CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-581

CORRESPONDENCE

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 721-9669

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 256-7855

April 7, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

ORIG AMENDMENT

N/FA

ANDA # 75-581
KETOCONAZOLE CREAM, 2%
TELEPHONE AMENDMENT- RESPONSE TO APRIL 6, 2000 TELEPHONE CONTACT

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA in response to a telephone contact between Elaine Hu, Paul Schwartz and the reviewing chemist of the Office of Generic Drugs and Philip Erickson, Associate Director of Regulatory Affairs on April 6, 2000. Ms. Hu, Mr. Schwartz and the reviewing chemist phoned regarding the viscosity specification that we proposed in a March 16, 2000 facsimile amendment for release and stability testing of Ketoconazole Cream, 2%. The specification proposed in that amendment is :

As a result of the contact initiated by Ms. Hu, our chemist conducted viscosity testing on a lot of innovator product, Nizoral® Cream, 2% to compare the result with results obtained from testing performed on our pivotal batch as well as experimental work done to set our specification. It was determined that innovator product and TEVA's product have very comparable viscosity. A report compiling data from our experimental work as well as from testing innovator product is provided herein to further support the specification we have proposed.

In addition, please note that on February 22, 2000, personnel from Brookfield, the instrument manufacturer, visited TEVA Pharmaceuticals USA at our request to conduct a training seminar on use of the

Therefore, we are confident that this equipment is being used appropriately and consistently.

This information is submitted for your continued review and approval of this pending application. If you have any questions, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8105.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 10 2000
OGD

Sincerely,

Deborah Jaskot

DAJ/jbp
Enclosures

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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March 16, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT

FA

ANDA # 75-581
KETOCONAZOLE CREAM, 2%
FACSIMILE AMENDMENT- RESPONSE TO MARCH 1, 2000 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a facsimile amendment to the above-referenced pending ANDA in response to a review letter addressed to TEVA Pharmaceuticals USA from the Office of Generic Drugs dated March 1, 2000. Comments contained in the letter are addressed below in the order in which they were presented. Please note that a copy of the letter is provided in Attachment 1 for ease of review.

A. Deficiencies

1. As requested, esting has been added as a release and stability parameter to be monitored for this product. An updated Finished Product Procedure Manual containing the method and specification for for product release is provided in Attachment 2. In addition, the Finished Product Stability Protocol for this product has been updated to ensure this parameter is monitored during stability studies. A copy of the revised protocol is provided in Attachment 3.

2. Description of the drug substance has been added as a raw material control and as such, the Raw Material Procedure Manual has been revised to include this parameter as a release test. In addition, other compendial revisions were made to this manual per USP 24. The revised procedure manual is provided in Attachment 4.

3. We acknowledge that the presence of *Salmonella* species is undesirable in pharmaceutical preparations. Accordingly, we have validated and implemented a microbiological method which is able to recover *Salmonella* species and will be used to confirm the absence thereof in Ketoconazole Cream 2% for product release and stability. The Finished Product Procedure Manual and the Finished Product Stability Protocol have been revised to include a specification for the absence of *Salmonella* species. Please refer to the revised manual in Attachment 2 and the revised stability protocol in Attachment 3 for this additional specification.

This information is submitted for your continued review and approval of this pending application. If you have any questions, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

DAJ/jbp
Enclosures

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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December 6, 1999

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

ANDA # 75-581
KETOCONAZOLE CREAM, 2%
TELEPHONE AMENDMENT - STATISTICAL INFORMATION

Dear Mr. Sporn:

As requested by Mr. Harvey Greenberg of your office on November 18, 1999, and at the request of the reviewing statistician, TEVA Pharmaceuticals USA herein submits, in hard copy as well as on diskette, an informational table. As requested by the statistician, this table presents the types of infection, the infecting organism and the overall cure data for both the "Intent to Treat" subjects as well as the "Per Protocol" subjects.

This information is submitted toward the continued review and ultimate approval of this ANDA. If there are any further questions, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah A Jaskot

DAJ/emb
Enclosures

ORIG

MEDICAL OFFICER SUMMARY
January 27, 2000

ANDA 75-581
Drug Product: Ketoconazole, 2% Cream
Sponsor: TEVA Pharmaceuticals

Review of statistical report

The statistical report concludes that: "Both active treatment arms appear to be effective when compared to the placebo arm. The submitted data support the claim that TEVA's Ketoconazole and the reference drug, Nizoral, are equivalent."

Conclusion

The submitted study supports the claim that the test drug, TEVA's Ketoconazole is bioequivalent to the reference drug, Nizoral.

Mary M. Fanning, M.D., Ph.D.
Associate Director for Medical Affairs
Office of Generic Drugs

2.1

MAR 1

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-581 APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Ketoconazole Cream, 2%

The deficiencies presented below represent FAX deficiencies.

A. Deficiencies:

1. We disagree that the viscosity testing for product release and stability is unnecessary. The viscosity is an important parameter to measure the quality of the product in addition to visual inspection. The test and specifications of viscosity of the ketoconazole cream 2% for release and stability should be submitted for evaluation.

2. We disagree with your assessment that the description of the drug substance is not necessary as a raw material control. The visual inspection of the drug substance performed by a trained laboratory person is an important test parameter to document the physical attributes of the drug substance. The description of the ketoconazole drug substance should be included in the raw material specification.

3. We disagree with your statement that to test a topical product for the absence of salmonella species is inappropriate. In any kind of pharmaceutical preparation, the presence of [illegible] pathogenic salmonella species is undesirable. The absence of salmonella species should be tested for the release and stability

[illegible]

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-581 APPLICANT: TEVA Pharmaceuticals

DRUG PRODUCT: Ketoconazole Cream, 2%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-581 APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Ketoconazole Cream, 2%

The deficiencies presented below represent FAX deficiencies.

A. Deficiencies:

1. We disagree that the viscosity testing for product release and stability is unnecessary. The viscosity is an important parameter to measure the quality of the product in addition to visual inspection. The test and specifications of viscosity of the ketoconazole cream 2% for release and stability should be submitted for evaluation.

2. We disagree with your assessment that the description of the drug substance is not necessary as a raw material control. The visual inspection of the drug substance performed by a trained laboratory person is an important test parameter to document the physical attributes of the drug substance. The description of the ketoconazole drug substance should be included in the raw material specification.

3. We disagree with your statement that to test a topical product for the absence of salmonella species is inappropriate. In any kind of pharmaceutical preparations, the bacterial contamination including pathogenic salmonella species is undesirable. The absence of salmonella species should be tested for the drug product release and stability.

Sincerely yours,

7/11/00

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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September 20, 1999

ORIG AMENDMENT
N/AC

MAJOR AMENDMENT

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-581
KETOCONAZOLE CREAM, 2%
MAJOR AMENDMENT- RESPONSE TO JULY 30, 1999 REVIEW LETTER

Dear Mr. Sporn:

We submit herewith a major amendment to the above referenced pending ANDA in response to a review letter addressed to TEVA Pharmaceuticals USA from the Office of Generic Drugs dated July 30, 1999. Comments contained in the letter are addressed below in the order in which they were presented. Please note that a copy of the letter is provided in Attachment 1 for ease of review.

A. Deficiencies

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

9/20/99

B. We note and acknowledge the following:

1. The bioequivalence information we provided is under review, and any comments

generated will be communicated to us under separate cover.

2. Representatives of the Philadelphia District Office have requested samples of the finished dosage form for methods validation; product was provided to them June 25, 1999. A copy of the letter that accompanied the samples is provided in Attachment 9.

3. The firms referenced in our ANDA relative to the manufacturing and testing of the product must be in compliance with cGMP at the time of approval.

4. Please find 24 month stability data for each package size provided in Attachment 8.

C. Labeling Deficiencies

1. CONTAINER

a. The established name and strength of this product appear as the most prominent information on the label.

b. The "Contains" statement has been revised to read, "Each gram contains: ketoconazole 20 mg...sodium sulfite, anhydrous."

c. The "Rx only" statement has been moved to appear on the principal display panel.

d. The storage temperature has been revised such that the degrees Celsius appears before degrees Fahrenheit.

2. CARTON

a. All revisions were made to the carton as noted above under "Container."

3. INSERT

a. Insert labeling has been revised throughout to refer to the product as "ketoconazole cream, 2%" rather than "ketoconazole 2% cream".

b. Description

i. The first paragraph under "Description" has been revised as requested to read, "...agent, ketoconazole 2%. Each gram, for topical administration, contains ketoconazole 20 mg and is formulated....sodium sulfite, anhydrous."

ii. The molecular weight and formula have been added in the "Description" section.

c. Under "Adverse Reactions," "5.0%" has been changed to "5%" in the first sentence of the first paragraph.

d. The storage temperature has been revised as in C(1)(d) above.

Please note that in some instances, minor format changes were necessary due to space limitations on the carton. Insert labeling has been revised as noted above, and twelve final printed copies are provided in Attachment 10. Regarding container labels and carton labels, current lead time for receipt of such labels from our vendor are approximately sixteen weeks. So as to avoid delay of the review of this ANDA, we have provided the twelve final printed copies of container labels and carton labels in final printed paper representation, identical in all respects to the actual labels that are proposed for use commercially.

This information is submitted for your continued review and approval of this pending application. If you have any questions, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

DAJ/jpb
Enclosures

TEVA

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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February 23, 1999

NEW CORRESP
NC

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-581
KETOCONAZOLE CREAM, 2%
NEW CORRESPONDENCE-REQUEST FOR WITHDRAWAL OF BIO-IND # 15-295

Dear Sir/Madam:

In accord with instructions received yesterday from Ms. Saundra Middleton of your office, we hereby request that Bio-IND # 15-295 be withdrawn. The clinical study has been completed, the data analyzed, and the corresponding ANDA, which is the subject of this communication, has been submitted to your office.

Should you require further information or have additional questions or comments please contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

DAJ/pe
Enclosures

RECEIVED
FEB 24 1999
GENERIC DRUGS

1.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-581 APPLICANT: TEVA Pharmaceuticals

DRUG PRODUCT: Ketoconazole Cream, 2%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUL 30 1999

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-581 APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Ketoconazole Cream, 2%

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Please provide a complete, detailed impurity profile and specify the limits for each known impurity in the drug substance.

2. Please provide the description of the ketoconazole drug substance as a raw material control.

3. Please provide the analytical procedures for the determination of particle size of the ketoconazole drug substance.

4. In the manufacturing instruction, Step calls for the transfer of the cream to a mixing tank (p.6837). Yet, there is no mixing tank used in the process flow diagram on page 6845. Please clarify.

5. Please include the blend uniformity testing as a process control test for the ketoconazole cream 2%. The blend uniformity test should be comprised of assaying from different points in the final mixing vessel prior to filling and setting specifications for assay range and RSD value (a minimum of six samples). Please note that we recommend that the limits be specified as for ketoconazole assay.

6. Please include the test, test method, and specification of viscosity of the ketoconazole cream 2% for release and stability.

7. Please test for the absence of salmonella species in the drug product release and stability.

8. In analytical method number for the ketoconazole cream 2%, the assay and impurity/degradant, the system suitability test requirements should include the specifications of the tailing factor and column efficiency. You failed to show system suitability data in the validation report. Please provide system suitability results including tailing factor, column efficiency, resolution factor and RSD value.

9. The stability commitment (p. 7191) should state that acceptable full shelf life data on three lots of production batches are required to extend the expiration date. Please revise accordingly.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The bioequivalence information which you have provided is under review. After this review is completed, comments will be communicated to you under a separate cover.

2. Representatives of our FDA district office will request samples of the finished dosage form for the methods validation.

3. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP at the time of approval.

4. Please submit 24 months stability data.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-581

Teva Pharmaceuticals USA
Attention: Deborah A. Jaskot
1510 Delph Drive
Kulpsville, PA 19443

MAR 16 1999

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Ketoconazole Cream, 2%

DATE OF APPLICATION: February 12, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 16, 1999

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Joe Buccine
Project Manager
(301) 827-5848

Sincerely yours,

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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ack for filing 3/30/99
S. Middleton
505(j)

February 12, 1999

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
KETOCONAZOLE CREAM, 2%

Dear Mr. Sporn:

We submit herewith an abbreviated new drug application for the drug product Ketoconazole Cream, 2%.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs April 1997 Guidance for Industry: Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application. These copies are presented in a total of 45 volumes; 22 for the archival copy and 23 for the review copy.

The application contains a full report of a multi-center, double-blind, three-way parallel design clinical study. This study compared Ketoconazole Cream, 2% manufactured by TEVA Pharmaceuticals USA to the reference listed drug, Nizoral® (ketoconazole) 2% Cream manufactured by Janssen Pharmaceutica.

Two separately bound copies of the finished product analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

A certification regarding financial interests and arrangements of clinical investigators is provided in Section III of this application.

Please note that we have recently undergone a change in corporate name. As such, some documents may reference our previous name of LEMMON Company instead of the current name of TEVA Pharmaceuticals USA. No change in facilities, procedures, or commitments are made in conjunction with this change in name.

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 256-8400, ext. 5249, or by facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot/PE

DAJ/asg
Enclosures