	5/20/02, and 11/25/03, Labeling Meetings (reflected in labeling)
• Other	N/A

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	7/24/02, 12/9/03
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	5/30/02 (Primary), 5/30/02 (TL), 12/9/03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	5/21/02, 11/26/03
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	p. 58 of 5/30/02, MOR, p.4 of 12/9/03 MOR
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Yes
❖ Statistical review(s) *(indicate date for each review)*	5/6/02
❖ Biopharmaceutical review(s) *(indicate date for each review)*	5/3/02, 11/5/03, 12/9/03
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	5/14/02
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	7/19/02, 11/25/03
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	7/19/02, 11/25/03
• Review & FONSI *(indicate date of review)*	7/19/02, 11/25/03
• Review & Environmental Impact Statement *(indicate date of each review)*	7/19/02, 11/25/03
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	2/27/02
❖ Facilities inspection (provide EER report)	Date completed: **(X)** Acceptable **(** **)** Withhold recommendation
❖ Methods validation	**(** **)** Completed **(X)** Requested **(** **)** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	5/17/02 (Primary), 5/17/02 (TL), 11/26/03
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

4 Page(s) Withheld

47 Draft Labeling Page(s) Withheld