CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74943

CORRESPONDENCE

ANDA 74-943

SEP 29 1997

Apotex U.S.A., Inc., agent for
TorPharm, Inc.
Attention: Marcy Macdonald
1641 Barclay Boulevard
Buffalo Grove, IL 60089

Dear Madam:

Reference is made to the Abbreviated New Drug Application amendment submitted on May 1, 1997, for Diltiazem Hydrochloride Extended Release Capsules USP, 240 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The dissolution testing data were submitted for 6 units instead of 12 units. The data should be submitted for 12 units each, the test and reference products.

2. The media used at various pH were not buffer solutions. Please submit comparative dissolution data using buffer solutions with pH 4.0-4.5, pH 6.0-6.5, and pH 7.0-7.5.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

/.1

ANDA 74-943

FEB 14 1997

Apotex USA Inc.
Attention: Marcy Macdonald
U.S. Agent for: TorPharm Inc.
1641 Barclay Blvd.
Buffalo Grove IL 60089

Dear Madam:

Reference is made to the Abbreviated New Drug Application submitted on August 16, 1996, for Diltiazem Hydrochloride Extended-Release Capsules USP, 240 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The proposed dissolution assay methodology, medium and its volume, and proposed specifications should be submitted for lot #50041B. If medium is water, then the dissolution testing data should be submitted for it.

2. The firm has submitted dissolution data using solutions with pH 1.0-1.5, pH 4.0-4.5, pH 6.0-6.5, and pH 7.0-7.5. The media of the above solutions should be submitted.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL (847) 573-9999 • FAX (847) 573-1001

May 1, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

OPIS AMENDMENT
N/AM

TELEPHONE AMENDMENT

RE: ANDA 74-943
Diltiazem Hydrochloride Extended-Release Capsules, USP
(Once-a-day dosage) 240 mg

To Whom It May Concern:

Apotex Corp., as the U.S. agent for TorPharm, a Division of Apotex, Inc., is submitting this telephone amendment as per telephone conversation with Marcy Macdonald dated April 23, 1998.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs

RECEIVED
MAY 05 1998
GENERIC DRUGS

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APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL (847) 573-9999 • FAX (847) 573-1001

June 1, 1998

ORIG AMENDMENT
N/Am

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT

RE: ANDA 74-943
Diltiazem Hydrochloride Extended-Release
Capsules, USP (Once-a-day dosage)
240 mg

To Whom It May Concern:

Apotex Corp., as the U.S. agent for TorPharm, a Division of Apotex, Inc., is submitting this amendment in response to the request for information made during the teleconference of May 30, 1998.

A copy of this amendment will follow in the mail.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs

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APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL (847) 573-9999 • FAX (847) 573-1001

FAX AMENDMENT

March 6, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 74-943
Diltiazem Hydrochloride Extended Release Capsules, 240 mg
Fax Amendment-Submission of Confirmation of Patent Noninfringement Notification Receipt

To Whom It May Concern:

As per a March 4, 1998 telephone conversation with Mr Tim Aimes, the Project Manager for the above referenced ANDA, Apotex Corp. as the US agent for TorPharm is submitting confirmation that the patent holders Rhone Poulenc Rorer and Jagetec did receive notice of noninfringement from TorPharm.

The notices of noninfringement were sent by Canadian Certified Mail and the verifications were included in an amendment dated May 1, 1997 page 543 (enclosed). We are aware of the fact that these documents were not submitted by US Certified Mail so we are providing additional documentation from Rhone Poulenc Rorer that the notifications were received and the day on which they were received.

In addition, this is confirmation that within the statutory limits of notification, a lawsuit was not filed by the associated parties in relation to TorPharm's notices of noninfringement.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald
Associate Director,
Regulatory Affairs

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GENERIC DRUGS

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL (847) 573-9999 • FAX (847) 573-1001

FAX AMENDMENT

NEW CORRESP BIOAVAILABILITY

NC/BIO

February 27, 1998

Document Control Room
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #74-943
Diltiazem HCl Extended-Release Capsules , 240 mg
Fax Amendment

Dear Ms. Chamberlin:

As per the deficiency letter of September 29, 1997 and subsequent follow up telephone conversations, Apotex Corp. as the US agent for TorPharm, the ANDA holder, is submitting a 12 capsule dissolution profile comparison between the innovator and the test drug. This dissolution profile follows the USP method as required. All test conditions surrounding the comparison are detailed on the attached report.

In addition, we are also enclosing the test conditions surrounding the dissolution profile comparison performed in buffer that was previously submitted.

Please add this information to our file.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director,
Regulatory Affairs

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GENERIC DRUGS

labels + labeling satisfactory for approval - labeling review drafted 2/6/98 AVzza

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL (847) 573-9999 • FAX (847) 573-1001

January 29, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N/AM

2/3/98 AM noted - To Chemistry reviewer then labeling reviewer for review.

MINOR AMENDMENT

RE: ANDA 74-943
Diltiazem Hydrochloride Extended-release
Capsules USP (Once-a-day dosage), 240 mg

To Whom It May Concern:

Apotex Corp, as the US agent for TorPharm, a Division of Apotex, Inc., is providing the minor amendment for the above-listed ANDA in response to the FDA Deficiency Letter dated November 6, 1997.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director,
Regulatory Affairs

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JAN 30 1998
GENERIC DRUGS

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kk/98/010

NAI
"Non-infringement cert"
To P Rickman for Review
12/13/96

APOTEX USA INC.
1641 BARCLAY BOULEVARD • BUFFALO GROVE • ILLINOIS 60089 • Tel: (847) 541-1141 • Fax: (847) 541-1143

NEW CORRESP

November 27, 1996

NC

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

RE: ANDA # 74-943
Diltiazem Hydrochloride Extended-Release Capsules, USP, 240 mg
Amendment

Dear Sir:

Apotex USA, Inc. as the U.S. agent for TorPharm Inc. is forwarding an amendment to the above referenced ANDA that includes a statement that notice of certification of invalidity or noninfringement of a patent notice has been provided to each person identified under 21 CFR 314.95(a) and that the notice met the content requirements of 21 CFR 314.95(c).

Please feel free to contact me if any further information is required.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Manager, Regulatory Affairs

Madini 12.4.96

APOTEX CORP.

1641 BARCLAY BOULEVARD • BUFFALO GROVE • ILLINOIS 60089 • Tel: (847) 541-1141 • Fax: (847) 541-1143
28101 BALLARD ROAD • LAKE FOREST • ILLINOIS 60045 • Tel: (847) 816-9350 • Fax: (847) 816-9356

MAJOR AMENDMENT

May 1, 1997

ORIG AMENDMENT
N/A

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

RE: ANDA #74-943
Diltiazem HCl Extended-Release Capsules USP, 240 mg
Response to Communications of February 14 and February 24, 1997.
Original Submission

Dear Mr. Sporn:

We are writing in response to your communications of February 14 and February 24, 1997 concerning the above referenced ANDA. We will respond to the items as presented.

We appreciate an expeditious review of this information. If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Manager, Regulatory Affairs

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MAY 0 5 1997
GENERIC DRUGS

APOTEX USA INC.
1641 BARCLAY BOULEVARD • BUFFALO GROVE • ILLINOIS 60089 • Tel: (847) 541-1141 • Fax: (847) 541-1143

August 16, 1996

RECEIVED
AUG 20 1996
GENERIC DRUGS

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

VIA Federal Express

RE: Original ANDA Submission
Diltiazem Hydrochloride Extended Release Capsules, 240 mg

Dear Mr. Sporn:

Pursuant to Section 505(j) of the Federal, Food, Drug and Cosmetic Act as amended September 24, 1984, Apotex USA, Inc. as US agent for TorPharm Inc. of Ontario, Canada, hereby submits an original abbreviated new drug application for Diltiazem Hydrochloride Extended Release Capsules, 240 mg.

We are submitting an archival copy under a blue cover (9 volumes), a chemistry review copy plus an additional copy of the analytical methods section under a red cover and the bioavailability/bioequivalence review section under an orange cover.

Apotex, USA hereby certifies that in accordance with 21 CFR 314.94 (d)(5) a true field copy of the technical sections of this submission under a burgundy cover is also included as this ANDA is being submitted by a foreign applicant.

We appreciate an expeditious review of this application. Please direct any inquiries regarding this application to me at the address listed above.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Manager, Regulatory Affairs