CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-147

CORRESPONDENCE

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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

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November 23, 1998

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

TELEPHONE AMENDMENT

ANDA #75-147
ISOSORBIDE MONONITRATE TABLETS, 20 mg
TELEPHONE AMENDMENT - METHODS VALIDATION COMMITMENT

Dear Mr. Sporn:

In accord with a telephone conversation held earlier today with Mr. Tim Ames of your office, TEVA Pharmaceuticals USA hereby provides a statement of commitment with regards to the resolution of any deficiencies or issues that may arise during the FDA district laboratories review and validation of the methods contained in this pending ANDA.

It is our opinion that the submission of this commitment completes all outstanding issues with the review of the above referenced application. If there are any questions regarding this submission or additional information is needed, please do not hesitate to contact me at (215)-256-8400 ext. 5249 or by facsimile at (215)-256-8105.

We anxiously await your review and approval.

Sincerely,

Deborah Jaskot /PE

DAJ/rsv
Enclosures

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ANDA #75-147

ISOSORBIDE MONONITRATE TABLETS, 20 mg

TELEPHONE AMENDMENT - METHODS VALIDATION COMMITMENT

In accord with the 21 CFR 314.96(b), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Division of Emergency Investigations Operations.

Deborah Jaskot, PE
Deborah A. Jaskot
Senior Director, Regulatory Affairs

Nov. 23, 1998
Date

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ANDA# 75-147

ISOSORBIDE MONONITRATE TABLETS, 20 mg

TEVA Pharmaceuticals USA hereby commits to fully cooperate with FDA district laboratories towards resolving any deficiencies or issues that may be brought forth during the review and validation of the test methods contained in this Abbreviated New Drug Application.

Deborah A. Jaskot
Senior Director, Regulatory Affairs

Nov. 23, 1998
Date

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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Labeling review
Drafted 8/11/98
AVS

ORIG AMENDMENT

N/RC

March 11, 1998

MAJOR AMENDMENT

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

ANDA #75-147
ISOSORBIDE MONONITRATE TABLETS, 20 mg
MAJOR AMENDMENT - CHEMISTRY, MANUFACTURING & CONTROLS, BIOEQUIVALENCE & LABELING

Dear Mr. Sporn:

We submit herewith a major amendment to the above referenced pending ANDA in response to your letter of January 21, 1998. The deficiencies presented in the aforementioned letter are addressed in the order in which they were presented.

CHEMISTRY, MANUFACTURING & CONTROLS COMMENTS

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry deficiencies

3/11/98

BIOEQUIVALENCE COMMENTS:

We acknowledge the recommended dissolution parameters of 900 mL water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm with a test specification of " of the labeled amount of the drug in the dosage form is dissolved in 15 minutes." The release specification sheet and the commercial stability protocol provided in Attachment 7 have been revised to reflect these requirements. Also provided in this attachment are revised methods for the release and stability testing of this product which incorporate the dissolution parameters specified.

LABELING COMMENTS:

Revisions have been made in accord with your comments with the exception of comments 1 and 2.g.i. With regard to comment 1, please note that the thirty tablet containers contained in the original submission utilized two closures. One closure was child resistant while the other was a metal screw cap. The data on the thirty tablet bottle with the metal screw cap was provided for stability bracketing purposes only and is not proposed for use in the commercial manufacturing and marketing of this product. The only thirty count bottle proposed for marketing is the one utilizing the child resistant closure.

Comment 2.g.i. encourages the addition of our NDC number in the HOW SUPPLIED section of the product insert. It is TEVA Pharmaceuticals USA position not to include the NDC number on our insert so as to keep it neutral. This strategy prevents the creation of multiple inserts for multiple distributors thereby eliminating potential mix up between distributor specific inserts. Comment 2.g.ii. noted a discrepancy in the description of the scoring/embossing of the tablet. The original draft insert was found to be in error and has been corrected in the version attached. Final print labels and labeling are provided as Attachment 11.

The information provided herein represents, in our opinion, a complete response to your letter of January 21, 1998. This information is submitted towards the review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215)-256-8400 ext. 5249 or by facsimile at (215)-256-8105.

Sincerely,

Deborah Jashat

DAJ/rsv
Attachments

TEVA

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ANDA #75-147
ISOSORBIDE MONONITRATE TABLETS, 20 mg

MAJOR AMENDMENT -CHEMISTRY, MANUFACTURING & CONTROLS, BIOEQUIVALENCE & LABELING

In accord with the 21 CFR 314.96(b), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Division of Emergency Investigations Operations.

Deborah A. Jaskot
Senior Director, Regulatory Affairs

3/11/98
Date

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-147 APPLICANT: TEVA Pharmaceuticals

DRUG PRODUCT: Isosorbide Mononitrate Tablets, 20 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. In regard to the active ingredient we have the following comments:

   a. Please submit information regarding the material used as Reference Standard Isosorbide- Describe the characterization of the material which establishes its suitability for use as a reference standard.

   b. Please submit validation data regarding the method for residual solvent testing ubmit examples of typical chromatograms obtained.

   c. Please submit copies of the methods used for Particle Size and Bulk Density Testing.

2. In regard to the container/closure systems we have the following comments:

   a. Please submit results of USP 23 <671> Container - permeation testing for each container/closure system proposed for marketing.

   b. Please confirm if the 30 tablet bottle with metal cap is proposed for marketing (Refer to pp. 2177 & 2491).

3. In regard to the analytical methods used for the finished drug product, we have the following comments:

   a. The method validation did not appear to include data for the active ingredient subjected to various stress conditions. Please submit this additional data.

   b. Please submit any information regarding your attempts to identify any impurities/degradants other than Additionally, a limit of for any unidentified impurity is too high and is not supported by data. Also, the limit of for Total Impurities appears to be too high

based on the data submitted. Since these comments also apply to stability testing, revised product release and stability specifications should be submitted.

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

1. Drug Master File for the manufacture of the drug substance has been reviewed and found to be inadequate. The holder has been notified of the deficiencies. All deficiencies must be satisfactorily resolved prior to the approval of the ANDA.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-147 APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Isosorbide Mononitrate Tablets, 20 mg

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

Please acknowledge that the following dissolution testing specifications have been incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

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

TEVA

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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December 17, 1997

ORIG AMENDMENT
N/AA

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

ANDA #75-147
ISOSORBIDE MONONITRATE TABLETS, 20 mg
AMENDMENT - CORRECTION TO REFERENCED DRUG MASTER FILES

Dear Mr. Sporn:

We submit herewith an amendment to the above referenced pending ANDA. It has been recently brought to our attention that the Letter of Authorization to reference Drug Master provided in our original ANDA submission is no longer the correct DMF reference. DMF refers to of the pure active drug substance. Teva does not purchase the pure drug substance from but rather receives a blend of active drug substance and The process used to create this mixture is the basis of recently submitted DMF A Letter of Authorization from for DMF# is provided herein. The form 356h provided in this submission has been prepared to include the list of all DMF references provided in our original application and contains the correction described above. This 356h may replace that which was submitted in our original application.

We regret any inconvenience this change in DMF reference may cause. This information is submitted towards the review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215)-256-8400 ext. 5249.

Sincerely,

Deborah Jaskot

DAJ/rsv
Enclosures

RECEIVED
DEC 19 1997
GENERIC DRUGS

TEVA

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ANDA# 75-147

ISOSORBIDE MONONITRATE TABLETS, 20 mg

AMENDMENT - CORRECTION TO REFERENCED DRUG MASTER FILES

In accord with the 21 CFR 314.70(a), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Division of Emergency Investigations Operations.

Deborah A. Jaskot
Senior Director, Regulatory Affairs

12/17/97
Date

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-147 APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Isosorbide Mononitrate Tablets, 20 mg

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

Please acknowledge that the following dissolution testing specifications have been incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

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

TEVA

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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August 15, 1997

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

NEW CORRESP

ANDA #75-147
ISOSORBIDE MONONITRATE TABLETS, 20 mg
SUBMISSION OF REQUESTED BIOEQUIVALENCE DATA DISKETTES

Dear Mr. Sporn:

In response to your correspondence of July 29, 1997, which acknowledges receipt of the above referenced original ANDA, we provide herewith an additional set of diskettes containing the data from both bioequivalence studies contained in the original application. The diskettes have been formatted as requested and are provided for both the archival and review copies of the original ANDA. Print outs of the data are also enclosed.

This information is submitted towards the review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215)-256-8400 ext. 5249.

Sincerely,

Deborah Jaskot /RE

DAJ/rsv
Enclosures

RECEIVED
AUG 18 1997
GENERIC DRUGS

ANDA 75-147

TEVA Pharmaceuticals USA
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

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: Isosorbide Mononitrate Tablets, 20 mg

DATE OF APPLICATION: June 13, 1997

DATE OF RECEIPT: June 18, 1997

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

However, in the interim, please submit a diskette in ASCII format containing pharmacokinetic data and the model codes used in statistical analyses should be submitted. For each study, two separate files should be configured as follows:

(a) subj seq trt per AUC_{0-t} AUC_{inf} (Where applicable) C_{max} T_{max} K_{el} and $t_{1/2}$;...

(b) subj seq per trt C_1 C_2 C_3.....C_n,

where C is the concentration at various sampling times. Fields should be delimited by one blank space and each missing value should be denoted by a period (.).

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

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

1/28/97

cc:

Amanda J. Middleton 7/21/97 505(j)

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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June 13, 1997

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
ISOSORBIDE MONONITRATE TABLETS, 20 mg

Dear Mr. Sporn:

We submit herewith an abbreviated new drug application for the drug product Isosorbide Mononitrate Tablets, 20 mg.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs Policy and Procedure Guide #30-91. These copies are presented in a total of **19** volumes; **9** for the archival copy and **10** for the review copy. The application contains a full report of two *in vivo* bioavailability studies. These studies compared Isosorbide Mononitrate Tablets, 20 mg manufactured by TEVA Pharmaceutical Industries Ltd. to the reference listed drug, Monoket® under both fasting and post-prandial conditions.

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

Please note, we have recently undergone a change in corporate name from LEMMON Company to TEVA Pharmaceuticals USA. This change does not affect any of the systems or facilities presented in this application. However, some of the documents supplied herein may refer to our previous corporate name.

We look forward to your review and comment.

Sincerely,

Deborah Jaskot

DAJ/rsv
Enclosures

TEVA

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ISOSORBIDE MONONITRATE TABLETS, 20 mg

ORIGINAL ABBREVIATED NEW DRUG APPLICATION

In accord with the 21 CFR 314.70(a), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Philadelphia District Office.

Deborah A. Jaskot

Deborah A. Jaskot
Senior Director, Regulatory Affairs

6/13/97
Date