CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74928

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-928 Date of Submission: July 16, 1996

Applicant's Name: Genpharm Inc.

Established Name: Nicardipine Hydrochloride Capsules, 20 mg and 30 mg

Labeling Deficiencies:

1. GENERAL

   a. Please define the storage recommendations of your product in terms of a specific temperature or range.

   b. In the container specifications for dispensing statement, indicate whether a well-closed or tight container should be used.

2. CONTAINER (100s and 500s)

   a. We encourage the use of boxing, contrasting colors, or other means to differentiate the strengths of your product.

   b. Make the following revision, "USUAL DOSAGE:", rather than "USUAL DOSE".

3. UNIT DOSE CONTAINER

   We note that you have not submitted unit dose container labels. Prepare and submit unit dose container labels for our review and comment.

4. UNIT DOSE CARTON

   See GENERAL comments and comments under CONTAINER.

5. INSERT

   a. GENERAL

      i. Use a lower case "n" to begin "nicardipine" except where the word begins a sentence throughout the text of your insert labeling.

ii. Revise to read "nicardipine hydrochlo[illegible], rather than "nicardipine" in the follo[illegible], locations:

- CLINICAL PHARMACOLOGY, Pharmacokine[illegible] and Metabolism;

  Second sentence of seventh paragraph (first occurrence).

  Last sentences of the eighth and ninth paragraphs.

- CLINICAL PHARMACOLOGY, Effects in Angina Pectoris, second sentence.

- PRECAUTIONS, Use in the Elderly, first sentence.

iii. Revise to read "nicardipine", rather than "nicardipine hydrochloride" in the following locations:

- CLINICAL PHARMACOLOGY, Electrophysiologic Effects, last sentence of the second paragraph.

- PRECAUTIONS, first sentence.

- PRECAUTIONS, Nursing Mothers.

- ADVERSE REACTIONS, first sentence and under Angina, last paragraph.

iv. Use consistent format for headings throughout the package insert, e.g.,

PRECAUTIONS

General
Blood Pressure...

Drug Interactions
Beta-Blockers

v. When expressing a range of values use "to" rather than a hyphen (-).

b. DESCRIPTION

i. Make the following revisions in the last sentence of the second paragraph, "...*m*-nitrophenyl... following structural formula:".

ii. The structural formula appearing in this section is incorrect. We refer you to the USAN and USP Dictionary of Drug Names for guidance.

iii. Make the following revisions to the final paragraph:

Each capsule, for oral administration, contains 20 mg or 30 mg nicardipine hydrochloride. In addition, each capsule contains the following inactive ingredients...

iv. Please include "gelatin" in the listing of inactive ingredients.

v. Include any dyes associated with the imprinting ink used for this product in the listing of inactive ingredients.

vi. Please alphabetize your listing of inactive ingredients.

c. CLINICAL PHARMACOLOGY

i. Pharmacokinetics and Metabolism

a) Make the following revision in the third sentence of the third paragraph, "...133 ng/mL...", ("mL" rather than "mg").

b) Sixth paragraph, third sentence, ...(over 90%) was...

c) Penultimate paragraph, "...mg/dL...", (capital "L").

ii. Hemodynamics

a) Sixth sentence

...usually increased by...

b) Seventh sentence

...significant increases...

iii. Effects in Hypertension (sentence before the table)

...times daily are...

d. CONTRAINDICATIONS

Nicardipine hydrochloride is contraindicated...

e. PRECAUTIONS

i. Use in Patients with impaired renal function

Make the following revision in the last line, "...DOSAGE AND ADMINISTRATION.)".

ii. Drug Interactions

a) Maalox

Revise this subsection heading to read "Aluminum and Magnesium Hydroxides" and make the following revision, "...of an antacid containing 600 mg aluminum hydroxide and 300 mg magnesium hydroxide had...".

b) Make the following revision in the last sentence, "...or *naproxen*...", ("or" not italicized).

iii. Carcinogenesis, Mutagenesis, Impairment of Fertility (First sentence)

...(at concentrations...

iv. Pregnancy

a) Second sentence

...mortality in the treated doe...

b) Last sentence

Nicardipine should be...

f. ADVERSE REACTIONS

i. Revise the section heading to read as above ("REACTIONS", plural).

ii. Angina

Make the following revision in the second sentence, "...placebo (N=310)...".

g. OVERDOSAGE

Make the following revision in the last sentence

of the first paragraph, "...vital signs...".

h. DOSAGE AND ADMINISTRATION

i. Make the following revision throughout this section, "...nicardipine...", rather than "...nicardipine hydrochloride capsules..." [also, see comment iii. a) below].

ii. Make the following revision throughout this section, "...PRECAUTIONS, Drug Interactions ...", rather than "DRUG INTERACTIONS".

iii. Hypertension

a) Revise to read, "The dose of nicardipine hydrochloride should...".

b) Make the following revision in the second sentence, "...effective doses in...", (plural).

c) Make the following revisions in the penultimate sentence of the first paragraph, "...Blood Pressures, INDICATIONS AND USAGE, CLINICAL PHARMACOLOGY, Effects in...".

i. HOW SUPPLIED

See general comments regarding storage conditions.

Please prepare and submit final printed container labels, carton and package insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon further changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

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

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-928

Date of Submission: June 4, 1997

Applicant's Name: Genpharm Inc.

Established Name: Nicardipine Hydrochloride Capsules, 20 mg and 30 mg

LABELING DEFICIENCIES

1. CONTAINER:

   a. 20 mg and 30 mg - 100s and 500s

      General Comment

      We accept computer generated labels as final print, if they are of true size, color and clarity. The labels you have submitted fail to meet these criteria.

   c. 20 mg and 30 mg - unit dose

      Satisfactory in draft.

2. CARTON: (Unit Dose 100s)

   Satisfactory

3. INSERT:

   a. General Comment

      The package insert labeling submitted falls below the minimum threshold of quality for final printed labeling. For computer generated labeling to be acceptable as final print the clarity and readability must be representative of the final printed labeling which will accompany this product on the market.

   b. DESCRIPTION

      i. Include the molecular formula.

ii. Include the dyes present in the imprinting ink in your list of inactive ingredients.

iii. Revise "starch" to read "pregelatinized starch" as in seen in your first submission and/or comment.

c. PRECAUTIONS

Revise "General" and "Drug Interactions" to be consistent with the format of your other subsection headings.

d. ADVERSE REACTIONS

Revise "nicardipine hydrochloride" to read "nicardipine" in the first sentence.

e. DOSAGE AND ADMINISTRATION (Hypertension)

First paragraph

... PHARMACOLOGY, Effects ...
[Replace the period with a comma].

f. HOW SUPPLIED

We note that the color description, [i.e., "light blue/light blue" verses "light blue/dark blue"]. of your 30 mg drug product is not consistent with your physical description of your finished dosage form in the application. Please revise and/or comment.

Please revise your labels and labeling, as instructed above, and submit final printed container labels, unit dose blister labels and package insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/s/ for /

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74928

CORRESPONDENCE

GENPHARM

NAT "Bio Consigned" Jones 1/16/97

BIOAVAILABILITY

NEW CORRESP

NC/Bio

January 03, 1997

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

RE: Bioequivalence Amendment to ANDA for NICARDIPINE HCl CAPSULES 20 & 30 mg

(ANDA No. 74-928)

Dear Sirs:

Please find our response to your letter dated 12/10/96 which concerned bioequivalence information of the above mentioned ANDA.

This amendment contains 2 volumes, and volume 1 is accompanied by a form FDA 356h signed by our US agent, Dr. Anita Goodman of Lipha Pharmaceuticals, Inc., New York, N.Y. Two copies of volume 1, and 2 are submitted, an archival copy (blue colour folder) and review copy (orange colour folder). We also have directed a desk copy to the attention of Ms. Sanchez.

The reply is provided in a question and answer format, based on the comments of the reviewer.

The Contract Research Orgainization produced all the raw data on the form of appendices. These appendices have been rearranged so that the relevant appendix follows each comment or question.

Should you have any questions, please contact the undersigned at 1-800-661-7134.

Thank you for your prompt handling of this submission.

RECEIVED
JAN 06 1997
GENERIC DRUGS

Yours Sincerely,
Genpharm Inc.

Richard K. Pike
Director Regulatory Affairs

Received 1-7-97

GENPHARM INC. 37 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S6 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

ANDA 74-928

FEB 20 1997

Lipha Pharmaceuticals, Inc.
U.S. Agent for Genpharm, Inc.
Attention: Anita M. Goodman
9 West 57th Street, Suite 3825
New York, NY 10019-2701

Dear Madam:

Reference is made to the Abbreviated New Drug Application dated July 16, 1996 for Nicardipine Hydrochloride Capsules, 20 mg and 30 mg; and the additional information dated October 23, 1996 and January 6, 1997.

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

1. The dissolution testing using 0.1N HCl conducted on 20 mg and 30 mg products does not meet the Agency's specifications. Since there is no USP dissolution testing procedure specified for nicardipine hydrochloride capsules, you should conduct the following dissolution testing recommended by the Office:

   900 mL of 0.0333M citrate buffer (pH 4.5),
   using USP 23 apparatus 2 (paddles) at 50 rpm.
   The dissolution testing should meet the following specifications:

   Not less than of the labeled amount of the drug product in the capsule is dissolved in 30 minutes.

   Comparative dissolution data for test and reference products should be submitted. The lot used for the dissolution testing should be the same as the one used in the *in vivo* bioequivalence study.

2. Information on the lot/batch size of the test product, as well as the assay potency and content uniformity data for both the test and reference products 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,

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

GENPHARM

NAI "Bio Amendment" 3/24/97

NEW CORRESP. BIO... NC/AC

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

BIOEQUIVALENCE AMENDMENT

Amended 3/14/97

Re: ANDA #74-928
Nicardipine Capsules
20 mg and 30 mg

This **Bioequivalence Amendment** to our abbreviated new drug application is in response to your letter, dated February 25, 1997, from Rabindra Patnaik, Acting Director, Division of Bioequivalence, which we received on February 25, 1997. As instructed, a copy of this correspondence is presented following the table of contents.

For the reviewers' convenience, each comment made by the reviewer has been restated in **bold** print and is followed by our response.

We have enclosed one (1) archival and one (1) review copy of the application in accordance with 21 CFR § 314.55.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at 1-800-661-7134 or you may contact our U.S. agent, Ms. Anita M. Goodman, at (212) 223-1282.

Yours sincerely

R. A. Pike

Richard Pike
Director, Regulatory Affairs
GENPHARM INC.

14th March 97
(date)

cc: Ms. Anita M. Goodman, M.D.
Executive Vice President & Chief Operating Officer
Lipha Pharmaceuticals, Inc.
9 West 57th St., Suite 3825
New York, NY 10019-2701

RECEIVED
MAR 14 1997
GENERIC DRUGS

Madhu 3/18/97 Rec'd with original

FAX TRANSMITTAL COVER SHEET

FDA/Division of Drug Analysis
1114 Market Street, Room 1002
St. Louis, Missouri 63101

O: Norman Gregory — Telephone No. (301) 827-5849
FAX No. (301) 443-3839

ROM: Myron Rhodes
HFD-920 — Telephone No. (314) 539-2011 x165
FAX No. (314) 539-2113

1 Pages transmitted including this coversheet

Norman,

Please refer to ANDA #74-928 Nicardipine Capsules, the company's response to the reviewer's comments (which you FAXed to me on 12/15/97). Their proposed changes satisfy my concerns. Method is suitable for both control and Regulatory purposes. Again, let me thank you for this feed back.

Myron
12/17/97

GENPHARM

AM noted
To Chemistry Reviewer
for review

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

TELEPHONE AMENDMENT

BIOAVAILABILITY

NC

NEW CORRESP

Re: ANDA #74-928
Nicardipine Capsules
20 mg and 30 mg

This **Telephone Amendment** to our abbreviated new drug application is in response to a telephone conversation on June 25, 1997, between Lizzie Sanchez, Project Manager, and Anita Goodman, U.S. Agent for Genpharm.

For the reviewers' convenience, the comment made by the reviewer has been restated in **bold** print and is followed by our response.

We have enclosed one (1) archival and one (1) review copy of the application in accordance with 21 CFR § 314.55.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at 1-800-661-7134 or you may contact our U.S. agent, Ms. Anita M. Goodman, at (212) 223-1282.

Yours sincerely

R. K. Pike

Richard Pike
Director, Regulatory Affairs
GENPHARM INC.

JUN 25 1997
(date)

cc: Ms. Anita M. Goodman, M.D.
Executive Vice President & Chief Operating Officer
Lipha Pharmaceuticals, Inc.
9 West 57th St., Suite 3825
New York, NY 10019-2701

RECEIVED
JUN 30 1997
GENERIC DRUGS

Madam
7-10-97

GENPHARM

NAI
"Bio Assigned
11/8/96

GENERIC DRUGS

OCT 28 1996

RECEIVED

BIOAVAILABILITY
NEW CORRESP
NC Bio

October 23, 1996

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

Attention: Mr. Larry Galvin

REF: ANDA 74-928
NICARDIPINE HCl Capsules 20 mg & 30 mg

Re: Bioequivalence Data Diskettes

disks removed
10/28/96
Larry A

Further to a call from Mr. Larry Galvin we have included diskettes (total 2 diskettes) containing the Biostudy data for 30 mg Nicardipine HCl capsules. One diskette contains the data for the project no EP143, and the other diskette contains the data for the project no EP131.

Also attached are the hard copies of EP143.inf & EP131.inf on attached diskettes.

Two copies of the information is being submitted - Review Copy (Orange Folder), and Archival Copy (Blue Folder).

We trust the information provided is satisfactory for your review. Should you have any questions or require further clarification please do not hesitate to contact us.

Sincerely,
Genpharm Inc.

Richard K. Pike

Richard K. Pike
Director, Regulatory Affairs

Nadine 10-4-96

GENPHARM INC. 37 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S6 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

FEB 7 1997

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-928 APPLICANT: Genpharm Inc.

DRUG PRODUCT: Nicardipine Hydrochloride Capsules 20 & 30 mg

The deficiencies presented below represent MINOR deficiencies.

Chemistry Deficiencies:

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

Please be advised that the suitability of the proposed dissolution procedure and specification will be established upon completion of review by the Division of Bioequivalence. Samples for methods validation will not be requested until this issue is resolved.

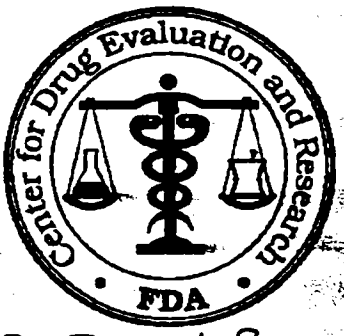
Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.

Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

MINOR AMENDMENT FEB 7 1997

ANDA/~~AADA~~: 74-928



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 ([redacted])

TO: APPLICANT Genpharm, Inc. PHONE 212-223-1282
ATTN: Anita Goodman, M.D. FAX 212-223-1398
U.S. Agent

FROM: Jim Ames PROJECT MANAGER (301-594-0309)

Dear Sir/Madam:

This facsimile is in reference to your abbreviated new drug/ ~~antibiotic~~ application dated July 16, 1996, submitted pursuant to Section 505(j)/507 of the Federal Food, Drug and Cosmetic Act for Nicardipine Hydrochloride Capsules, 20 mg + 30 mg.

Reference is also made to your amendment(s) dated September 27, 1996.

The application is deficient and, therefore not approvable under Section 505/~~507~~ of the Act for the reasons provided in the attachments (7 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactiveated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You h[redacted]en/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing. For further clarification or assistance please contact the Project Manager listed above.

SPECIAL INSTRUCTIONS:

x:\new\ogdadmin\faxtrak\faxcov.min

GENPHARM

RECEIVED
OCT 0 9 1996
GENERIC DRUGS

September 27, 1996

Mr. Jerry Phillips
Director, Division of Labeling and Program Support
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REF: ANDA 74-928
NICARDIPINE HCl Capsules 20 mg & 30 mg

Dear Mr. Phillips:

Reference is made to your letter dated September 13, 1996 regarding Nicardipine HCl Capsules. We would like to amend our ANDA by submitting the additional information you requested. A copy of your letter is included. This amendment consists of 1 volume containing responses to each comment cited in the above mentioned letter. Please find three copies of this amendment - Archival Copy (Blue Folder), Review Copy Chemistry Section (Red Folder) and Field Copy (Burgundy Folder).

A FDA Form 356h signed by our US agent Dr. Anita Goodman, Lipha Pharmaceuticals, Inc. is also presented and is included in **Attachment 1**.

Please note, a Field copy (sections 1 to 5 and 7 to 20) of our original ANDA dated July 16, 1996 was submitted to the Office of Generic Drugs. For your information, **Attachment 2** contains a copy of the original cover letter that accompanied our ANDA, along with a copy of the letter addressed to the District Director. Both these letters indicate that a Field copy was filed.

As requested, a new certification and convictions list with original signatures is provided in **Attachment 3.**

A side-by-side comparison of our proposed labeling with the approved labeling (CARDENE) is included in **Attachment 4.** To facilitate review, all changes between the proposed labeling and approved labeling have been highlighted in yellow. In addition,

we have resubmitted section 5.4 of our ANDA which clearly explains the differences between the proposed labeling and approved labeling.

Currently we do not have available a copy of the approved labeling for the unit dose blister packs, therefore a side-by-side comparison cannot be made with our proposed unit dose blister pack labels. We have, however, included a copy of our proposed labeling for the unit dose blister packs, as was submitted in our original ANDA.

We trust the information provided is satisfactory for your review. Should you have any questions or require further clarification please do not hesitate to contact us.

Sincerely,
Genpharm Inc.

Richard K. Pike
Director, Regulatory Affairs

ANDA 74-928

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

SEP 13 1996

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: Nicardipine Hydrochloride Capsules, 20 mg and 30 mg

DATE OF APPLICATION: July 16, 1996

DATE OF RECEIPT: July 19, 1996

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

For future submissions, please note that foreign applicants should submit the field copy to the Office of Generic Drugs. Refer to Sections 21 CFR 314.94(d)(5) and 314.440 of the Final Rule, published in the Federal Register, September 8, 1993, pages 47351 and 47352.

Although you have provided a debarment certification and a list of convictions as required by the Generic Drug Enforcement Act (GDEA) of 1992 sections 306(k)(1) and (2), these did non contain an original signature. Please provide a new certification and convictions list with original signatures.

We note that you have provided similarities and differences between your container labels and package inserts to the reference listed drug. However, this comparison is incomplete, please provide a side-by-side comparison of your proposed labeling with the approved labeling for the reference listed drug product with all differences annotated and explained [21CFR 314.94(a)(8)(iv)].

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) 594-0305

Sincerely yours,

9/13/96

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

ANDA 74-928
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief, RS 9/11/96 date
HFD-615/HGreenberg, CSO 9/11/96 date
HFD-647/JSimmons, Sup. Chem. _____ date
X:\NEW\FIRMSAM\GENPHARM\LTRS&REV\74928.ACK
F/T bcw/8-26-96
ANDA Acknowledgement Letter!

GENPHARM

July 16, 1996

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

RECEIVED
JUL 19 1996
GENERIC DRUGS

REF: ANDA for NICARDIPINE HCl Capsules 20 mg & 30 mg

Dear Director, Office of Generic Drugs:

Genpharm Inc. submits today an original abbreviated new drug application (ANDA) seeking approval to market Nicardipine HCl Capsules that are equivalent to the listed drug, Cardene(R) (nicardipine hydrochloride) 20 mg and 30 mg Capsules, manufactured by Syntex Laboratories Inc. (USA).

This ANDA consists of 8 volumes. We are filing archival copies (in blue folders) of the ANDA that contain all the information required in the ANDA and technical review copies (in red folders) which contain all the information in the archival copy with the exception of the Bioequivalence section (VI). A separate copy of the Bioequivalence section is provided in orange folders.

For more detailed information of the organization of this ANDA, please refer to the introduction page, "EXECUTIVE SUMMARY -- Organization of the ANDA."

A letter from Genpharm Inc. appointing Dr. Anita Goodman as the Agent in the United States immediately follows the Executive Summary.

This also certifies that, concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) is being submitted to our local district office. This "field copy" is contained in a burgundy folder.

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 authorized member of your Office.

...../2

Should you have any questions regarding the information in this submission, please do not hesitate to call me at 1-800-661-7134.

Thank you for your prompt handling of this submission.

Sincerely,
Genpharm Inc.

Richard K. Pike
Director Regulatory Affairs

GENPHARM

AM filed
To Chemistry Reviewer
for review.
12/12/97

N/AM

TELEPHONE AMENDMENT

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

Re: ANDA #74-928
Nicardipine Capsules
20 mg and 30 mg

This **Telephone Amendment** to our abbreviated new drug application is in response to a telephone conversation on December 8, 1997, between Norman Gregory, Review Chemist, and Anita Goodman, U.S. Agent for Genpharm.

For the reviewers' convenience, the comment made by the reviewer has been restated in **bold** print and is followed by our response.

We have enclosed one (1) archival and one (1) review copy of the application in accordance with 21 CFR § 314.55.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at 1-800-661-7134 or you may contact our U.S. agent, Ms. Anita M. Goodman, at (212) 223-1282.

Yours sincerely

Jo-anne Richardson

Jo-anne Richardson
Regulatory Affairs Associate
GENPHARM INC.

DEC 15 1997
(date)

12/15/97

GENPHARM

Ref. Canada

NC hard copy

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

TELEPHONE AMENDMENT

Re: ANDA #74-928
Nicardipine Capsules
20 mg and 30 mg

This **Telephone Amendment** to our abbreviated new drug application is in response to a telephone conversation on February 4, 1998, between Tim Ames, Project Manager, and Bruce Goddard, U.S. Agent for Genpharm.

For the reviewers' convenience, the comment made by the reviewer has been restated in **bold** print and is followed by our response.

We have enclosed one (1) archival, one (1) review copy and one (1) field copy of the application in accordance with 21 CFR § 314.55. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at 1-800-661-7134 or you may contact our U.S. agent, Ms. Anita M. Goodman, at (212) 223-1282.

Yours sincerely

Jo-anne Richardson

Jo-anne Richardson
Regulatory Affairs Associate
GENPHARM INC.

RECEIVED
MAR 16 1998
(date) MAR 16 1998
GENERIC DRUGS

File ANDA

Telephone Conversation Memorandum

ANDA: 74-928

DRUG: Nicardipine Capsules, 20 mg and 30 mg

FIRM: Genpharm Inc.

PERSONS INVOLVED: Bruce Goodard, Lipha Pharmaceuticals, Inc., US Agent
Tim Ames, FDA

PHONE NUMBER: 212-223-1399

DATE: 2/4/98

Called firm to request the following information about the drug substance at the request of FFang, Dep. Div. Director, Chem II.

Regarding the drug substance:

I indicated this information should be provided as a telephone amendment similar to the 12/15/97 submission. Mr. Goodard took down these requests and indicated he would file the information as soon as it was available.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Branch 6, OGD

cc: ANDA 74-928
Division file (1)
HFD-617/TAmes/PHONE.167
File: X:\new\firmsam\genpharm\telecons\phone.167

RECORD OF TELEPHONE CONVERSATION

DATE: 12/8/97

PRODUCT NAME: Nicardipine Capsules, 20 mg & 30 mg

ANDA/AADA NUMBER: 74-928

FIRM NAME: Genpharm Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Ms. Anita M. Goodman, M.D.
Executive Vice President & Chief Operating Officer
Lipha Pharmaceuticals, Inc.
(212) 223-1282
Fax (212) 223-1398

PARTICIPANT(S) TELEPHONE:
Mr. Norman R. Gregory, Review Chemist, Branch VI , OGD, CDER, FDA

MINUTES OF CONVERSATION:
I called the firms U.S Agent to inform them of the following concerns regarding the Method Validation:

NAME OF OGD REPRESENTATIVE: Norman R. Gregory

SIGNATURE OF OGD REPRESENTATIVE:

DIVISION/BRANCH: Office of Generic Drugs
Division II, Branch VI.

MINUTES PREPARED BY:

Mr. Norman R. Gregory, Review Chemist, Branch VI , OGD, CDER, FDA

GENPHARM

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

MINOR AMENDMENT

NDA
AMENDMENT

Re: ANDA #74-928
Nicardipine Capsules
20 mg and 30 mg

This **Minor Amendment** to our abbreviated new drug application is in response to your fax, dated February 7, 1997, from Tim Ames, Project Manager, which we received on February 10, 1997.

For the reviewers' convenience, each comment made by the reviewer has been restated in **bold** print and is followed by our response.

We have enclosed one (1) archival, one (1) review, and one (1) field copy of the application in accordance with 21 CFR § 314.55. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Ms. Anita M. Goodman at (212) 223-1282 or you may contact Genpharm directly at 1-800-661-7134.

Yours sincerely

Richard Pike
Director, Regulatory Affairs
GENPHARM INC.

JUN 04 1997
(date)

cc: Ms. Anita M. Goodman, M.D.
Executive Vice President & Chief Operating Officer
Lipha Pharmaceuticals, Inc.
9 West 57th St., Suite 3825
New York, NY 10019-2701

RECEIVED
JUN 05 1997
GENERIC DRUGS

GENPHARM

Labeling satisfactory for approval
Review drafted 9/26/97

FPL
AMENDMENT
N, A-M

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

MINOR AMENDMENT

Re: ANDA #74-928
Nicardipine Capsules
20 mg and 30 mg

This **Minor Amendment** to our abbreviated new drug application is in response to your fax, dated August 4, 1997, from Tim Ames, Project Manager, which we received on August 5, 1997.

For the reviewers' convenience, each comment made by the reviewer has been restated in **bold** print and is followed by our response.

We have enclosed one (1) archival, one (1) review, and one (1) field copy of the application in accordance with 21 CFR § 314.55. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Ms. Anita M. Goodman at (212) 223-1282 or you may contact Genpharm directly at 1-800-661-7134.

Yours sincerely

for Richard Pike
Director, Regulatory Affairs
GENPHARM INC.

SEP 05 1997
(date)

cc: Ms. Anita M. Goodman, M.D.
Executive Vice President & Chief Operating Officer
Lipha Pharmaceuticals, Inc.
9 West 57th St., Suite 3825
New York, NY 10019-2701

RECEIVED
SEP 08 1997
GENERIC DRUGS

GENPHARM

NC L. Pa

NEW CORRESP.

LAT 3/12/98

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

TELEPHONE AMENDMENT

Re: ANDA #74-928
Nicardipine Capsules
20 mg and 30 mg

This **Telephone Amendment** to our abbreviated new drug application is in response to a telephone conversation on December 8, 1997, between Norman Gregory, Review Chemist, and Anita Goodman, U.S. Agent for Genpharm.

For the reviewers' convenience, the comment made by the reviewer has been restated in **bold** print and is followed by our response.

We have enclosed one (1) archival and one (1) review copy of the application in accordance with 21 CFR § 314.55.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at 1-800-661-7134 or you may contact our U.S. agent, Ms. Anita M. Goodman, at (212) 223-1282.

Yours sincerely

Jo-anne Richardson

DEC 15 1997

Jo-anne Richardson
Regulatory Affairs Associate
GENPHARM INC.

(date)

RECEIVED
DEC 17 1997
GENERIC DRUGS

AUG 4 1997

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-928 APPLICANT: Genpharm Inc.

DRUG PRODUCT: Nicardipine Hydrochloride Capsules 20 & 30 mg

The deficiencies presented below represent Facsimile deficiencies.

Chemistry Deficiencies:

A. 1. Regarding Laboratory Controls (Finished Dosage):

2. Regarding Stability:

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

We have submitted your methods for validation by FDA laboratories and await the results.

Sincerely yours,

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

FACSIMILE AMENDMENT

AUG 4 1997

ANDA/~~NDA~~ 74-928

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 [redacted]

TO: APPLICANT Genpharm PHONE 212-223-1282
ATTN: Anita Goldman FAX 212-223-1398

FROM: Tim Ames, PROJECT MANAGER (301-827-5849)

Dear ~~Sir~~/Madam:

This facsimile is in reference to your abbreviated new drug/antibiotic application dated 7/16/96, submitted pursuant to Section 505(j)/~~507~~ of the Federal Food, Drug, and Cosmetic Act for Nicardipine HCl Capsules 20mg + 30mg

Reference is also made to your amendment(s) dated June 4, 1997

Attached are 4 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/~~will be~~ notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

X:\new\ogdadmin\faxtrak\faxcov.fax

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Testing and Applied Analytical Development
1114 Market Street, Room 1002
St. Louis, MO 63101
Tel (314) 539-2168
FAX Tel (314) 539-2113

Date: August 26, 1997

From: Henry D. Drew, Ph.D., Deputy Director, Laboratory II (HFD-920)

Subject: **Evaluation of ANDA - MVP for Nicardipine Hydrochloride Capsules (ANDA: 74-928) Submitted by Genpharm, Inc., Etobicoke, Ontario, Canada**

To: Norman Gregory, OGD Review Chemist (HFD-647)

The evaluation of the Nicardipine Hydrochloride Capsules ANDA - MVP has been completed and all methods are acceptable with minor modifications for quality control and regulatory purposes. Please refer to specific comments from the evaluating chemist, Myron O. Rhodes, presented on the attached memorandum and worksheets.

As per program requirements, we are forwarding the original worksheets. We shall **retain the reserve sample for 90-days before disposal of remaining sample**. If you feel that the reserve sample should be held longer, please contact DTAAD.

Henry D. Drew, Ph.D.
Deputy Director, Laboratory II