CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-188

CORRESPONDENCE

ALPHAPHARM
PHARMACEUTICALS

ALPHAPHARM
Pty Limited
ACN 002 359 739

Head Office
12 Queen Street
GLEBE NSW 2037
PO Box 36
CAMPERDOWN
NSW 2050
Tel 02 9692 9777
Fax 02 9566 4686

Manufacturing
15 Garnet Street
CAROLE PARK
QLD 4300
Tel 07 3271 3244
Fax 07 3271 5037

7th January, 1999

Dr. D.L. Sporn,
Director of Generic Drugs,
Centre for Drug Evaluation and Research,
MPN-II, HFD-600,
5600 Fishers Lane,
***Rockville,** MD 20857*
USA

Re: Telephone Amendment for Amiodarone Hydrochloride Tablets 200 mg: A.N.D.A. #75-188

Dear Dr. Sporn,

The comments and deficiencies of 6th January 1999 have been addressed in the enclosed Telephone Amendment for Amiodarone Hydrochloride Tablets 200 mg, A.N.D.A. #75-188.

Please find enclosed 2 copies of the Telephone Amendment - an Archival copy (Blue folder) and Chemistry section (Red folder) both with signed 356h forms included.

A copy of this Telephone Amendment was forwarded via facsimile, on the 7th January 1999, to Dr. Brenda Arnwine.

Should there be any further questions regarding the information in this Telephone Amendment, please do not hesitate to contact our USA agent, Par Pharmaceutical, Inc.

Yours sincerely
Alphapharm Pty. Ltd.

Brett Mooney, Ph.D.,
Research and Development Manager

RECEIVED
JAN 12 1999
GENERIC DRUGS

Encl.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-188 APPLICANT: Alphapharm PTY. LTD.

DRUG PRODUCT: Amiodarone HCl 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 pH 5 Sodium Acetate Buffer with 1.0% (w/v) Sodium Lauryl Sulphate at 37° C using USP 23 Apparatus 2 (paddle) at 75 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,

/S/

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

CC:

X:\NEW\FIRMSAM\ALPHAPHARM\ltrs&rev\75188SDA.298
Printed in final on 09/01/98

Endorsements: (Final with Dates)
HFD-658/ F. Nouravarsani, , 9/1/1998
HFD-658/ B. Davit [S] 11/4/98
HFD-650/ D. Conner

BIOEQUIVALENCY - ACCEPTABLE

submission dates: February 12, 1998
July 30, 1998,
August 19, 1998,
August 27, 1998

1. **STUDY AMENDMENT** (STA) 2/12/98 Strength: 200 mg
7/30/98 **Outcome: AC**
+ study Amendments 8/19/98
8/27/98

Outcome Decisions: **AC** - Acceptable

WinBio Comments: The bio-study and dissolution testing amendments were found acceptable.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-188 APPLICANT: Alphapharm PTY. LTD.

DRUG PRODUCT: Amiodarone HCl Tablets, 200 mg

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

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Sincerely yours,

/S/

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

ALPHAPHARM
PHARMACEUTICALS

8th May, 1998

ALPHAPHARM
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Dr Kassandra Sherrod,
OFFICE OF GENERIC DRUGS
Document Control Room,
Metro Park North II,
7500 Standish Place, Room 150
***ROCKVILLE,** MD 20855-2773*

RE: MAJOR AMENDMENT for Amiodarone Hydrochloride Tablets 200 mg: A.N.D.A. #75-188

Dear Dr Sherrod,

Further to your correspondence of March 31st 1998 detailing comments and deficiencies pertaining to the above ANDA, enclosed is the Major Amendment for Amiodarone Hydrochloride Tablets 200 mg.

The Division of Bioequivalence received the Bioavailability Deficiency Response mid February, 1998, and it is currently awaiting review.

The comments and deficiencies in the Chemistry section and Labelling section have been addressed in the enclosed Major Amendment.

Please find enclosed two complete copies of this amendment- Archival copy (Blue Folder) and Chemistry section (Red folder). A signed Certification of the Field copy (Red Folder) as a true copy of the Major Amendment is also included.

In a separate Archival copy (Blue Folder) there is a secure copy of each of the following; final Printed Labels, final Patient Information leaflet, the side by side comparison of Alphapharms' revised patient information leaflet and the original patient information leaflet with annotated differences. Also attached to this folder (in plastic sleeves) are 12 copies of the final Printed Labels and final Patient Information leaflets and 4 copies of the side by side comparison with annotated differences.

The updated stability data is included.

Copies of the deficiency letter and the FDA Form 356h, signed by our U.S. agent, Lipha Pharmaceuticals Inc., are included.

Should you have any further questions regarding the information in this Major Amendment, please do not hesitate to contact our agent, Lipha Pharmaceuticals.

Yours sincerely
ALPHAPHARM PTY. LTD.

Brett Mooney, Ph. D.,
RESEARCH AND DEVELOPMENT MANAGER

Encl.

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7th January, 1999

Dr. D.L. Sporn,
Director of Generic Drugs,
Centre for Drug Evaluation and Research,
MPN-II, HFD-600,
5600 Fishers Lane,
Rockville, MD 20857
USA

Re: ***Telephone Amendment for Amiodarone Hydrochloride Tablets 200 mg: A.N.D.A. #75-188***

Dear Dr. Sporn,

The comments and deficiencies of 6th January 1999 have been addressed in the enclosed Telephone Amendment for Amiodarone Hydrochloride Tablets 200 mg, A.N.D.A. #75-188.

Please find enclosed 2 copies of the Telephone Amendment - an Archival copy (Blue folder) and Chemistry section (Red folder) both with signed 356h forms included.

A copy of this Telephone Amendment was forwarded via facsimile, on the 7th January 1999, to Dr. Brenda Arnwine.

Should there be any further questions regarding the information in this Telephone Amendment, please do not hesitate to contact our USA agent, rmaceutical, Inc.

Yours sincerely
Alphapharm Pty. Ltd.

Brett Mooney, Ph.D.,
Research and Development Manager

Encl.

RECEIVED
JAN 12 1999
GENERIC DRUGS

ALPHAPHARM

PHARMACEUTICALS

FACSIMILE

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Pty Limited
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TO	Dr. Brenda Arnwine Food and Drug Administration
FROM	Dr. Brett Mooney
DATE	7th January 1999
FAX NO.	0011 1 301 4433839
NO. OF PAGES (incl. cover page)	11
SUBJECT	Telephone Amendment for Amiodarone HCl Tablets 200 mg A.N.D.A. #75-188

Dear Dr. Arnwine,

Please find accompanying our response to the Telephone Deficiency for Amiodarone Hydrochloride Tablets 200 mg, A.N.D.A. #75-188, dated 6th January, 1999.

This response is also being forwarded to Dr. D.L. Sporn as an Archival copy (Blue folder) and Chemistry copy (Red folder).

Thank you for your assistance.

Yours sincerely,

Brett Mooney, Ph.D.,
R. & D. Manager

ALPHAPHARM
PHARMACEUTICALS

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16th September, 1997.

Dr. Greg Davis,
FDA Generic Drug Division,
MPN-II, HFD-600
5600 Fishers Lane,
***ROCKVILLE,** MD 20857*
U.S.A.

NEW CORRESP

RE: ORIGINAL ABBREVIATED NEW DRUG APPLICATION FOR AMIODARONE HYDROCHLORIDE TABLETS 200 mg.

Dear Dr Davis,

As discussed during our telephone conversation of the 16th September 1997, please find the Archival Copy (Blue Folder) enclosed.

This folder contains 4 copies of each of the product labels, the PI leaflet, the comparator's PI leaflet and the side by side comparison of the comparator's label and our label. These pages are direct copies from the ANDA with the exception of the proposed PI leaflet and the comparison between label's.

Yours sincerely
ALPHAPHARM PTY. LTD.

Mooney

Brett Mooney, Ph.D.,
RESEARCH AND DEVELOPMENT MANAGER

RECEIVED
OCT 22 1997
GENERIC DRUGS

505(j) ltr OK 10/15/97

NEW CORRESP

ALPHAPHARM
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ACN 002 359 739

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8th October, 1997

Dr. Greg Davis,
Office of Generic Drugs,
Food and Drug Administration,
Regulatory Support Branch,
HFD - 620 Metro Park North II,
7500 Standish Place, Room 150,
Rockville, ***USA***

Dear Dr. Davis,

Re: ANDA #75-188 - Amiodarone Hydrochloride Tablets 200 mg

Further to our conversation of 8th October 1997, please find enclosed 4 copies of the side by side comparison of the Product Information Leaflet of Amiodarone and Cordarone.

Thank you for your assistance with our application.

Yours sincerely,
Alphapharm Pty. Ltd.

Mooney

Brett Mooney, Ph.D.,
Research and Development Manager

Encl.

RECEIVED
OCT 14 1997
GENERIC DRUGS

JAN 12 1998

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-188 APPLICANT: Alphapharm PTY. LTD.

DRUG PRODUCT: Amiodarone HCl Tablets, 200 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You have stated that "results from rejected batches, if any, are not included in the report".

   The rejected runs, if any, and the reason(s) for rejecting should be submitted.

2. The analytes in plasma samples were found to be stable at 22^{o} C for 5.0 hours. Please clarify that the 5.0 hours was an adequate time for the short term stability study of the analytes.

3. The batch size and manufacturing date of the test product were not reported.

4. The CV% was not reported for dissolution testing data at each sampling time point.

5. Please submit the method of assay and calculation of the dissolution testing data.

Sincerely yours,

/S/

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

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-188 APPLICANT: Alphapharm PTY. LTD.

DRUG PRODUCT: Amiodarone HCl Tablets, 200 mg

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3. The batch size and manufacturing date of the test product were not reported.

4. The CV% was not reported for dissolution testing data at each sampling time point.

5. Please submit the method of assay and calculation of the dissolution testing data.

Sincerely yours,

/S/

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

ANDA 75-188

Lipha Pharmaceuticals, Inc.
U.S. Agent for: Alphapharm Pty. Ltd.
Attention: Anita M. Goodman, M.D.
9 West 57th St., Suite 3825
New York, NY 10019-2701

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.

Reference is also made to the telephone conversations dated September 9, September 15, October 1, and October 10 as well as the correspondence dated September 16, October 8, and October 14, 1997.

NAME OF DRUG: Amiodarone Hydrochloride Tablets, 200 mg

DATE OF APPLICATION: August 8, 1997

DATE OF RECEIPT: August 21, 1997

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:

Tim Ames
Project Manager
(301) 827-5848

Sincerely yours,

/S/

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

cc:

date 10/21/97

ALPHAPHARM
PHARMACEUTICALS

8th August, 1997.

505(j)(2)(a) ok
9/20/97

Dr. D.L. Sporn,
Director of Generic Drugs,
Centre for Drug Evaluation and Research,
MPN-II, HFD-600,
5600 Fishers Lane,
***ROCKVILLE**, MD 20857*
U.S.A.

ALPHAPHARM
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RE: ORIGINAL ABBREVIATED NEW DRUG APPLICATION FOR AMIODARONE HYDROCHLORIDE TABLETS 200 mg.

Dear Dr. Sporn,

Pursuant to Section 505 (j) of the Food, Drug and Cosmetics Act, Alphapharm Pty. Ltd. herewith submits an Abbreviated New Drug Application for Amiodarone Hydrochloride Tablets 200 mg. This Application is submitted on our behalf by our agent Lipha Pharmaceuticals Inc.. A letter appointing Lipha Pharmaceuticals Inc. as our Agent in the United States immediately follows this cover letter.

In support of this Application, the information outlined below is provided:

1) *Patent Certification.*

2) *356h Form, signed by our Agent, Lipha Pharmaceuticals Inc*

3) *Index.*

4) *Chemistry, Manufacturing and Controls Information.*

5) *Draft labels/labelling (The copies of the Draft Labels/labelling are presented in a separate folder).*

6) *Methods Validation Package (one copy in the Archival (Blue folder), one copy in the Review (Red) Folder and one copy in the Field Submission (Brown) folder.*

7) *Bioavailability Study of Amiodarone Hydrochloride Tablets 200 mg.*

"Comparative, Randomized, 2-Way Crossover Bioavailability Study of Alphapharm and Wyeth-Ayerst (Cordarone) 200 mg Amiodarone HCl Tablets in Healthy Adult Males Under Fasting Conditions Following Administration of a 400 mg Dose"

Also find enclosed a diskette containing plasma amiodarone and desethylamiodarone concentration and pharmacokinetic data from this study. This information can be found in the files entitled "FDA.1" and "FDA.2". A copy of this data, as written on the diskette, is also enclosed.

Enclosed please find three copies of this application. An Archival copy (Blue Folder), a Review copy divided into two parts: a Chemistry, Manufacturing and Controls data part (Red Folder), and a Bioavailability/bioequivalence data part (Orange Folder); and a Field Submission copy (Maroon Folder) of the Chemistry, Manufacturing and Controls Information for use prior to Preapproval Inspections.

We request that all information in this file be treated as confidential within the meaning of 21 CFR section 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorised member of your Office.

If you should have any questions regarding the information in this submission, please do not hesitate to contact our Agent, Lipha Pharmaceuticals Inc.

Yours Sincerely,
ALPHAPHARM PTY. LTD.

Mooney

Brett Mooney, Ph.D.
RESEARCH AND DEVELOPMENT MANAGER

ALPHAPHARM
PHARMACEUTICALS

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8th August, 1997.

Dr. D.L. Sporn,
Director of Generic Drugs,
Centre for Drug Evaluation and Research
MPN-II, HFD-600
5600 Fishers Lane,
***ROCKVILLE,** MD 20857*
U.S.A.

RE: ORIGINAL ABBREVIATED NEW DRUG APPLICATION FOR AMIODARONE HYDROCHLORIDE TABLETS 200 mg.

Dear Dr. Sporn,

This is to advise that Alphapharm Pty. Ltd. has nominated and appointed Lipha Pharmaceuticals Inc., 9 West 57th Street, Suite 3825, New York, NY 10019-2701, as its U.S. Agent and that Dr. Anita M. Goodman and other counsel in Lipha Pharmaceuticals Inc. are authorised to personally represent Alphapharm Pty. Ltd. in connection with this application and regulatory matters until further notice.

Yours sincerely
ALPHAPHARM PTY. LTD.

Mooney

Brett Mooney, Ph.D.,
RESEARCH AND DEVELOPMENT MANAGER