CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20125

CORRESPONDENCE

K. BONGIOVANNI

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-125

SEP 24 1992

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Attention: Irwin G. Martin, Ph.D.
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48106-1047

Dear Dr. Martin:

Please refer to your December 13, 1990 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Accuretic (quinapril HCl/hydrochlorothiazide) 10 mg/12.5 mg, 20 mg/12.5 mg, 20 mg/25 mg Tablets.

We also acknowledge receipt of your correspondence and amendments dated May 22, July 29, and September 1, 1992.

We have completed our review and find the information presented is inadequate and the application is not approvable. The deficiencies may be summarized as follows:

Under section 505(d) of the Act and 21 CFR 314.125(b), the data and information submitted do not establish safety and efficacy of Accuretic (quinapril HCl/hydrochlorothiazide) Tablets.

In our March 12 to May 22, 1992 inspection of your establishment in Vega Baja, Puerto Rico, significant current good manufacturing practice (CGMP) deviations were found in all manufacturing areas. Until we verify in a subsequent inspection that you are operating in compliance with CGMP regulations (21 CFR Parts 210 and 211), we cannot conclude that the methods, facilities, and controls used for the production of the proposed drug preparation(s) are adequate to assure the identity, strength, quality and purity of the product. Furthermore, this application cannot be approved until there has been a satisfactory inspection of all the other manufacturing facilities associated with this NDA for conformance with CGMP.

Our review of this application revealed no additional deficiencies. If other deficiencies become evident relating to the safety and effectiveness of this drug, they will have to be resolved before approval.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Z. McDONAIN

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-125

NOV 3 1992

Parke-Davis
Pharmaceutical Research Division
Warner-Lambert Company
Attention: Irwin G. Martin, Ph.D.
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48106-1047

Dear Dr. Martin:

We acknowledge the receipt of your communication dated October 23, 1992 requesting withdrawal of your new drug application for Accuretic (quinapril HCl/hydrochlorothiazide) Tablets.

In compliance with your request and as provided under 21 CFR 314.65, the application is withdrawn as of the date of our receipt of your request for withdrawal, October 27, 1992. This withdrawal does not prejudice any future resubmission. You may request that the information contained in the withdrawn application be considered in conjunction with any resubmission.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-125

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Attention: Richard N. Spivey, Pharm.D., Ph.D.
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48106-1047

MAY 15 1992

Dear Dr. Spivey:

Please refer to your December 13, 1990 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Accuretic (quinapril/hydrochlorothiazide) 10 mg/12.5 mg, 20 mg/12.5 mg, and 20 mg/25 mg Tablets.

We also acknowledge receipt of your amendments and correspondence dated February 27, April 24, May 22, June 6, November 4, 13 (two), and 25, and December 18, 1991; January 9, 10, and 27 (two), February 7, 26, and 27, and March 2, 1992.

We have completed the review of this application as submitted with draft labeling. Before the application may be approved, however, it will be necessary for you to submit final printed labeling for the drug.

The enclosed draft labeling should serve as the model for your final printed labeling. In a few places, footnotes in the draft explain the reasons for our choice of language. Other footnotes draw your attention to unresolved questions. Except in these latter areas, your final printed labeling should be essentially identical in content to the enclosed draft. If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

Please submit twelve copies of the printed labels and other labeling, seven of which are individually mounted on heavy weight paper or similar material.

In addition, we would appreciate your submitting copies of the introductory promotional material that you propose to use for this product. Please submit one copy to this division and a second, along with a copy of the package insert, directly to:

Division of Drug Marketing, Advertising and Communication, HFD-240
5600 Fishers Lane, Room 11B06
Rockville, Maryland 20857

Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

We remind you that a satisfactory inspection of your manufacturing facilities for conformance with current good manufacturing practices (CGMP) is required before this application may be approved.

The recommended dissolution method and Q specifications are as follows:

Method - USP apparatus I (basket), 100 rpm, 900 ml of water at 37°C

Q specifications - not less than [ ] minutes for both quinapril and hydrochlorothiazide

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-125

OCT 28 1999

Parke-Davis Pharmaceuticals, Limited
Attention: Mr. Timothy Cunniff
2800 Plymouth Road
Ann Arbor, MI 48105

Dear Mr. Cunniff:

Please refer to your pending April 30, 1999 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Accuretic (quinapril/HCTZ) 10/12.5, 20/12.5 and 20/25mg Tablets.

We also refer to your amendment dated July 14, August 10 and 16 and October 6 and 8, 1999.

To complete our review of the Chemistry, Manufacturing and Controls section of your submission, we request the following:

1. Please state if all USP tests are performed for acceptance of the drug substance hydrochlorothiazide.

2. For drug product, the original submission included a method in addition to retention times for identification that is missing in the resubmission. Please include the test or perform a combination test like for identification.

3. For drug product, please provide the precolumn used for the assay.

4. Please explain how the compliance specification of % was determined since the test was not performed for stability. For stability studies of the product, please include a test as it was in the original NDA.

5. In the DESCRIPTION section of the Package Insert, please explain why some of the inactive ingredients are not listed.

6. In the How Supplied section of the Package Insert, please rewrite the "Manufactured by" section. We suggest the following wording:
Manufactured for:
Parke-Davis Pharmaceuticals, Ltd.
Vega Baja, PR 00640

The same changes should be made to the container labels.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Ms. Zelda McDonald
Regulatory Project Manager
301-594-5333

Sincerely yours,

/S/

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Z. McDonald

JUN 11 1999

NDA 20-125

Parke-Davis Pharmaceuticals Limited
Attention: Irwin G. Martin, Ph.D.
2800 Plymouth Road
Ann Arbor, MI 48105

Dear Dr. Martin:

Please refer to your new drug application (NDA) for Accuretic (quinapril/HCTZ) Tablets.

In reviewing your submission of April 30, 1999, our Biopharmaceutist has raised a number of questions that require your attention. Our comments on your submission are detailed as part of this correspondence (see enclosure).

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure
T Parmelle's 5/21/99 review

cc:
Original NDA
~~HFD-110~~
HFD-110/Z McDonald
sb/6/11/99
filename: 20125gc990611.doc

GENERAL CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-125

Parke-Davis Pharmaceutical Research
Attention: Irwin G. Martin, Ph.D.
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48106-1047

MAY 7 1999

Dear Dr. Martin:

We have received your new drug application (NDA) resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Accuretic (quinapril HCTZ) Tablets

Therapeutic Classification: Standard (S)

Date of Application: April 30, 1999

Date of Receipt: May 3, 1999

Our Reference Number: 20-125

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 1, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 3, 1999.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this fixed dose combination product application at this time.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, please contact:

Ms. Zelda McDonald
Regulatory Health Project Manager
(301) 594-5333

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 20-125
HFD-110/Div. Files
DISTRICT OFFICE
HFD-110/Z McDonald
sb/5/4/99;5/7/99
filename: 20125ac.doc

ACKNOWLEDGEMENT (AC)

KB

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-125

Parke-Davis
Pharmaceutical Research Division
Warner-Lambert Company
Attention Irwin G. Martin, Ph.D.
2800 Plymouth Road
Ann Arbor, MI 48106-1047

Dear Dr. Martin:

Please refer to your new drug application submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for Accuretic (quinapril HCl/hydrochlorothiazide) Tablets.

We have completed our review of the manufacturing and controls section of your submission and have the following recommendations and requests:

1. Please clarify the resolution requirements described under hydrochlorothiazide in the assay for unknown impurities. Are the resolution requirements stated in the submission between hydrochlorothiazide and quinapril (Volume 1.2, Attachment 1, page 071) or between hydrochlorothiazide and quinaprilat (Volume 1.2, Attachment 1, page 070 the preparation of the resolution solution for unknown impurities)?

2. Please submit letters of authorization so we can refer to the files of the manufacturers of and for used in the packaging of the product.

3. Please specify which resin was used for the manufacture of the containers for product stability studies included in the submission, both for the product manufactured and stored in in Vega Baja facility.

4. In the future reports of the stability studies, please consider including resin information in the description of the container/closure system. In addition, please include a commitment that product will be placed in the stability program when there is a change in the container resin used to package the product.

5. Please correct the following typographical errors: Volume 1.2, page 057 the GC column dimensions on page 057 - should be as written and Volume 1.3 page 163 reference to DMF should be and not as written.

6. Please submit the drawing for the blisters/backing packaging system and include the acceptance sampling procedure and classification of defects of blisters.

7. In the system suitability requirements for the assay procedures and content uniformity procedure for quinapril/hydrochlorothiazide tablets, please specify the number of replicate injections necessary for determination of for system precision (all three procedures). In the hydrochlorothiazide procedure, please include representative retention time for chlorothiazide (Volume 1.2, page 156).

8. In the accelerated stability (developmental) data included in the NDA, the amount of degradation (quinaprilat) appeared to be greater (especially in blisters) for the product manufactured in Vega Baja facility than for the product manufactured in When the product was manufactured and stored in the product packaged in blisters had only slightly higher amount of decomposition than the product in containers when stored at accelerated (45°C) conditions. When the product was manufactured in Vega Baja facility, the decomposition for the product in blisters was at least ten times greater than for the product in containers. Please explain. The explanation provided in Volume 1.2, page 45 would hold for Vega Baja facility but not for

9. Additional stability data will be needed, especially for the product manufactured in Puerto Rico, before 24 month expiration date would be acceptable.

10. We reserve comment on the dissolution method and specifications until the Division of Biopharmaceutics has completed its review. Nevertheless, based on our preliminary review, it appears that the specifications can be tighten.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEC 20 '90

NDA 20-125

Parke-Davis
Pharmaceutical Research Division
Warner-Lambert Company
Attention: Irwin G. Martin, Ph.D.
2800 Plymouth Road
Ann Arbor, MI 48105

Dear Dr. Martin:

We have received your new drug application submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the following:

Name of Drug Product: Accuretic (quinapril hydrochloride/hydrochlorothiazide) Tablets

Date of Application: December 13, 1990

Date of Receipt: December 14, 1990

Our Reference Number: NDA 20-125

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b)(1) of the Act on February 12, 1991 in accordance with 21 CFR 314.101(a).

If the application is filed, the due date is June 12, 1991.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Should you have any questions concerning this NDA, please contact:

Ms. Kathleen Dongiovanni
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc
DET-DO
Orig. NDA
HFD-110
HFD-110/CSO
HFD-110/KDongiovanni/12/20/90
clb/12/20/90/3384C
R/D: NMorgenstern/12/20/90

ACKNOWLEDGEMENT

PARKE-DAVIS
Pharmaceutical Research Division
Warner-Lambert Company

March 11, 1991

NDA 20-125
Ref. No. 4
Accuretic (quinapril/
hydrochlorothiazide) Tablets

Re: General Correspondence

Mr. George Scott
Division of Drug Information
Resources (HFD-84)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Mr. Scott:

On December 13, 1990, the Parke-Davis Research Division of Warner-Lambert Company submitted New Drug Application 20-125 for Accuretic (quinapril/hydrochlorothiazide) Tablets. The application was submitted under 21 U.S.C. 355(b)(1).

As indicated in the October 11, 1984 letter regarding the implementation of the Drug Price Competition and Patent Term Restoration Act, we are hereby submitting to you a copy of the patent and exclusivity information provided in NDA 20-125 (Volume 1.1 page 212-216). The information is provided in the suggested format.

Sincerely yours,

Richard N. Spivey

Richard N. Spivey, Pharm.D., Ph.D.
Associate Director
Worldwide Regulatory Affairs

RNS/ma3691

Attachment

cc: Ms. Kathleen Bongiovanni (CSO, Cardio-Renal Drug Products)

NDA ORIG AMENDMENT

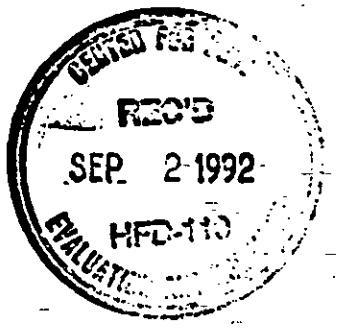
(AF)

ARKE-DAVIS
maceutical Research Division
r-Lambert Company

September 1, 1991

NDA 20-125
Ref. No. 23
Accuretic® (quinapril HCl/
hydrochlorothiazide) Tablets

Re: Dissolution Testing; Final
Printed Labeling



Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug
Products (HFD-110)
Document Control Room 16B-30
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Lipicky:

Reference is made to our pending NDA for Accuretic (quinapril HCl/hydrochlorothiazide) Tablets, NDA 20-125.

Additional reference is made to your letter of May 15, 1992 which recommended dissolution specifications and our response of July 29, 1992. During an August 24, 1992 telephone conversation, Ms. Bongiovanni, of your Division, stated that our proposal for a dissolution specification of %(Q) for both active ingredients in minutes was acceptable as a tentative specification, provided that we commit to collect dissolution data at 15 minutes and 30 minutes on the first 6 to 10 production lots of Accuretic. We, hereby, commit to collect the aforementioned data.

Please also note the Accuretic immediate container labels provided as Final Printed Labeling did not contain the lot number and expiration date since this information is printed on the label at the time of packaging.

Further reference is made to the facsimile transmission from Ms. Bongiovanni on August 13, 1992 (Attachment 1) concerning changes requested to the Final Printed Labeling (FPL) for Accuretic, previously provided in our submission of July 29, 1992. Twelve copies of revised FPL is provided in Attachment 2 which incorporates the requested changes.

ORIGINAL

Upon your receipt of this submission, we have completed all outstanding issues for NDA approval as outlined in your May 15, 1992 approvable letter but for inspection of manufacturing facilities.

Should you have any questions regarding this submission, please feel free to call me at 313/996-7756 or FAX 313/996-7890.

Sincerely,

Irwin G. Martin, Ph.D.
Senior Director
Worldwide Regulatory Affairs

IM/rt/9192.23

Attachment

Desk copy: K. Bongiovanni

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

H.M. James Hung
Division of Biometrics
FDA
Room 18B-45, HFD-713
5600 Fishers Lane
Rockville, MD 20857

October 24, 1991

Dr. Richard N. Spivey
Associate Director
Worldwide Regulatory Affairs
Parke-Davis Pharmaceutical Research
2800 Plymouth Road
P.O.Box 1047
Ann Arbor, Michigan 48106-1047

Dear Dr. Spivey:

Reference is made to your NDA 20-125 for Accuretic Tablets. This is written to request data of two controlled studies, 906-241 and 906-303. Please provide the following information:

patient ID
center ID
baseline characteristics (e.g., gender, race, age, etc.)
all blood pressures taken at baseline
all blood pressures (peak and trough) taken during the treatment period
peak and trough measurements used in your analyses

Data are needed for intent-to-treat and evaluable patient analyses. Please use a 3.5" diskette readable by IBM machine. For any questions, please contact me at (301)-443-2814.

Sincerely,

H.M. James Hung, Ph.D.
Mathematical Statistician

cc: NDA 20-125
HFD-110
HFD-110/K. Bongiovanni ✓
HFD-713/G. Chi