

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20125

CHEMISTRY REVIEW(S)

NOV 30 1999

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-125

DATE REVIEWED: 29-Nov-99

REVIEW #: 7

REVIEWER: Danute G. Cunningham

ADDENDUM

In a telephone conversation between Dr. Kasturi Srinivasachar and Dr. Philip Simonson, an agreement was reached to monitor moisture content in the drug product stability studies by performing [] test. (The test was performed on original submission, but was dropped on resubmission.) A shelf-life specification for [] would be established, if appropriate, in addition to the current release criterion of []

Recommendations:

The Applicant should be reminded of their commitment to monitor water content in the drug product stability studies by performing the [] test. A shelf-life acceptance criterion for [] should be established, if appropriate, in addition to the current release limit of []

EER was acceptable on November 29, 1999.

/S/

11-29-99
/S/

81

NOV 15 1993

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-125 **DATE REVIEWED:** 15-Nov-99

REVIEW #: 7 **REVIEWER:** Danute G. Cunningham

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	13-Dec-90	14-Dec-90	19-Dec-90
AMENDMENT (Resubmission)	30-Apr-99	03-May-99	04-May-99
AMENDMENT	08-Nov-99	09-Nov-99	10-Nov-99
AMENDMENT	10-Nov-99	12-Nov-99	15-Nov-99

NAME & ADDRESS OF APPLICANT:
PARKE-DAVIS PHARMACEUTICALS LIMITED
P.O. Box 4119
Vega Baja, Puerto Rico 00694-4119

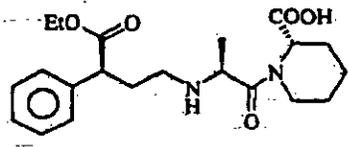
DRUG PRODUCT NAME
Proprietary: ACCURETIC (quinapril hydrochloride and hydrochlorothiazide)
Established: Tablets
Code Name/#: ACCURETIC
Chem.Type/Ther.Class: Quinapril hydrochloride and hydrochlorothiazide
CI-955
4 S

PHARMACOL. CATEGORY/INDICATION: Treatment of hypertension

DOSAGE FORM: Tablets
STRENGTHS: 10/12.5, 20/12.5, and 20/25 mg
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: Rx OTC
SPECIAL PRODUCTS: Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

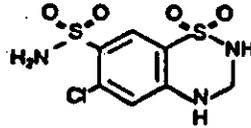
Quinapril Hydrochloride



Chemical Name: (3S-(2[R*(R*)], 3R*)))-2-(2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl)-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid

Molecular Formula: C₂₅H₃₆N₂O₅·HCl **Molecular Weight:** 438.52 (474.97 HCl salt)

Hydrochlorothiazide, USP



Chemical Name: 2H-1,2,4-Benzothiazine-7-sulfonamide, 6-chloro-3,4-dihydro, 1,1-dioxide
 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiazine-7-sulfonamide 1,1-dioxide

Molecular Formula: C₇H₇ClN₂O₄S₂

Molecular Weight: 297.73

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date
DMF/ /	Hydrochlorothiazide		Adequate	Rev. by V. Sayeed on 7/1/99
DMF/ /			Adequate	Listed under Non-Compendial Ingredients
DMF/ /	(orig) Peelable lidding foil Push thru foil		Adequate	Rev. by Dale L. Koble on 8/16/99 (CR #2) Rev. Dale L. Koble on 11/9/97 (CR#6)
DMF/ /	Push thru Foil		Adequate	Rev. by DCunningham on 2/16/99

RELATED DOCUMENTS (if applicable):

NDA 18-885 Accupril (quinapril hydrochloride) Tablets
 IND
 IND

CONSULTS: Biopharmaceutics. On July 30, 1999 Parke-Davis agreed to amend the dissolution specification for both quinapril and hydrochlorothiazide for the combination tablets to Q % in minutes.

CDER Labeling and Nomenclature Committee has reevaluated the name ACCURETIC and found to be acceptable.

REMARKS:

An NDA for Accuretic tablets was previously submitted on December 31, 1990, and withdrawn before approval on October 23, 1992. The NDA was resubmitted on April 30, 1999.

The previous manufacturing site for Accuretic was the Vega Baja, Puerto Rico facility. The Parke-Davis facility at Freiburg, Germany has manufactured quinapril hydrochloride 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.

Foreign marketing - Accuretic has been approved in 31 countries. List is included in the resubmission.

Patent Information was updated.

- A. US Patent # 4,344,949
Expiration date: October 3, 2002,
Patent Type: Compound, Formulation, Method of Use
Patent Owner: Warner-Lambert Company
201 Tabor Road
Morris Plains, NJ 07950

- B. US Patent # 4,743,450
Expiration date: February 24, 2007
Patent Type: Formulation
Patent Owner: Same as above.

Request for Market Exclusivity is included. The company is requesting a 3-year period for market exclusivity for Accuretic Tablets.

Expiration date requested and approved is 24 months, based on data submitted.

EER status : The inspection for _____ plant is ndyet performed. Other plants are acceptable.

Response to IR letter is included. The response was satisfactory.

CONCLUSIONS & RECOMMENDATIONS:

Approvable pending satisfactory EER report.

cc:
Org. NDA 20-125
HFD-110/Division File
HFD-810/CunninghamD
HFD-110/PM/Zelda McDonald
HFD-810/Kasturi Srinivasachar
HFD-810/John Simmons
R/D Init by:

JS/
11-15-99

JS/
Danute G. Cunningham, Review Chemist

filename: 20125R07.NDA

Z. McDonald

OCT 20 1993

NDA 20-125 Rev. 6

page 1

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-125 **DATE REVIEWED:** 19-Oct-99
REVIEW #: 6 **REVIEWER:** Danute G. Cunningham
SUBMISSION TYPE **DOCUMENT DATE** **CDER DATE** **ASSIGNED DATE**
ORIGINAL 13-Dec-90 14-Dec-90 19-Dec-90
AMENDMENT 30-Apr-99 03-May-99 04-May-99
(Resubmission)
AMENDMENT 08-Oct-99 10-Oct-99 13-Oct-99

NAME & ADDRESS OF APPLICANT:

PARKE-DAVIS PHARMACEUTICALS LIMITED
P.O. Box 4119
Vega Baja, Puerto Rico 00694-4119

DRUG PRODUCT NAME

Proprietary:
Established:
Code Name/#:
Chem. Type/Ther. Class:

ACCURETIC (quinapril hydrochloride and hydrochlorothiazide)
Tablets
ACCURETIC
Quinapril hydrochloride and hydrochlorothiazide
CI-955
4 S

PHARMACOL. CATEGORY/INDICATION:

Treatment of hypertension

DOSAGE FORM:

Tablets

STRENGTHS:

10/12.5, 20/12.5, and 20/25 mg

ROUTE OF ADMINISTRATION:

Oral

Rx/OTC:

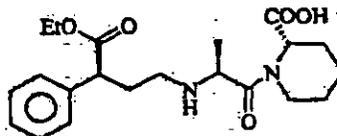
Rx OTC

SPECIAL PRODUCTS:

Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Quinapril Hydrochloride



Chemical Name: (3S-[2(R*(R*), 3R*)]-2-(2-([1-(Ethoxycarbonyl)-3-phenylpropyl]amino)-1-oxopropyl)-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid

Molecular Formula: C₂₅H₃₀N₂O₅·HCl

Molecular Weight: 438.52 (474.97 HCl salt)

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Patent Type: Compound, Formulation, Method of Use
Patent Owner: Warner-Lambert Company
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Expiration date: February 24, 2007
Patent Type: Formulation
Patent Owner: Same as above.

Request for Market Exclusivity is included. The company is requesting a 3-year period for market exclusivity for Accuretic Tablets.

Expiration date requested and approved is 24 months, based on data submitted.

EER status : The inspection for plant is not yet performed. Other plants are acceptable.

CONCLUSIONS & RECOMMENDATIONS:

Approvable pending satisfactory EER report and response to deficiencies.

cc:

Org. NDA 20-125
HFD-110/Division File
HFD-810/CunninghamD/date
HFD-110/PM/Zelda McDonald
HFD-810/Kasturi Srinivasachar
HFD-810/John Simmons
R/D Init by:

JS
10-20-99

JS

Danute G. Cunningham, Review Chemist

filename: 20125R06.NDA

SEP 14 1992

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Evaluation of Chemistry, Manufacturing and Controls Data
Chemist's Review #5

NDA 20-125

Date Completed: September 9, 1992

- A. 1. Applicant: Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105
(Contact Richard N. Spivey, Pharm.D., Ph.D
313-996-7061)
2. Product Name (s): ACCURETIC (quinapril hydrochloride and
hydrochlorothiazide) Tablets
- Proprietary: ACCURETIC
- Nonproprietary: Quinapril hydrochloride
Hydrochlorothiazide
- USAN: Quinapril Hydrochloride
Hydrochlorothiazide
- Compendium: Not yet assigned (quinapril hydrochloride)
Hydrochlorothiazide
- Code Name and/or Number: CI-906 Hydrochloride
PD 109452-2 or CN 109452-2
PD 109452 or CN 109452
(quinapril free base)
CAS-90243-99-5 (quinapril hydrochloride monohydrate)
CAS-85441-61-8 (quinapril)
CAS-82586-55-8 (quinapril hydrochloride)
CAS-58-93-5 (hydrochlorothiazide)
- Chemical Type/Therapeutic Classification: 1C
- Rx/OTC: Rx
- Patent Information:
1. US 4,344,949
Expiration date - August 17, 1999
Patent type - claims active ingredient.
Assignee (owner) - Warner-Lambert Company.

Certification that the above patent claims both a pharmaceutical composition and a use of the compound including quinapril hydrochloride, one of the active ingredients of the ACCURETIC (quinapril hydrochloride plus hydrochlorothiazide) Tablets. The claimed use is for treating hypertension.

2. 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.

3. Dosage Form and Route of Administration:

Oral, tablets - 10/12.5 mg, 20/12.5 mg and 20/25 mg quinapril (as base/hydrochlorothiazide).

10/12.5 mg - pink, elliptical, biconvex film-coated tablets with product logo. Scoreline on one side.

20/12.5-mg - pink, triangular, biconvex film-coated tablets with product logo. Scoreline on one side.

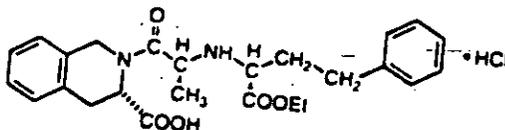
20/25 mg - pink, round, biconvex film-coated tablets with product logo. Scoreline on one side.

4. Pharmacological Category and/or Principal Indications:

Treatment of hypertension. ACCURETIC is a fixed-combination tablet that combines an angiotensin converting enzyme (ACE) inhibitor (quinapril) and a diuretic (hydrochlorothiazide).

5. Structural Formula and Chemical Name:

Quinapril hydrochloride



Chemical Name (s):

[3S-[2[R*(R*)],3R*]]-2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]-amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, monohydrochloride. (USAN)

3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, monohydrochloride, monohydrate, [3S-[R*(R*)]],3R*].

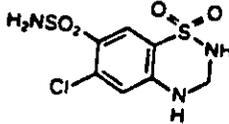
(S)-2-[(S)-N-[(S)-1-Carboxy-3-phenylpropyl]alanyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, 1-ethyl ester, monohydrochloride. (USAN)

Molecular Formula: $C_{12}H_{10}N_2O_2 \cdot HCl$

Molecular Weight: 474.98

MP: 108°C - 115°C

Hydrochlorothiazide



Chemical name(s):

2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro, 1,1-dioxide

6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Molecular Formula: $C_7H_7ClN_2O_2$

Molecular Weight: 297.73

MP: 273-275°C

1. Initial Submission:

Date Submitted: December 13, 1990

Date Received: December 14, 1990

Date to Chemist: December 19, 1990

2. Amendments:

September 1, 1991 - Dissolution testing; final printed labeling.

3. Supporting INDs, NDAs, DMFs and Letters of Authorization:

DMF

DMF
DMF
DMF

DMF
DMF
DMF
DMF

DMF

DMF

IND
IND

June 6, 1991 amendment

DMF

DMF

4. Related Documents (INDs, NDAs, etc.):

None.

5. Firms Involved (Names, Address and Responsibility):

Drug substances:

Quinapril hydrochloride

Manufacturer: Parke-Davis Manufacturing Division
Warner-Lambert Company
188 Howard Avenue
Holland, Michigan 49424 (DMF

Alternate supplier of side chain acid
[(S,S) N-[1-(1-Ethoxycarbonyl-3-phenylpropyl)]alanine]:

(DMF)

Alternate supplier of THIQ acid benzyl ester
- [(S) 1,2 3,4-Tetrahydro-3-isoquinolinecarboxylic acid benzyl
ester p-toluenesulfonic acid salt]:

(DMF)

Hydrochlorothiazide

(DMF)

(DMF)

Supplier:

<u>Drug product:</u>	Manufacturer: Parke-Davis Division of Warner-Lambert Inc. Km. 1.9 Road 689 Vega Baja, Puerto Rico
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(DMF)

Blister packaging (alternate):

(DMF)

- 6. Consults: CDER Labeling and Nomenclature Committee. Name - Accuretic - was acceptable.

C. Remarks:

Quinapril hydrochloride is manufactured by Parke-Davis Manufacturing Division in Holland, Michigan. Hydrochlorothiazide is manufactured by Accupril tablets will be manufactured at Parke-Davis Vega Baja facility.

Consult for the naming of the product - ACCURETIC - was requested on February 13, 1991. Name was acceptable (3/12/91).

Since the product manufacturing facility was ready for inspection in February, 1992, establishment inspections were requested for the firms listed under Facilities on February 3, 1992. EI report has not been received as of 9/9/92.

Methods validation was requested on 7/11/91. DET-DO and DDA will be validating the methodology. Report from DDA was received on 7/22/92. DET-DO - no report as of 9/9/92.

Environmental assessment report is included. It addresses the points specified in 21 CFR §25.31a.

9/1/92 amendment - final printed labeling is included. Satisfactory for DESCRIPTION and HOW SUPPLIED sections. Accuretic immediate container labels - lot number and expiration date is printed on the label at the time of the packaging.

9/1/92 amendment included a commitment to collect dissolution data at and minutes on the first 6 to 10 production lots of Accuretic before final specification for dissolution will be made. Tentative dissolution specification is % for both active ingredients in minutes.

D. Conclusions and/or Recommendations:

Manufacturing and controls data is satisfactory except for the establishment inspections which are still outstanding.

ISI

Danute G. Cunningham

cc:
Orig.
HFD-110
HFD-110/CSO
HFD-110/DGCunningham
N20125R5

u/ ISI 9/14/92

Aug 17 1992

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Evaluation of Chemistry, Manufacturing and Controls Data
Chemist's Review #4

NDA 20-125

Date Completed: August 12, 1992

A. 1. Applicant: Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105
(Contact Richard N. Spivey, Pharm.D., Ph.D
313-996-7061)

2. Product Name (s): ACCURETIC (quinapril hydrochloride and hydrochlorothiazide) Tablets

Proprietary: ACCURETIC

Nonproprietary: Quinapril hydrochloride
Hydrochlorothiazide

USAN: Quinapril Hydrochloride
Hydrochlorothiazide

Compendium: Not yet assigned (quinapril hydrochloride)
Hydrochlorothiazide

Code Name and/or Number: CI-906 Hydrochloride
PD 109452-2 or CN 109452-2
PD 109452 or CN 109452
(quinapril free base)
CAS-90243-99-5 (quinapril hydrochloride monohydrate)
CAS-85441-61-8 (quinapril)
CAS-82586-55-8 (quinapril hydrochloride)
CAS-58-93-5 (hydrochlorothiazide)

Chemical Type/Therapeutic Classification: 1C

Rx/OTC: Rx

Patent Information:

- 1. US 4,344,949
Expiration date - August 17, 1999
Patent type - claims active ingredient.
Assignee (owner) - Warner-Lambert Company.

Certification that the above patent claims both a pharmaceutical composition and a use of the compound including quinapril hydrochloride, one of the active ingredients of the ACCURETIC (quinapril hydrochloride plus hydrochlorothiazide) Tablets. The claimed use is for treating hypertension.

2. 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.

3. Dosage Form and Route of Administration:

Oral, tablets - 10/12.5 mg, 20/12.5 mg and 20/25 mg quinapril (as base/hydrochlorothiazide).

10/12.5 mg - pink, elliptical, biconvex film-coated tablets with product logo. Scoreline on one side.

20/12.5 mg - pink, triangular, biconvex film-coated tablets with product logo. Scoreline on one side.

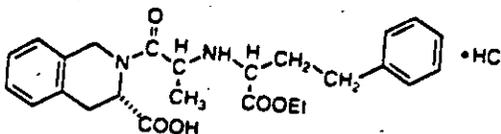
20/25 mg - pink, round, biconvex film-coated tablets with product logo. Scoreline on one side.

4. Pharmacological Category and/or Principal Indications:

Treatment of hypertension. ACCURETIC is a fixed-combination tablet that combines an angiotensin converting enzyme (ACE) inhibitor (quinapril) and a diuretic (hydrochlorothiazide).

5. Structural Formula and Chemical Name:

Quinapril hydrochloride



Chemical Name (s):

[3S-[2(R*(R*)),3R*]]-2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]-amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, monohydrochloride. (USAN)

3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, monohydrochloride, monohydrate, [3S-(R*(R*)),3R*].

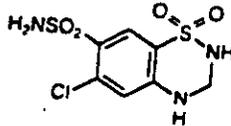
(S)-2-[(S)-N-[(S)-1-Carboxy-3-phenylpropyl]alanyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, 1-ethyl ester, monohydrochloride. (USAN)

Molecular Formula: $C_{12}H_{10}N_2O_4 \cdot HCl$

Molecular Weight: 474.98

MP: 108°C - 115°C

Hydrochlorothiazide



Chemical name(s):

2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro, 1,1-dioxide

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Molecular Formula: $C_7H_7ClN_2O_4S_2$

Molecular Weight: 297.73

MP: 273-275°C

1. Initial Submission:

Date Submitted: December 13, 1990

Date Received: December 14, 1990

Date to Chemist: December 19, 1990

2. Amendments:

July 29, 1992 Response to FDA letter of 5/15/92

3. Supporting INDs, NDAs, DMFs and Letters of Authorization:

DMF

DMF
DMF
DMF

DMF
DMF
DMF
DMF

DMF

DMF

IND
IND

June 6, 1991 amendment
DMF

DMF

4. Related Documents (INDs, NDAs, etc.):

None.

5. Firms Involved (Names, Address and Responsibility):

Drug substances:

Quinapril hydrochloride.

Manufacturer: Parke-Davis Manufacturing Division
Warner-Lambert Company
188 Howard Avenue
Holland, Michigan 49424 (DMF)

Alternate supplier of side chain acid
[(S,S) N-[1-(1-Ethoxycarbonyl-3-phenylpropyl)]alanine]:

(DMF 6875)

Alternate supplier of THIQ acid benzyl ester
- [(S) 1,2 3,4-Tetrahydro-3-isoquinolinecarboxylic acid benzyl
ester p-toluenesulfonic acid salt]:

(DMF)

Hydrochlorothiazide Manufacturer:

(DMF)

Manufacturing facility:

(DMF)

Supplier:

Drug product:

(DMF)

Blister packaging (alternate):

(DMF)

6. Consults: CDER Labeling and Nomenclature Committee.

C. Remarks:

Quinapril hydrochloride is be manufactured by Parke-Davis Manufacturing Division in Holland, Michigan. Hydrochlorothiazide is manufactured by

Accupril tablets will be manufactured at Parke-Davis Vega Baja facility.

Consult for the naming of the product - ACCURETIC - was requested on February 13, 1991. Name was acceptable (3/12/91).

Since the product manufacturing facility will be ready for inspection in February, 1992, establishment inspections were requested for the firms listed under Facilities on February 3, 1992. EI report has not been received as of 8/12/92.

Methods validation was requested on 7/11/91. DET-DO and DDA will be validating the methodology. Report from DDA was received on 7/22/92. DET-DO - no report as of 8/12/92.

Enviro.ental assessment report is included. It addresses the points specified in 21 CFR §25.31a.

7/29/92 amendment - final printed labeling and response to the FDA dissolution recommendation.

D. Conclusions and/or Recommendations:

After approval, a commitment to perform dissolution at two testing intervals (min as per FDA recommendation and min as per applicant's request) on 6 to 10 production lots is needed. In addition, need information if lot # and expiration dating is applied to Unit Dose labels and Unit dose cartons at the time of the manufacture.

cc:
Orig.
HFD-110
HFD-110/CSO
HFD-110/DGCunningham
N20125R4

151
Danute G. Cunningham

151
8-14-92

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Evaluation of Chemistry, Manufacturing and Controls Data
Chemist's Review #3

NDA 20-125

Date Completed: February 5, 1992

A. 1. Applicant: Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105
(Contact Richard N. Spivey, Pharm.D., Ph.D
313-996-7061)

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Compendium: Not yet assigned (quinapril hydrochloride)
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(quinapril free base)
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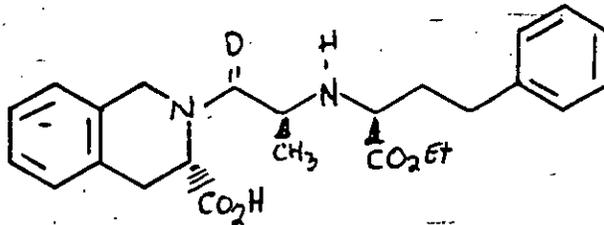
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Chemical Name (s):

[3S-[2[R*(R*)],3R*]]-2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]-amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, monohydrochloride. (USAN)

3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, monohydrochloride, monohydrate, [3S-[R*(R*)]],3R*].

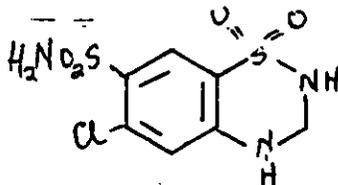
(S)-2-[(S)-N-[(S)-1-Carboxy-3-phenylpropyl]alanyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, 1-ethyl ester, monohydrochloride. (USAN)

Molecular Formula: $C_{23}H_{30}N_2O_5 \cdot HCl$

Molecular Weight: 474.98

MP: 108°C - 115°C

Hydrochlorothiazide



Chemical name(s):

2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro, 1,1-dioxide

6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Molecular Formula: $C_7H_8ClN_2O_2S_2$

Molecular Weight: 297.73

MP: 273-275°C

1. Initial Submission:

Date Submitted: December 13, 1990

Date Received: December 14, 1990

Date to Chemist: December 19, 1990

2. Amendments:

June 6, 1991 Response to FDA letter of 3/8/91
December 18, 1991 SBA

3. Supporting INDs, NDAs, DMFs and Letters of Authorization:

DMF

DMF
DMF
DMF

DMF
DMF
DMF
DMF

DMF

DMF

IND
IND

June 6, 1991 amendment

DMF

DMF

4. Related Documents (INDs, NDAs, etc.):

None.

5. Firms Involved (Names, Address and Responsibility):

Drug substances:

Quinapril hydrochloride

Manufacturer: Parke-Davis Manufacturing Division
Warner-Lambert Company
188 Howard Avenue
Holland, Michigan 49424 (DMF)

Alternate supplier of side chain acid
[(S,S) N-(1-(1-Ethoxycarbonyl-3-phenylpropyl)alanine):

(DMF)

Alternate supplier of THIQ acid benzyl ester
- [(S) 1,2 3,4-Tetrahydro-3-isoquinolinecarboxylic acid benzyl
ester p-toluenesulfonic acid salt]:

(DMF :)

Hydrochlorothiazide Manufacturer:

(DMF

Supplier:

Drug product:

(DMF

Blister packaging (alternate):

(DMF

6. **Consults:** CDER Labeling and Nomenclature Committee.

C. **Remarks:**

Quinapril hydrochloride is be manufactured by Parke-Davis Manufacturing Division in Holland, Michigan. Hydrochlorothiazide is manufactured by

Accupril tablets will be manufactured at Parke-Davis Vega Baja facility.

Consult for the naming of the product - ACCURETIC - was requested on February 13, 1991. Name was acceptable (3/12/91).

Since the product manufacturing facility will be ready for inspection in February, 1992, establishment inspections were requested for the firms listed under Facilities on February 3, 1992.

Methods validation was requested on 7/11/91. DET-DO and DDA will be validating the methodology. No reports received as of 2/5/92.

Environmental assessment report is included. It addresses the points specified in 21 CFR §25.31.

December 18, 1991 - SBA - manufacturing and controls section is satisfactory with the exception of the section titled E. Establishment and Pre-Approval Inspections. The inspections are in progress and have not been completed as yet.

D. Conclusions and/or Recommendations:

NAI. Responses to the deficiencies were satisfactory.

ISI
Danute G. Cunningham

cc:
Orig.
HFD-110
HFD-110/CSO
HFD-110/DGCunningham
N20125R3

ISI
2-7-92

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Evaluation of Chemistry, Manufacturing and Controls Data
Chemist's Review #2

NDA 20-125

Date Completed: June 26, 1991

A. 1. Applicant: Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105
(Contact Richard N. Spivey, Pharm.D., Ph.D
313-996-7061)

2. Product Name (s): ACCURETIC (quinapril hydrochloride and
hydrochlorothiazide) Tablets

Proprietary: ACCURETIC

Nonproprietary: Quinapril hydrochloride
Hydrochlorothiazide

USAN: Quinapril Hydrochloride
Hydrochlorothiazide

Compendium: Not yet assigned (quinapril hydrochloride)
Hydrochlorothiazide

Code Name and/or Number: CI-906 Hydrochloride
PD 109452-2 or CN 109452-2
PD 109452 or CN 109452
(quinapril free base)
CAS-90243-99-5 (quinapril hydrochloride monohydrate)
CAS-85441-61-8 (quinapril)
CAS-82586-55-8 (quinapril hydrochloride)
CAS-58-93-5 (hydrochlorothiazide)

Chemical Type/Therapeutic Classification: 1C

Rx/OTC: Rx

Patent Information:

- 1. US 4,344,949
Expiration date - August 17, 1999
Patent type - claims active ingredient.
Assignee (owner) - Warner-Lambert Company.

Certification that the above patent claims both a pharmaceutical composition and a use of the compound including quinapril hydrochloride, one of the active ingredients of the ACCURETIC (quinapril hydrochloride plus hydrochlorothiazide) Tablets. The claimed use is for treating hypertension.

2. 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.

3. Dosage Form and Route of Administration:

Oral, tablets - 10/12.5 mg, 20/12.5 mg and 20/25 mg quinapril (as base/hydrochlorothiazide).

10/12.5 mg - pink, elliptical, biconvex film-coated tablets with product logo. Scoreline on one side.

20/12.5 mg - pink, triangular, biconvex film-coated tablets with product logo. Scoreline on one side.

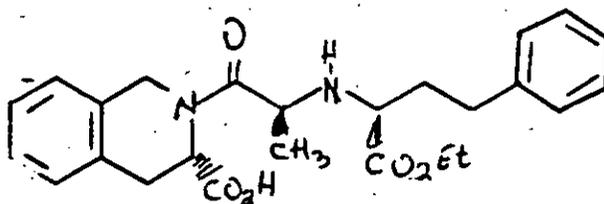
20/25 mg - pink, round, biconvex film-coated tablets with product logo. Scoreline on one side.

4. Pharmacological Category and/or Principal Indications:

Treatment of hypertension. ACCURETIC is a fixed-combination tablet that combines an angiotensin converting enzyme (ACE) inhibitor (quinapril) and a diuretic (hydrochlorothiazide).

5. Structural Formula and Chemical Name:

Quinapril hydrochloride



Chemical Name (s):

[3S-[2[R*(R*)],3R*]]-2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]-amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, monohydrochloride. (USAN)

3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, monohydrochloride, monohydrate, [3S-[R*(R*)]],3R*].

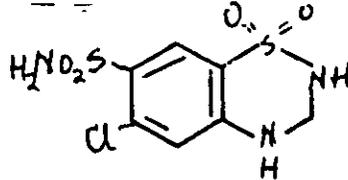
(S)-2-[(S)-N-[(S)-1-Carboxy-3-phenylpropyl]alanyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, 1-ethyl ester, monohydrochloride. (USAN)

Molecular Formula: $C_{22}H_{30}N_2O_3 \cdot HCl$

Molecular Weight: 474.98

MP: 108°C - 115°C

Hydrochlorothiazide



Chemical name(s):

2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro, 1,1-dioxide

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Molecular Formula: $C_7H_7ClN_2O_2S_2$

Molecular Weight: 297.73

MP: 273-275°C

1. Initial Submission:

Date Submitted: December 13, 1990

Date Received: December 14, 1990

Date to Chemist: December 19, 1990

2. Amendments:

June 6, 1991 Response to FDA letter of 3/8/91

3. Supporting INDs, NDAs, DMFs and Letters of Authorization:

DMF

DMF
DMF
DMF

DMF
DMF
DMF
DMF

DMF

DMF

IND
IND

June 6, 1991 amendment
DMF

DMF

4. Related Documents (INDs, NDAs, etc.):

None.

5. Firms Involved (Names, Address and Responsibility):

Drug substances:

Quinapril hydrochloride (reference - NDA 19-885)

Manufacturer: Parke-Davis Manufacturing Division
Warner-Lambert Company
188 Howard Avenue
Holland, Michigan 49424 (DMF)

Alternate supplier of side chain acid
[(S,S) N-[1-(1-Ethoxycarbonyl-3-phenylpropyl)]alanine]:

(DMF)

Alternate supplier of THIQ acid benzyl ester
- [(S) 1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid benzyl
ester p-toluenesulfonic acid salt]:

(DMF)

Hydrochlorothiazide Manufacturer:

(DMF

Manufacturing facility:

(DMF

Supplier:

Drug product:

(DMF

Blister packaging (alternate):

(DMF

6. Consults: CDER Labeling and Nomenclature Committee.

C. Remarks:

Quinapril hydrochloride is to be manufactured by Parke-Davis Manufacturing Division in Holland, Michigan. Hydrochlorothiazide is manufactured by

Accupril tablets will be manufactured at Parke-Davis Vega Baja facility.

Consult for the naming of the product - ACCURETIC - was requested on February 13, 1991. Name was acceptable (3/12/91).

Establishment Inspections were requested for the firms listed under Facilities on February 13, 1991. No response as of June 26, 1991.

Methods validation will be requested.

Environmental assessment report is included. It addresses the points specified in 21 CFR §25.31a.

D. Conclusions and/or Recommendations:

NAI. Responses to the deficiencies were satisfactory.

/S/

Danute G. Cunningham

cc:
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HFD-110
HFD-110/CSO
HFD-110/DGCunningham
N20125R2

/S/
0 6/17/90

BONGIOVANNI

FEB 21 1991

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Evaluation of Chemistry, Manufacturing and Controls Data
Chemist's Review #1

NDA 20-125

Date Completed: February 15, 1991

A. 1. Applicant: Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105
(Contact Richard N. Spivey, Pharm.D., Ph.D
313-996-7061)

2. Product Name (s): ACCURETIC (quinapril hydrochloride and
hydrochlorothiazide) Tablets

Proprietary: ACCURETIC

Nonproprietary: Quinapril hydrochloride
Hydrochlorothiazide

USAN: Quinapril Hydrochloride
Hydrochlorothiazide

Compendium: Not yet assigned (quinapril hydrochloride)
Hydrochlorothiazide

Code Name and/or Number: CI-906 Hydrochloride
PD 109452-2 or CN 109452-2
PD 109452 or CN 109452
(quinapril free base)
CAS-90243-99-5 (quinapril hydrochloride monohydrate)
CAS-85441-61-8 (quinapril)
CAS-82586-55-8 (quinapril hydrochloride)
CAS-58-93-5 (hydrochlorothiazide)

Chemical Type/Therapeutic Classification: 1C

Rx/OTC: Rx

Patent Information:

1. US 4,344,949
Expiration date - August 17, 1999
Patent type - claims active ingredient.
Assignee (owner) - Warner-Lambert Company.

Certification that the above patent claims both a pharmaceutical composition and a use of the compound including quinapril hydrochloride, one of the active ingredients of the ACCURETIC (quinapril hydrochloride plus hydrochlorothiazide) Tablets. The claimed use is for treating hypertension.

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 Expiration date - May 10, 2005
 Patent type - claims composition containing
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 (b) an alkaline earth metal carbonate, and
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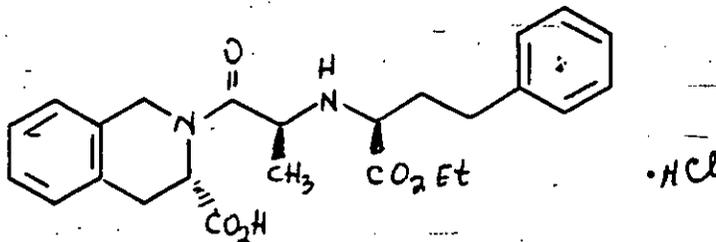
20/25 mg - pink, round, biconvex film-coated tablets with product logo. Scoreline on one side.

4. Pharmacological Category and/or Principal Indications:

Treatment of hypertension. ACCURETIC is a fixed-combination tablet that combines an angiotensin converting enzyme (ACE) inhibitor (quinapril) and a diuretic (hydrochlorothiazide).

5. Structural Formula and Chemical Name:

Quinapril hydrochloride



Chemical Name (s):

[3S-[2[R*(R*)],3R*]]-2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, monohydrochloride. (USAN)

3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, monohydrochloride, monohydrate, [3S-[R*(R*)]],3R*].

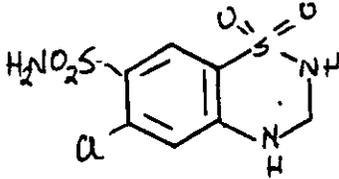
(S)-2-[(S)-N-[(S)-1-Carboxy-3-phenylpropyl]alanyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, 1-ethyl ester, monohydrochloride. (USAN)

Molecular Formula: $C_{25}H_{30}N_2O_5 \cdot HCl$

Molecular Weight: 474.98

MP: 108°C - 115°C

Hydrochlorothiazide



Chemical name(s):

2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro, 1,1-dioxide

6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Molecular Formula: $C_7H_8ClN_3O_4S_2$

Molecular Weight: 297.73

MP: 273-275°C

1. Initial Submission:

Date Submitted: December 13, 1990

Date Received: December 14, 1990

Date to Chemist: December 19, 1990

2. Amendments: None.

3. Supporting INDs, NDAs, DMFs and Letters of Authorization:

DMF

DMF
DMF
DMF

DMF
DMF
DMF
DMF

DMF

DMF

IND
IND

4. Related Documents (INDs, NDAs, etc.):

None.

5. Firms Involved (Names, Address and Responsibility):

Drug substances:

Quinapril hydrochloride

Manufacturer: Parke-Davis Manufacturing Division
Warner-Lambert Company
188 Howard Avenue
Holland, Michigan 49424 (DMF)

Alternate supplier of side chain acid
[(S,S)-N-[1-(1-Ethoxycarbonyl-3-phenylpropyl)]alanine]

DMF

Alternate supplier of THIQ acid benzyl ester
- [(S) 1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid benzyl
ester p-toluenesulfonic acid salt]

(DMF

Hydrochlorothiazide Manufacturer:

(DMF

Manufacturing facility:

(DMF

Supplier:

Drug product: Manufacturer: Parke-Davis Division of Warner-Lambert Inc. Km. 1.9 Road 689 Vega Baja, Puerto Rico (DMF

Blister packaging (alternate):

(DMF

6. Consults: CDER Labeling and Nomenclature Committee.

C. Remarks:

Quinapril hydrochloride is be manufactured by Parke-Davis Manufacturing Division in Holland, Michigan. Hydrochlorothiazide is manufactured by Accupril tablets will be manufactured at Parke-Davis Vega Baja facility.

Consult for the naming of the product - ACCURETIC - was requested on February 13, 1991.

Establishment Inspections were requested for the firms listed under Facilities on February 13, 1991.

Methods validation will be requested.

Environmental assessment report is included. It addresses the points specified in 21 CFR §25.31a.

D. Conclusions and/or Recommendations:

Deficiencies are noted in the Draft Letter to Applicant.

/S/

Danute G. Cunningham

cc: Orig. HFD-102/CKumkumian HFD-110 HFD-110/CSO HFD-110/DGCunningham N20125R1

Handwritten notes: /S/ 2-20-91

Consult #32 (HFD-110)

Accuretic Tablets Quinapril and Hydrochlorothiazide Tablets

A review did not reveal names which look or sound like the proposed name. The only concern expressed was that "accu-" implies "accurate". The Committee is normally opposed to the use of a "puffery" term such as this; however, it was noted that "accu-" is already associated with quinapril hydrochloride tablets in the branded product, Accupril.

The Committee has no reason to find the proposed name unacceptable.

GDER Labeling and Nomenclature Committee

/S/

3-11-91, Chair