CENTER FOR DRUG EVALUATION AND RESEARCH

75-273

APPLICATION NUMBER:

CORRESPONDENCE

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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4/6
AM called to Chemistry reviewer for review. Labeling Review complete & acceptable for AP.

FPL

ORIG AMENDMENT

AM

March 23, 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

ANDA # 75-273
KETOCONAZOLE TABLETS USP, 200 MG
90 DAY AMENDMENT - LABELING, CHEMISTRY, MANUFACTURING & CONTROLS

Dear Mr. Sporn:

As required by our letter of tentative approval on 10/28/98, we submit herewith an amendment to our above referenced ANDA. The intent of this correspondence is to disclose any revisions that have been made to the CMC documentation since the application was tentatively approved. All CMC changes are summarized below.

1.

A study was conducted by Analytical R&D to establish that analysis performed with either diluent composition provides equivalent results (see the Supplemental Method Validation Report from Analytical R&D provided in Attachment 1). Six replicate samples of Ketoconazole USP raw material were prepared in the specified diluent compositions and analyzed. A summary of the results is presented in tabular form (Attachment 1), along with a copy of the updated Raw Material Procedure Manual (Attachment 2).

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GENERIC DRUGS

2. The following table illustrates all revisions that were made to any additional control documentation:

Document	Revision Date	List of Revisions
Finished Product Procedures Manual	12/17/98	A note was included throughout the Finished Product Procedures Manual which states to " (Attachment 3).
DMF #	)1/27/99	informed TEVA Pharmaceuticals USA that an update was submitted to the Agency regarding the Ketoconazole Drug Master File (DMF) e have enclosed a copy of the letter that was issued to TEVA as well as an updated DMF authorization (Attachment 4).
l Silicon Dioxide,	02/27/98	Revised pH specifications from in accord with NF 18, Supplement 6 (Attachment 5).
Purified Water	09/04/98	Revised the ime for USP Sucrose and removed the test for Substances in accord with USP 23/NF 18, Supplement 8 (Attachment 6).

3. In addition to the aforementioned CMC updates, we have provided 12 copies of final print labeling for this product (Attachment 7). This labeling is identical to the draft labeling submitted for tentative approval.

This information is submitted for review and retention in your files. If there are any questions regarding information presented in this amendment, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot/PE

DAJ/jg
Enclosures

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KETOCONAZOLE TABLETS USP, 200 mg

90 DAY AMENDMENT - LABELING, CHEMISTRY, MANUFACTURING & CONTROLS

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 Philadelphia District Office.

Deborah Jasko RPE
Deborah A. Jasko
Sr. Director, Regulatory Affairs

March 23, 1998
Date

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-273 APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Ketoconazole Tablets, 200 mg

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP Apparatus #2 (Paddle) at 50 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Note: In future redosing of subjects with unusual drug plasma levels, you are advised to include "control" subjects, who also participated in the original study and were without unusual plasma levels of the drug.

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

2.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-273 APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Ketoconazole Tablets, 200 mg

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Revised 9/23/98

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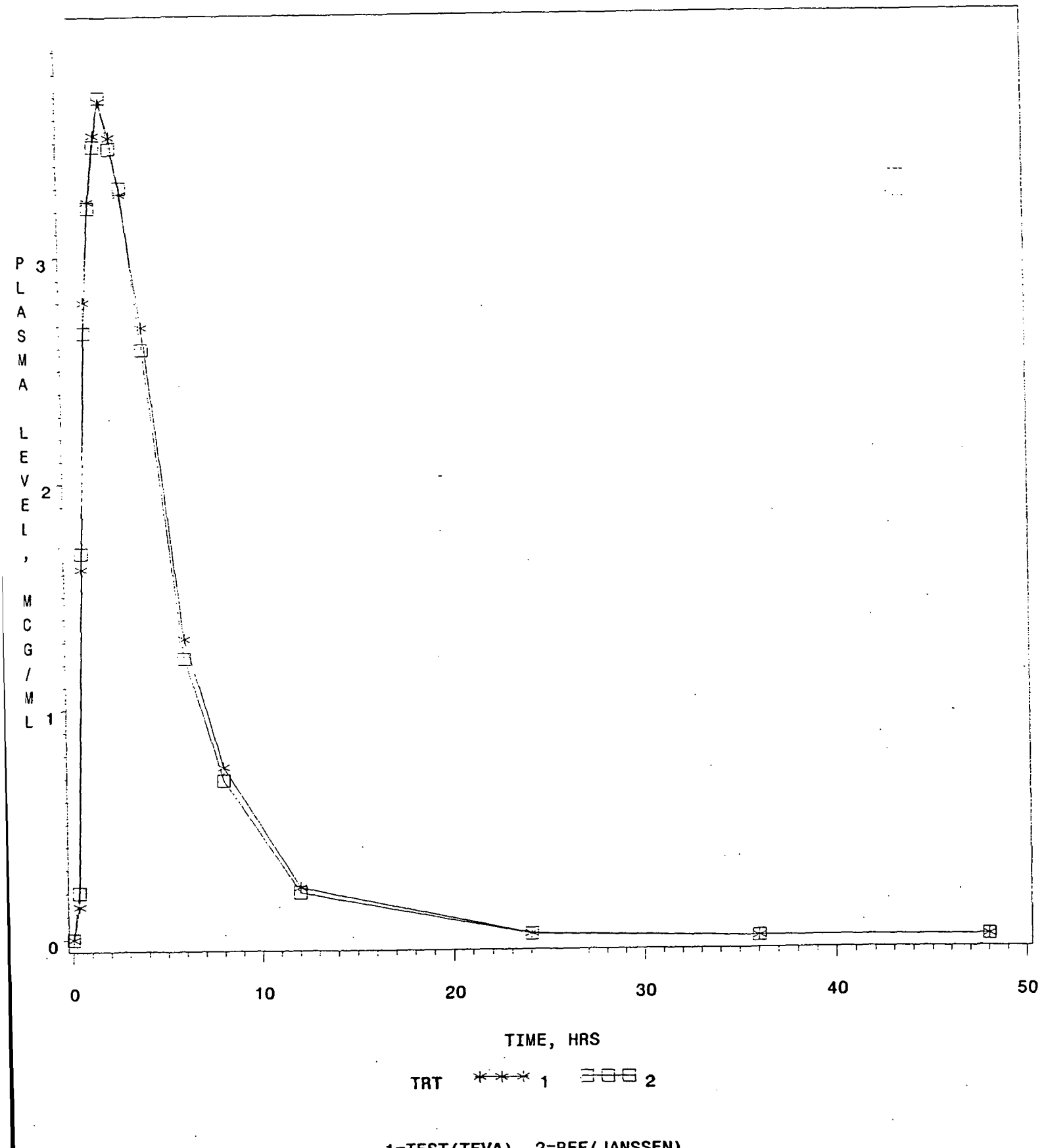
Sincerely yours,

Dale P. Conner

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

FIG #1 PLASMA KETOCONAZOLE LEVELS

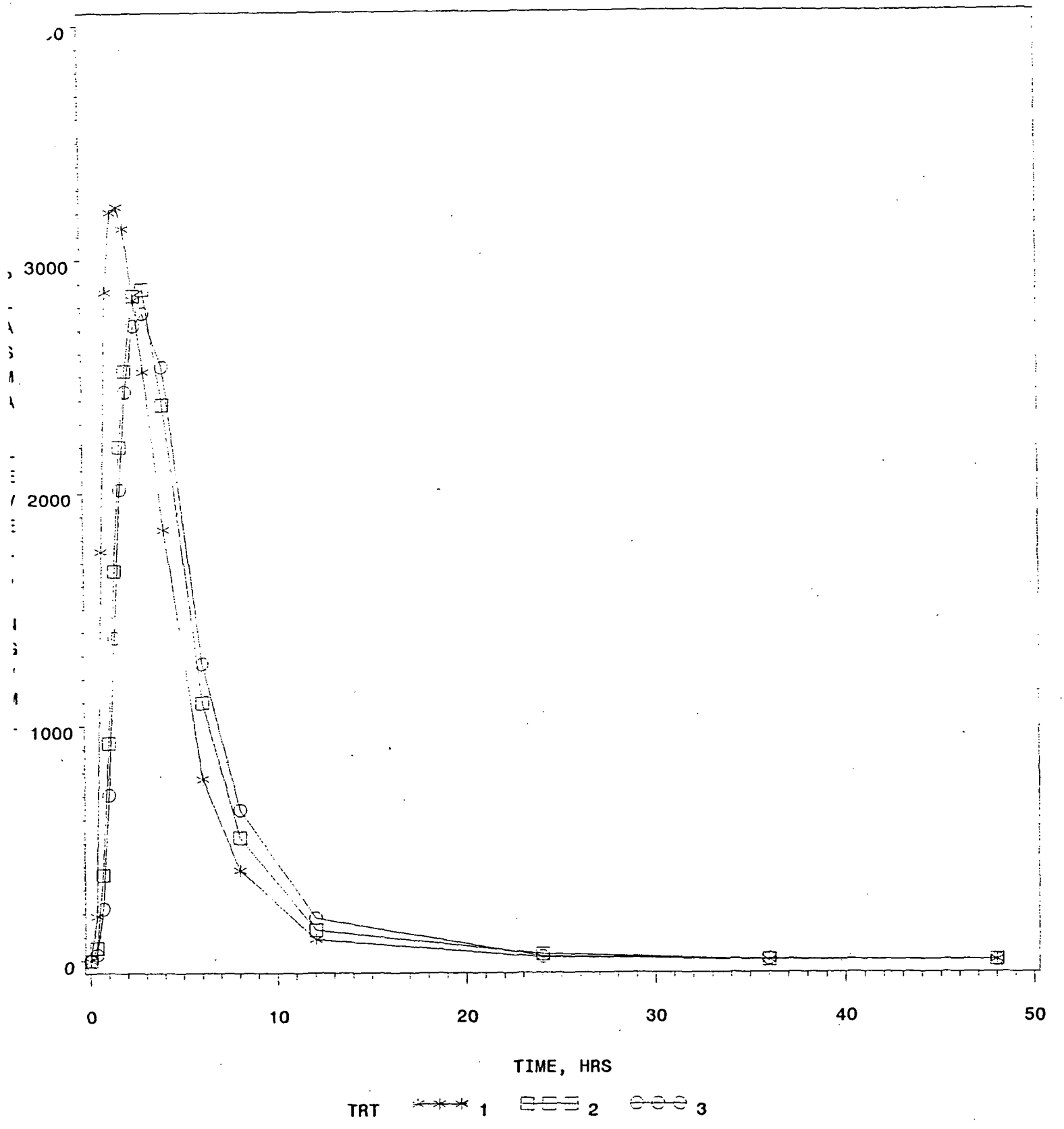
KETOCONAZOLE TABLETS, 200 MG, ANDA #75-273
UNDER FASTING CONDITIONS
DOSE=1 X 200 MG



1=TEST(TEVA) 2=REF(JANSSEN)

FIG #2 PLASMA KETOCONAZOLE LEVELS

KETOCONAZOLE TABLETS, 200 MG, ANDA #75-273
UNDER FASTING/NONFASTING CONDITIONS
DOSE=1 X 200 MG



1=TEST-FAST(TEVA) 2=TEST-FED(TEVA) 3=REF-FED(JANSSEN)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-273 APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Ketoconazole Tablets, 200 mg

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> Not less than of the labeled amount of the drug in the dosage form is dissolved in minutes.

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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.

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Dale P. Conner

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NDA [illegible] AMENDM[illegible]

N/AB

March 27, 1998

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

TELEPHONE AMENDMENT
BIOEQUIVALENCE

ANDA 75-273
KETOCONAZOLE TABLETS USP, 200 mg
TELEPHONE AMENDMENT - BIOEQUIVALENCE

Dear Mr. Sporn:

We submit herewith an updated diskette containing fasting bioequivalence data for the above referenced pending ANDA in response to a telephone request made March 12, 1998 by Ms. Nancy Chamberlain of the Division of Bioequivalence. The diskette has been formatted in ASCII format with the headings ordered as instructed by Ms. Chamberlain.

The enclosed diskette is intended to replace the one originally submitted with our ANDA on December 12, 1997. Copies are provided for both review and archival copies of our submission for your records. This information is provided for your continued review and approval of this ANDA.

Sincerely,

Deborah Jaskot

DAJ/pe
Enclosure

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MAR 31 1998

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