# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20125

## ADMINISTRATIVE DOCUMENTS

RHPM Overview of NDA 20-125
Accuretic (quinapril/HCTZ) 10/12.5, 10/12.5 and 20/25 mg Tablets
Revised December 15, 1999

**Type: 4S**
**Receipt Date: May 3, 1999**
**User Fee Goal Date: March 3, 1999**

BACKGROUND
The original NDA 20-125 for Accuretic was submitted by Parke-Davis on December 13, 1990. FDA issued an "approvable letter" on May 15, 1992 and requested final printed labeling, which was submitted by Parke-Davis on September 1, 1992. FDA issued a "not approvable" letter on September 24, 1992 due to the unavailability of a manufacturing site for the final product. On October 23,1992, Parke-Davis requested that the NDA be withdrawn, and FDA acknowledged this withdrawal on November 3, 1992.

Foreign Marketing History - Accuretic has been approved in 31 countries, marketed in 21.

There is no CANDA.

MEDICAL -
The original studies reviewed by Dr. Dern, March 6 and 12, 1992 were found to be approvable for safety and efficacy although Dr. Dern did not recommended this product for initial therapy. This submission provides information on deaths and nonfatal, serious adverse events that occurred between October 10, 1991 and February 8, 1999. These events were extracted from the Parke-Davis clinical Safety Database for 9 clinical studies ongoing after the second safety update (orig. application) cutoff date and from the Drug Safety Database from postmarketing studies and spontaneous reports.

In his review dated July 28, 1999, Dr. Williams recommended approval. His labeling changes have been incorporated into the draft labeling.

MEDICAL GROUP LEADER MEMO
In his memo dated July 28, 1999, Dr. Chen recommended approval.

STATISTICAL -
In his review dated December 5, 1991, Dr. Hung concluded that this combination product is more effective than the single drugs alone. See review for more details.

BIOPHARMACEUTICS -
In his review dated May 2, 1999, Dr. Parmelee recommended the following:
The food-effect study is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. Comments will be forwarded to the sponsor. The dissolution specifications for both quinapril and hydrochlorothiazide from the combination tablet should be amended to Q not less than minutes. The labeling should be amended as outlined in the comment above. Otherwise, the resubmission of NDA 21-125 meets the Office of Clinical Pharmacology and Biopharmaceutics requirements and is approvable. Dr. Parmelee's review was sent to the firm. Dr. Parmalee's labeling changes have been incorporated into the draft labeling.

PHARMACOLOGY -
IN his review dated March 10, 1992, Dr. DeFelice recommended approval.

CHEMISTRY -
The Chemistry, Manufacturing and Controls section of the withdrawn application has been replaced and updated with this submission. The previous manufacturing site for Accuretic was the Vega Baja, Puerto Rico facility. The Parke-Davis facility at Freiburg, Germany has manufactured quinapril hydrochorlide and HCTZ combination tablets for worldwide markets since the early 1990s. Because of this long

manufacturing history the Freiburg facility was chosen to manufacture tablets for the US market. The formulation and basic manufacturing processes have not changed from the earlier clinical batches. Specifications and test methods are based on those approved in the NDA 19-885 for Accupril. An establishment inspection is scheduled for November 7 – 12, 1999.

In her review dated November 15, 1999, Ms. Cunningham states that this NDA is approvable pending a satisfactory EER report.

In her addendum dated November 30, 1999 to the November 15, 1999 review, Ms. Cunningham states that the sponsor should be reminded of their commitment to monitor water content in the drug product stability studies by performing test. A reminder has been added to the approvable letter.

**Chemistry Review**

Establishment Inspection:
This supplement did not include any new CMC information. EER was acceptable on November 29, 1999.

Methods Validation:
On November 16, 1999, Ms. Cunningham stated that methods validation will be requested upon completion of a satisfactory EER report.

Environmental Assessment:
Granted categorical exclusion.

**Division of Drug Marketing and Communications**

In her comments to the sponsor (FAXed by Ms. McDonald on November 2, 1999 and in the action package under Correspondence/Telecons/FAXes), Ms Norden states that "In the Pharmacodynamics and Clinical Effects section, the through effect of quinapril is described. Would it be possible to describe the trough effect of the combination of quinapril/HCTZ?" During a November 22, 1999 conversation between Msses. Norden and Willard (Regulatory Health Project Manager, Cardio-Renal Division), Ms. Norden stated that, upon reconsideration it is acceptable that the trough effect of the combination product not be placed in the labeling. Dr. Fenichel concurred with this decision.

**CSO Summary**
An approvable letter issued on November 30, 1999. Final Printed Labeling was submitted on December 9, 1999, received December 10, 1999, and is satisfactory.
An approval letter will be drafted for Dr. Lipicky's signature.

/S/
Zelda McDonald, RHPM

/S/
Sandy Birdsong, CSO

cc: Orig. NDA
HFD-110
HFD-111/McDonald

RHPM Overview of NDA 20-125
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This supplement did not include any new CMC information. EER was acceptable on November 29, 1999.

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On November 16, 1999, Ms. Cunningham stated that methods validation will be requested upon completion of a satisfactory EER report.

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**CSO Summary**
Pending an acceptable inspection, to my knowledge there are no other issues that might prevent approval. An approvable letter has been drafted for Dr. Lipicky's signature.

/S/
Zelda McDonald, RHPM

/S/
Sandy Birdsong, CSO

cc: Orig. NDA
HFD-110
HFD-110/McDonald
HFD-110/SBirdsong

K. BONGIOVANNI

CSO Review of Labeling

NDA: 20-125 Accuretic (quinapril HCl/HCTZ) Tablets

SEP 3 1992

Date of submissions: September 1 , 1992 (AF)

Applicant: Parke-Davis

**Background:** On May 15, 1992 we issued an approvable letter for NDA 20-125, asking for final printed labeling essentially identical in content to the enclosed draft labeling. Parke-Davis responded on July 29, 1992 with final printed labeling. The minor changes in the labeling from the enclosed draft labeling were agreed to by Dr. Chen (see CSO Review of Labeling, 8-13-92).

Our current policy for use of combination products combining an ACE inhibitor (with dose-independent, but no dose-dependent side effects) with hydrochlorothiazide (with both dose-dependent and dose-independent side effects) is that one should increase the dose of the ACE inhibitor before adding HCTZ, since one has the risk of the dose-independent side effects with low doses of the ACE inhibitor, and higher doses may give a greater effect with no greater risk of side effects.

The wording in the D & A section for Accuretic did not convey this policy, since it recommended adding HCTZ to quinapril doses of 10 or 20, and the dose range for quinapril monotherapy goes up to 80 mg/day. I pointed this out to Dr. Fenichel, and he and Drs. Temple, Chen, and Lipicky agreed to the following wording:
"Patients whose blood pressures are not adequately controlled with quinapril monotherapy may instead be given ACCURETIC 10/12.5 or 20/12.5. Further increases of either or both components could depend on clinical response. The hydrochlorothiazide dose should generally not be increased until 2 to 3 weeks have elapsed. Patients whose blood pressures are adequately controlled with 25 mg of daily hydrochlorothiazide, but who experience significant potassium loss with this regimen, may achieve blood pressure control with less electrolyte disturbance if they are switched to ACCURETIC 10/12.5 or 20/12.5."

I sent a facsimile transmission to Irwin Martin, Ph.D., at Parke-Davis on August 13, 1992, and asked him to submit FPL that includes this wording.

**Review:** The submitted final printed labeling includes the revised Dosage and Administration section and the changes that we agreed to in the July 29, 1992 submission. In addition, Parke-Davis has committed to collect dissolution data at 15 minutes and 30 minutes on the first 6 to 10 production lots of Accuretic.

**Recommendation:** The final printed labeling is revised as we requested. The Q specification is now settled. We are waiting for Compliance to give us clearance on this product. I will prepare an approval letter for Dr. Lipicky's signature pending word from Compliance.

/S/

Kathleen F. Bongiovanni

9-3-92

cc: NDA 20-125
HFD-110
HFD-111/KBongiovanni
HFD-111/SBenton

DEC 28 1999

RHPM Review of Final Printed Labeling
NDA 20-125

| | |
|---|---|
| Date of Submission: | December 9, 1999 |
| Date of Review | December 15, 1999 |
| Applicant Name: | Parke-Davis |
| Product Name: | Accuretic (quinipril/HCTZ) 10/12.5, 20/12/5, and 20/25 mg Tablets |

Evaluation:
This submission provides for final printed labeling in accordance with our approvable letter dated November 30, 1999.

Recommendation:
The submitted labeling is identical in content to the marked-up labeling that accompanied the Approvable letter dated November 30, 1999, except as follows:

Under Dosage and Administration: the current (December 1999) labeling has been changed in the second sentence to read: "12.5 to 50 mg" instead of 25 to 100 mg.

Under Indications and Usage, the first sentence: the statement, "This fixed combination is not indicated for the initial therapy of hypertension", is not in bold letters.

These changes were agreed upon in a telephone conversation of December 6, 1999 between Zelda McDonald, RHPM, and Dr. Timothy Cuniff of Parke-Davis.

The following minor changes need to be made at the time of the next printing:

Under Adverse Reactions/Postmarketing Experience subsection,

1. In the first sentence, insertion of the word "been" between the words "have" and "reported."

2. Under Skin and Appendages, deletion of the comma between the words "maculopapular" and "rash."

An Approval letter should issue for this application.

Sandra Birdsong, CSO

cc: orig. NDA
HFD-110
HFD-110/Birdsong
HFD-110/Blount
HF-2

13. PATENT AND MARKET EXCLUSIVITY INFORMATION

The subject of this NDA is Accuretic™ quinapril hydrochloride plus hydrochlorothiazide tablets. The NDA is being submitted under 21 U.S.C. 355(b)(1).

This section provides patent information required under section 21 U.S.C. 355(b)(1) and documents the market exclusivity period applicable to Accuretic™ tablets. All information is summarized in the attached table, in the format suggested in your letters dated October 11, 1984, October 31, 1986, and April 28, 1988, on implementation of the Drug Price Competition and Patent Restoration Act. An additional copy of this table will be provided to FDA's Division of Drug Information Resources shortly after the submission date of this NDA.

13.1. Patent Information

There are two effective US patents covering quinapril hydrochloride contained in the Accuretic™ tablets as described in the NDA. All required information regarding these patents is provided in the attached table below. The assignee (owner) of these patents is the Warner-Lambert Company, the parent of the Parke-Davis Pharmaceutical Research Division which is filing this NDA.

Patent 1 (US 4,344,949) claims quinapril hydrochloride, and also claims both a pharmaceutical composition and a use of a compound which includes quinapril hydrochloride.

Patent 2 (US 4,743,450) claims a pharmaceutical composition containing quinapril hydrochloride as the drug component.

13.2. Request and Justification for 3-Year Marketing Exclusivity (NDA 20-125)

Accuretic™ tablets qualify for 3 years exclusivity upon approval. Warner-Lambert Company certifies that the active moieties (quinapril hydrochloride and hydrochlorothiazide) of Accuretic™ (quinapril hydrochloride and hydrochlorothiazide) tablets meet the criteria for this exclusivity period specified in 21 U.S.C. 355(j)(4)(D)(iii) and 355(c)(3)(D)(iii).

Warner-Lambert requests 3 years market exclusivity for Accuretic™ tablets for the following reasons:

1. No drug product containing the same combination of active ingredients, quinapril hydrochloride plus hydrochlorothiazide, has been previously approved for which approval is sought in this application. The active ingredient, hydrochlorothiazide, as a single ingredient has been previously approved.

2. a. Seven new clinical investigations, other than bioavailability or bioequivalence studies, were submitted to support this application. Warner-Lambert Company certifies that, to the best of the applicant's knowledge, these clinical studies have not formed part of the basis of a finding of substantial evidence of effectiveness for a previously approved new drug application.

   b. The new clinical investigations can be found in Section 8 of the application, NDA No. 20-125, filed concurrently herewith.

3. a. A Horvath AM, et al reference* is the only published study or publicly available report of clinical investigations known to the applicant that is relevant to supporting the application.

   b. Warner-Lambert Company certifies that the applicant has thoroughly searched the scientific literature and that the list of published studies and publicly available reports is complete and accurate.

   c. Therefore, Warner-Lambert Company certifies that, in the applicant's opinion, the present application could not have been approved without the seven new clinical investigations. The one published study of pharmacokinetic drug-drug interaction, that is noted in 3a above and that can be found in Vol. 76, page 004505 in NDA 19-885 and corresponds to the research report submitted on Vol. 76, page 004131 in NDA 19-885, is not sufficient to support the approval of the application.

4. Warner-Lambert is the sponsor named in the Form FDA 1571 for IND[ ]under which the seven clinical investigations identified in 2. above were performed.

* Horvath AM, Ferry JJ, Sedman AJ, Colburn WA. Lack of a quinapril-hydrochlorothiazide pharmacokinetic drug-drug interaction in healthy volunteers. J Clin Pharmacol Sep 1987;27:720 (Abstr 61).

PATENT AND MARKET EXCLUSIVITY INFORMATION

FOR

ACCURETIC™ (QUINAPRIL HYDROCHLORIDE PLUS HYDROCHLOROTHIAZIDE) TABLETS

1. Active Ingredients: quinapril hydrochloride and hydrochlorothiazide

2. Strengths: 10 mg/12.5 mg, 20 mg/12.5 mg, and 20 mg/25 mg

3. Trade Name: Accuretic™

4. Dosage Form: Tablets

5. Applicant Firm Name: Warner-Lambert Company
Parke-Davis Pharmaceutical Research Division

6. NDA Number: 20-125

7. Approval Date: Pending

8. Exclusivity: Three years from date of NDA approval

9. Patent Information: Patent 1:
Number: US 4,344,949
Expiration Date: August 17, 1999
Patent Type: Claims active ingredient, composition and use therefor
Assignee (owner): Warner-Lambert Company

The undersigned certifies that quinapril hydrochloride, one of the active ingredients of Accuretic™ (quinapril hydrochloride plus hydrochlorothiazide) tablets is claimed by US Patent 4,344,949, a valid patent. Accuretic™ (quinapril hydrochloride plus hydrochlorothiazide)

tablets are the subject of this application for which approval is being sought under Section 505 of the Federal Food, Drug, and Cosmetic Act.

The undersigned further certifies that US Patent 4,344,949, a valid patent, claims both a pharmaceutical composition and a use of a compound including quinapril hydrochloride, one of the active ingredients of the Accuretic™ (quinapril hydrochloride plus hydrochlorothiazide) tablets. The claimed use is for treating hypertension.

Patent 2:
Number: US 4,743,450
Expiration Date: May 10, 2005
Patent Type: Claims composition containing (a) quinapril hydrochloride as the drug component, (b) an alkaline earth metal carbonate, and (c) a saccharide
Assignee (owner): Warner-Lambert Company

The undersigned certifies that US Patent 4,743,450, a valid patent, claims a pharmaceutical composition which contains (a) quinapril hydrochloride, (b) an alkaline earth metal carbonate, and (c) a saccharide which are ingredients of the Accuretic™ (quinapril hydrochloride plus hydrochlorothiazide) tablets for which approval is being sought.

December 11, 1990
Date

Joan Thierstein
Reg. No. 29,450
WARNER-LAMBERT COMPANY
2800 Plymouth Road
Ann Arbor, MI 48105
T: (313) 996-7190

EXCLUSIVITY SUMMARY FOR NDA # 20-125 SUPPL #_____

Trade Name Accuretic Tablets Generic Name quinapril/HCTZ

Applicant Name Parke-Davis HFD # 110

Approval Date If Known 12/15/99

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /✓/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 3

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

| | | |
|---|---|---|
| NDA# 19-885 | Accupril (quinapril HCl) Tablets | Parke-Davis |
| NDA# 11-835 | Hydrodiuril (hydrochlorothiazide) | MSD |
| NDA# 11-793 | Esidrix (hydrochlorothiazide) | Ciba-Geigy |
| 11-971 | Oretic (hydrochlorothiazide) | Abbott |

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /✓/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /✓/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

906-241, 906-303, 906-340

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? — (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

#3 No ✓

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

#3 No ✓

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

906-241 906-340

906-303 _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ____ YES /✓/ ! NO /___/ Explain: _____

Investigation #2

IND # ____ YES /✓/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

/S/
Signature
Title: Project Manager

7/1/99
Date

/S/
Signature of Office Director

12/15/99
Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

# PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

**NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at time of the last action.**

NDA/BLA # 20-125 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-110 Trade and generic names/dosage form: Accuretic (quinapril | HCTZ) Action: AP AE NA

Applicant Parke-Davis Pharmaceuticals Ltd. Therapeutic Class 45

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication proposed in this application _____

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

**IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS?** ___Yes (Continue with questions) _X_No (Sign and return the form)

**IN WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED?** (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__c. The applicant has committed to doing such studies as will be required.

- __ (1) Studies are ongoing,
- __ (2) Protocols were submitted and approved.
- __ (3) Protocols were submitted and are under review.
- __ (4) If no protocol has been submitted, attach memo describing status of discussions.

__d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__5. **If none of the above apply, attach an explanation, as necessary.**

**ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER?** ___ Yes ___No

**ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.**

This page was completed based on information from _____ (e.g., medical review, medical officer, team leader) Pediatric Studies are not required for combination products.

/S/ 7/8/99

Signature of Preparer and Title Date

cc: Orig NDA/BLA # 20-125
HFD 110 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

**FOR QUESTIONS ON COMPLETING THIS FORM, CONTACT KHYATI ROBERTS, HFD-6 (ROBERTSK)**

NDA 20-125
Accuretic™ (quinapril/HCTZ) Tablets



## ITEM 16.
## DEBARMENT CERTIFICATION

Warner-Lambert Company hereby certifies that it is not debarred, and did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

REQUEST FOR TRADEMARK REVIEW

TO: CDER Labeling and Nomenclature Committee
Attention: Dan Boring, R.Ph., Ph.D., HFD-530
9201 Corporate Blvd. Rm. N 461

FROM: Division of Cardio-Renal Drug Products
Attention: Danute G. Cunningham
HFD-110
Phone: 301-594-5351

DATE: June 16, 1999

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Proprietary Name: Accuretic™ (quinapril and hydrochlorothiazide) Tablets - NDA 20-125

Trademark status:

Company Name: Parke-Davis Pharmaceutical Research

Other proprietary names by the same firm for companion products:
Accupril Tablets

The name was approved by Ken Johnson in 3/12/91. I wanted to check with you if it is still acceptable. The original NDA 20-125 for Accuretic was submitted in December 13, 1990. Due to unavailability of a manufacturing site for the final product, was withdrawn. It is resubmission since they found manufacturing facility at Freiburg, Germany.

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. Dec.96

**Methods Validation has not been requested as of 11/16/99.**

**Parke-Davis requested a categorical exclusion for Accuretic.**
**(See page 22 of Dr. Cunningham's 10/20/99's review) ___**

Z. McDonald
JUL 28 1999

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CDER/ODE-I/DIV CARDIO-RENAL DRUG PRODUCTS

**Date**: 07/28/99
**From**: Shaw T. Chen, M.D., Ph.D., Medical Team Leader, HFD-110
**To**: Director, Division of Cardiorenal Drug Products, HFD-110

**Subject**: NDA 20-125, Quinapril/Hydrochlorothiazide combination, approvability

**Resume**:

This memorandum and the attached materials constitute the Team Leader's recommendation that this re-submitted NDA for quinapril and hydrochlorothiazide (HCTZ) combination be approved.

This application is a resubmission of NDA 20-125. The original submission was deemed approvable on May 15, 1992, but subsequently withdrawn by the sponsor due to lack of manufacturing site for the final product in October of the same year. The sponsor has decided to manufacture the drug at a German facility and has submitted a new CMC section for this NDA. The sponsor did not submit additional efficacy data this time, but did provide the following to support the new package:

In Integrated Summary of Safety (ISS): Summary of serious adverse events (SAEs) in the post-approvable database (during 10/10/91 to 02/08/99), including results of 9 studies with cutoff after the previous Safety Update, post-marketing experiences from 31 foreign countries and literature search by the sponsor.

One clinical pharmacology (food-kinetic effect) study report (Study 955-8)

Updated package insert to reflect the new data

All other information are cross-referenced to the original NDA submission.

## Summary of New Safety Data

During the period between October 1991 and February 1999, there were 7 deaths reported and 62 patients with complaints of SAEs. A rough estimate suggested that accumulated drug exposure were about half million patient-years (see Dr. Williams' review, Section 5.2)

The causes of the 7 deaths were not unusual (3 neoplasm, 1 viral encephalitis, 1 MI and 3 unknown) and there was no alarming trend when added to the accumulated experiences (Table 3 in Section 2.1 of NDA Item 8.3). In the newly submitted data, the most common organ systems involved in SAE's are body as whole (15), cardiovascular (15), skin and appendages (13), and metabolic and nutritional disorders (11) (Table 3, Dr. Williams' review). Of these SAEs (see Sections 5.5 and 5.6 of Dr. Williams' review and NDA Item 8.3, Table 4 in Section 2.2), angioedema (7) and hyponatremia (6) were the most consistently seen. Others were isolated

reports of rare events whose causalities were difficult to determine, but almost all had been listed in the labeling of quinapril and/or HCTZ. Cases reported in the literature (search limited to angioedema, eosinophilic pneumonitis or death) were described by the sponsor in Table 5, Section 3 of Item 8.3 in NDA and reviewed in Dr. Williams' report (Section 5.6). The reports were non-remarkable.

The review team agree that the new safety data do not change the conclusion about the safety of quinapril/HCTZ as a treatment of hypertension.

## Labeling

The revised draft labeling has been further edited by the reviewers. The new package insert was adopted from the 1992 approvable version and updated with changes implemented for the (mostly) quinapril labeling. Data from the new food-pharmacokinetic study and comments by the biopharmaceutical reviewers have been incorporated.

## Conclusion and Recommendation

Accumulated experiences since the previous withdrawal of the original submission still support the efficacy and safety of the combination drug. From the clinical perspective, the application should be approved.

/ / 1st /

/

Shaw T. Chen, M.D., Ph.D.
Medical Team Leader

original: NDA 20-125
cc:
HFD-110
HFD-110/Williams/McDonald
HFD-110/Chen

**FILING MEETING MINUTES**
June 14, 1999

| | |
|---|---|
| NDA Number: | 20-125 |
| Drug Name: | Accuretic (quinapril hydrochloride/hydrochlorothiazide) 10/12.5, 20/12.5, 20/25 mg Tablets |
| Indication: | Hypertension |
| Sponsor: | Parke-Davis Pharmaceuticals |
| Therapeutic Classification: | 4S |
| Date of Application: | April 30, 1999 (Resubmission) |
| Date of Receipt: | May 3, 1999 |
| User Fee Goal: | November 3, 1999 (6 month) |
| User Fee Status: | Paid: April 22, 1999 |
| Patent Information Included? | YES |
| Exclusivity Requested? | YES; 3 years |
| Debarment Statement Included? | YES |
| Financial Disclosure: | YES |
| Submission Complete As Required Under 21 CFR 314.50? | YES |

Attendees:

| | |
|---|---|
| Robert Fenichel, M.D., Ph.D. | Deputy Director, HFD-110 |
| Stephen Fredd, M.D. | Deputy Director, HFD-110 |
| Shaw Chen, M.D., Ph.D. | Team Leader, Medical, HFD-110 |
| Abrahm Karkowsky, M.D., Ph.D. | Team Leader, Medical, HFD-110 |
| Akinwole Williams, M.D. | Medical Officer, HFD-110 |
| Thomas Papoian, Ph.D. | Pharmacologist, HFD-110 |
| Natalia Morgenstern | Chief, Project Management, HFD-110 |
| Zelda McDonald | Regulatory Health Project Manager, HFD-110 |
| James Hung, Ph.D. | Acting Team Leader, Statistics, HFD-710 |
| Lu Cui, Ph.D. | Statistician, HFD-710 |
| Kasturi Srinivasachar, Ph.D. | Team Leader, Chemistry, HFD-810 |
| Danute Cunningham | Chemist, HFD-810 |

**BACKGROUND**

The original NDA 20-125 for Accuretic was submitted by Parke-Davis on December 13, 1990. FDA issued an "approvable letter" on May 15, 1992 and requested final printed labeling, which was submitted by Parke-Davis on September 1, 1992. FDA issued a "not approvable" letter on September 24, 1992 due to the unavailability of a manufacturing site for the final product. On October 23,1992, Parke-Davis requested that the NDA be withdrawn, and FDA acknowledged this withdrawal on November 3, 1992.

The submission contains an archival copy containing 12 volumes and review copes for each technical reviewer. In addition, a field copy of the Chemistry, Manufacturing, and Controls section of this NDA has been sent to the FDA District Office in North Brunswick, New Jersey.

Foreign Marketing History - Accuretic has been approved in 31 countries, marketed in 21.

There is no CANDA.

Assigned Reviewers:

| DISCIPLINE | REVIEWER | EXPECT COMPLETION DATE |
|---|---|---|
| Medical: | Dr. Williams | Mid July |
| Sec. Medical: | Dr. Chen | Mid July |
| Pharmacology: | NA | Completed in original submission |
| Chemist: | Ms. Cunningham | Mid September |
| Env. Assessment: | NA | |
| Statistician: | Dr. Cui | Nothing to review |
| Biopharmaceuticist: | Dr. Parmelee | Completed 5/21/99 |
| Microbiologist: | NA - Tablets | |
| DSI: | NA | Completed in original submission |
| Project Manager: | Ms. McDonald | |

**MEDICAL -**

The original studies reviewed by Dr. Dern, March 6 and 12, 1992 were found to be approvable for safety and efficacy although Dr. Dern did not recommend this product for initial therapy. The current submission provides information on deaths and nonfatal, serious adverse events that occurred between October 10, 1991 and February 8, 1999. These events were extracted from the Parke-Davis clinical Safety Database
for 9 ongoing clinical studies after the second safety update (orig. application) cutoff date and from the Drug Safety Database from postmarketing studies and spontaneous reports.

**STATISTICAL -**

In his review dated December 5, 1991, Dr. Hung concluded that this combination product is more effective than the single drugs alone. See review for more details.

**BIOPHARMACEUTICS -**

In his review dated May 2, 1999, Dr. Parmelee recommended the following:
The food-effect study is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. Comments will be forwarded to the sponsor. The dissolution specifications for both quinapril and hydrochlorothiazide from the combination tablet should be amended to Q not less than minutes. The labeling should be amended as outlined in the comment above. Otherwise, the resubmission of NDA 21-125 meets the Office of Clinical Pharmacology and Biopharmaceutics requirements and is approvable. Dr. Parmelee's review was sent to the firm on June 11, 1999.

**PHARMACOLOGY -**

In his review dated March 10, 1992, Dr. DeFelice recommended approval.

**CHEMISTRY -**

The Chemistry, Manufacturing and Controls section of the withdrawn application has been replaced and updated with this submission. The previous manufacturing site for Accuretic was the Vega Baja, Puerto Rico facility. The Parke-Davis facility at Freiburg, Germany has manufactured quinapril hydrochorlide and HCTZ combination tablets for worldwide markets since the early 1990s. Because of this long manufacturing history the Freiburg facility was chosen to manufacture tablets for the US market. The formulation and basic manufacturing processes have not changed from the earlier clinical batches. Specifications and test methods are based on those approved in the NDA 19-885 for Accupril. An establishment inspection is needed.

Did firm request categorical exclusion for environmental assessment? YES

EIR package transmitted? YES – District Goal Date August 31, 1999

Trade Name Review Requested? YES – Found acceptable March 12, 1991

**MICROBIOLOGY - NA**

**DSI - NA**

**REGULATORY REQUIREMENTS/ORGANIZATION -**
The application, on its face, appears to be well organized and indexed.

The application can be filed.

/S/ 7/7/99

Project Manager, HFD-110

cc:
Orig. NDA
HFD-110
HFD-110/SMatthews

RD:

| | |
|---|---|
| Cunningham | 6/28/99 |
| Srinivasachar | 6/28/99 |
| Cui | 6/29/99 |
| Hung | 7/1/99 |
| Papoian | 7/1/99 |
| Williams | 7/1/99 |
| Karkowsky | 7/1/99 |
| Chen | 7/1/99 |
| Fredd | 7/6/99 |
| Fenichel | 7/6/99 |
| Morgenstern | 7/6/99 |

APR 27 1992

In-House Meeting
April 22, 1992

Purpose: Second Mini-NDA Day to discuss the following applications with Dr. Temple:
NDA 20-033 Lotensin HCT (benazepril/HCTZ) Tablets
NDA 20-125 Accuretic (quinapril/HCTZ) Tablets
NDA 19-807 Kerledex (betaxolol/HCTZ)

**Attendees:**

| | |
|---|---|
| Robert Temple, M.D. | Director, Office of Drug Evaluation I, HFD-100 |
| Raymond Lipicky, M.D. | Director, Div. of Cardio-Renal Drug Products, HFD-110 |
| Robert Fenichel, Ph.D. M.D. | Acting Deputy Director, HFD-110 |
| Shaw Chen, M.D., Ph.D. | Group Leader and Medical Officer, HFD-110 |
| Abraham Karkowsky, M.D. | Group Leader and Medical Officer, HFD-110 |
| Kathleen Bongiovanni | CSO, HFD-111 |
| Zelda McDonald | CSO, HFD-111 |

**Background:**
The applications listed above on our pending list are considered approvable. This is the second meeting to discuss the labeling for combination products. In the first meeting, on April 2, 1992, was held to discuss the data and labeling for each combination to determine if initial therapy labeling was a viable option. After much discussion about the rationale for an initial therapy indication, the meeting ended with Dr. Lipicky stating that he and Dr. Fenichel would have to rethink the rules for initial therapy and work on changing the proposed labeling. The purpose of this meeting was to discuss the labeling that had been revised by Dr. Temple and Dr. Fenichel and revisit the initial therapy issue.

**Meeting:**

ACE inhibitor/thiazide combinations:

Dr. Temple concluded that the labeling should state the following prescribing rationale:

1. You have titrated with the single entities and want to switch to the combination for convenience (standard replacement therapy), or

2. You have given either the diuretic or the ACE inhibitor alone, have not gotten an adequate response, and wish to add the other component using the combination product.

Betaxolol/chlorthalidone:

Dr. Temple concluded that the labeling should state the following prescribing rationale:

1. You have titrated with the single entities and want to switch to the combination for convenience (standard replacement therapy), or

2. You have given either the diuretic or the ß-blocker, have not gotten an adequate response, and wish to add the other component using the combination product.

3. You want to use the combination as initial therapy to avoid dose-dependent side effects such as bradycardia (ß-blocker) and hypokalemia (diuretic); if the low initial dose does not give the desired effect, you could then increase the dose by adding either monotherapy or titrating with the combination.

In order to accurately label the betaxolol/chlorthalidone combination, we need to find out whether there is a 25 mg chlorthalidone on the market that is scored. Dr. Temple was sure there was; Dr. Lipicky thought there was not. (The innovator is not scored. Ms. McDonald has called Kent Johnson (Generics), and he is looking into the matter.)

Dr. Temple said he would like to see the Dosage and Administration section of the labeling before Dr. Lipicky signs the approvable letters for these combinations.

/S/ 4-24-92

Kathleen Bongiovanni, CSO

/S/

Zelda McDonald, CSO

cc: Orig. NDAs
HFD-110
HFD-111/Bongiovanni
HFD-111/McDonald
HFD-111/Benton
Drafted 4/23/92 ZM
R/D: KBongiovanni/4/24/92

K. BONGIOVANNI

APR 9 1992

In-House Meeting
April 2, 1992

Purpose: Mini-NDA Day to discuss the following applications with Dr. Temple:
NDA 20-033 Lotensin HCT (benazapril/HCTZ) Tablets
NDA 20-125 Accuretic (quinapril/HCTZ) Tablets
NDA 19-807 Kerledex (Betaxolol/HCTZ)

Attendees:

| | |
|---|---|
| Robert Temple, M.D. | Director, Office of Drug Evaluation I, HFD-100 |
| Raymond Lipicky, M.D. | Director, Div. of Cardio-Renal Drug Products, HFD-110 |
| Robert Fenichel, Ph.D. M.D. | Acting Deputy Director, HFD-110 |
| Shaw Chen, M.D., Ph.D. | Group Leader and Medical Officer, HFD-110 |
| Natalia Morgenstern | Chief, Project Management Staff, HFD-111 |
| Kathleen Bongiovanni | CSO, HFD-111 |
| Zelda McDonald | CSO, HFD-111 |

Background:
The applications listed above on our pending list are considered approvable. Dr. Fenichel has revised the labeling for benazapril/HCTZ to address the effects of a combination product better; this labeling includes dosing instructions for the use of the fixed combination as initial therapy in certain circumstances. The purpose of the meeting was to discuss the data and labeling for each combination to determine if, in fact, initial therapy labeling is a viable option.

Meeting:

Benazapril/HCTZ and Quinapril/HCTZ

The meeting began with a discussion of the benazapril/HCTZ labeling because labeling for the other initial therapy combinations would be patterned after it.

Dr. Temple began by suggesting some alternate wording for the Dosage and Administration section of the benazapril/HCTZ labeling (see attached).

He also suggested that the Cardio-Renal Advisory Committee be briefed on the new labeling. Dr. Fenichel suggested that it could be discussed at the upcoming meeting during the closed session (May 1, 1992).

Drs. Lipicky, Fenichel, and Chen then gave brief reviews of the data from the factorial trials of the combinations.

Dr. Temple outlined his reasons why a combination product may be approved for initial therapy: it is rational to begin with a combination if the doses of drugs in the combination are not available as monotherapy since alone they do not have a significant effect, or if one wishes to avoid dose-dependent side effects of the components, or if the drugs together offer some benefit (e.g., increased duration of effect or an effect unable to be achieved with either monotherapy at any dose).

Dr. Fenichel said that the effect of 10/12.5 of benazapril/HCTZ is not better than the effect of 40 mg of benazapril alone. Dr. Temple was surprised and asked why one would start with the combination instead of titrating with benazapril alone; since ACE inhibitors have no defined dose-dependent side effects, there is no cost to adding more until the maximal effect is achieved. He said that based on the quinapril data, he did not believe that there was an increase in the duration of the effect.

Dr. Fenichel noted that some patients, such as blacks, will do much better on the combination. Dr. Temple agreed that may be true, but it was not stated in the current labeling.

Dr. Lipicky said that using the combination will ameliorate the hypokalemic effects of hydrochlorothiazide. Dr. Temple countered that one could still titrate through the ACE inhibitor dose range before adding the thiazide.

Dr. Lipicky stated that physicians should have the choice of starting with the components or with the combination as initial therapy.

Dr. Temple thought that instead of using the phrase, "Not for initial therapy" the labeling could say ," is ordinarily not for use as initial therapy" thereby leaving room for use in blacks, or in other patients at the physician's discretion at some point.

Betaxolol/HCTZ 5/12.5 mg & 10/12.5 mg

Dr. Lipicky said that Dr. Temple should read his memo to the file for betaxolol/HCTZ that delineates the "wrinkles" in an otherwise straight-forward approval. He did discuss the following:

1. There is a difference in the bioavailability of all the chlorthalidones on the market, and the Division of Generic Drugs will be removing some of the AB ratings. There is no bioavailability study for Lorex's 12.5 mg chlorthalidone compared with one on the market, however, a 15 mg Thalitone (chlorthalidone), approved some time ago but never commercially distributed, will be on the market soon. The 25 mg Thalitone is scored, however, half a tablet would be more available than the 12.5 chlorthalidone in this combination. He thought this was true because the 25 mg Thalitone is much more bioavailable than 25 mg Hygroton (chlorthalidone), the innovator.

Dr. Temple asked if there were enough data to support the use of the 12.5 mg chlorthalidone and suggested that we find out what was used in the Systolic Hypertension in the Elderly Program (SHEP) study. He was uncomfortable with the idea of forcing the use of a ß-blocker in order to use a lower dose of diuretic and asked if the 12.5 mg chlorthalidone was fully effective. Dr. Lipicky said it was borderline and noted that the labeling would say the same thing as the ACE labeling, i.e., by using the low dose combination one would be avoiding dose dependent side effects such as bradycardia with betaxolol and hypokalemia with chlorthalidone.

2. A large study was done comparing the response of black with white hypertensive patients to the components and the combination product. The difference in response, in that blacks do better on the diuretic than the ß-blocker and *visa versa* for whites, detracts from the initial therapy recommendation.

In light of the discussion of the ACE labeling, the meeting ended with Dr. Lipicky stating that he and Dr. Fenichel would have to rethink the rules for initial therapy and work on changing the proposed labeling.

/S/

4-9-92

Kathleen Bongiovanni, CSO

/S/

Zelda McDonald, CSO

cc: Orig. NDAs
HFD-110
HFD-111/Bongiovanni
HFD-111/McDonald
HFD-111/Benton
Drafted 4/6/92 ZM
4/7/92 KB
RD: HFD-110/Fenichel 4/8/92
HFD-110/Chen 4/8/92
HFD-111/Morgenstern 4/8/92

K·BONGIOVANNI

JAN 2 8 1992

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

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DATE: January 28, 1992

FROM: Kathleen Bongiovanni, CSO, HFD-111 KB 1-28-92

SUBJECT: Accuretic package insert

TO: NDA 20-125 Accuretic (quinapril/HCTZ) Tablets

Richard Spivey, Pharm. D., of Parke-Davis, stopped by today to drop off desk copies of revised SBA pages. In response to a question about the package insert for the combination, I gave him a copy of the wording that we are having all HCTZ-containing drugs add to their package inserts (see attached). Dr. Spivey will include the NTP results in the revised draft package insert for Accuretic.

cc: NDA 20-125
HFD-110
HFD-111/KBongiovanni