CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20125

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BOILERPLATE

JUL 30 1999

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20-125
Serial # N- (028) BB
Accuretic (quinapril/HCTZ) tablets 10/12.5mg, 20/12.5mg, and 20/25mg
Parke-Davis Pharmaceuticals Limited
Submission Date: July 14, 1999

Reviewer: Thomas A. Parmelee, Pharm.D.

Type of Submission: Response to Biopharmaceutics Review and Labeling Comments

BACKGROUND

The original NDA 20-125 for Accuretic was submitted to the FDA in December 1990. The Agency subsequently issued an "approvable" letter in May 1992. The sponsor was unable to locate a manufacturing site for the final product, and the Agency then issued a "not approvable" letter in September 1992. The sponsor requested the NDA be withdrawn in October 1992.

The sponsor has recently decided to resubmit NDA 20-125 for Accuretic, and plans to cross-reference certain sections of the original application. The manufacturing site for the U.S. market will be in The current formulation and basic manufacturing processes for the combination product are unchanged from the original NDA submission.

The Office of Clinical Pharmacology and Biopharmaceutics reviewed the resubmission in May 1999 and forwarded comments regarding dissolution and labeling to the sponsor. This current submission is the response to the OCPB recommendations made regarding NDA 20-125.

RESULTS

1) The recommendation was made to amend the dissolution specifications for both quinapril and hydrochlorothiazide for the combination tablet to Q not less than minutes.

   RESPONSE: We agree to amend the dissolution specifications for both quinapril and hydrochlorothiazide to Q not less than minutes as recommended.

2) The recommendation was made to amend the product labeling as shown below:

The above should be amended to the following:

"The rate of quinapril absorption was reduced when ACCURETIC tablets were administered with a high-fat meal as compared to fasting. In a single study involving 12 healthy subjects, mean quinaprilat Cmax was decreased 14% and Tmax was prolonged 54% following a high-fat meal as compared to the fasted state. Mean hydrochlorothiazide Cmax was decreased 12% and Tmax was prolonged 19% following a high-fat meal as compared to the fasted state. The extent of absorption of quinaprilat and hydrochlorothiazide was not significantly affected by the administration of a high-fat meal. Therefore, ACCURETIC may be administered without regard to food."

RESPONSE: After considering FDA's suggestion, Parke-Davis is proposing the following for the Human Pharmacokinetics and Bioavailability section of the labeling:

"The rate of quinapril absorption was slightly reduced (14%) when ACCURETIC tablets were administered with a high-fat meal as compared to fasting, while the extent of absorption was not affected. The rate and extent of hydrochlorothiazide absorption (12%) was not significantly affected by the administration with a high-fat meal. Therefore, ACCURETIC may be administered without regard to food."

COMMENTS (for the clinical division)

The final labeling should read similar to the following:

"The rate of quinapril absorption was slightly reduced (14%) when ACCURETIC tablets were administered with a high-fat meal as compared to fasting, while the extent of absorption was not significantly affected. The rate of hydrochlorothiazide absorption was slightly reduced (12%) when ACCURETIC tablets were administered with a high-fat meal, while the extent of absorption was not significantly affected. Therefore, ACCURETIC may be administered without regard to food."

RECOMMENDATIONS

The final printed labeling should read similar to the above comment. No further action is warranted at this time.

/S/

Thomas A. Parmelee, Pharm.D. 7/30/99

RD/FT by Patrick Marroum, Ph.D. 7/30/1999

CC: NDA 20-125, HFD-110, HFD-860 (Mehta, Parmelee), CDER document room: Attn. ___
BIOPHARM- CDR

MAY 21 1999 K. Benjamin

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20-125
Serial # N- (RS)
Accuretic (quinapril/HCTZ) tablets
Parke-Davis Pharmaceuticals Limited
Submission Date: April 30, 1999

Reviewer: Thomas A. Parmelee, Pharm.D.

Type of Submission: NDA resubmission- Protocol 955-8 (food-effect study)

BACKGROUND

The original NDA 20-125 for Accuretic was submitted to the FDA in December, 1990. The Agency subsequently issued an "approvable" letter in May, 1992. The sponsor was unable to locate a manufacturing site for the final product, and the Agency then issued a "not approvable" letter in September, 1992. The sponsor requested the NDA be withdrawn in October, 1992.

The sponsor has recently decided to resubmit NDA 20-125 for Accuretic, and plans to cross-reference certain sections of the original application. The manufacturing site for the U.S. market will be in[ ]. The current formulation and basic manufacturing processes for the combination product are unchanged from the original NDA submission.

Section 6 (Human Pharmacokinetics and Bioavailability) of the current submission has cross-referenced four studies including a drug-drug interaction study between quinapril and hydrochlorothiazide, and three bioequivalence studies involving the combination product. These studies were reviewed (biopharm review dated 2/15/92), and determined to be acceptable. This original review is attached as Appendix 1. The sponsor has submitted the final report for Protocol 955-8, a food-effect study that was ongoing at the time of the original NDA submission and review. A review of this study is attached as Appendix 2.

The dissolution method, method validation, and dissolution specifications have not changed from the previous NDA submission. The sponsor has submitted dissolution profiles for the demonstration batches manufactured at the[ ]facility and are listed in Table 1. The proposed dissolution methodology and specifications have not changed from the previous submission. The sponsor proposes the following:

Method- USP Apparatus 1 (basket), 100 rpm, 900 mL of water at 37 C
Q specs- Not less than[ ]/minutes for both quinapril and HCTZ

TABLE 1: Dissolution Profiles* of Demonstration Batches

Lot#	Strength Quin/HCTZ	10 min. (%)	20 min. (%)	30 min. (%)
3000029	10.0			
	12.5			
3001029	10.0			
	12.5			
3000019	20.0			
	12.5			
3001019	20.0			
	12.5			
3000029	20.0			
	25.0			
3001029	20.0			
	25.0			

* Mean dissolution n= 12

The new site for commercial manufacturing for the U.S. market is
This is the same site where the 20.0/12.5 and 20.0/25.0 tablets used in the bioequivalency studies were manufactured. The 10.0/12.5 tablets used in the bio- studies were manufactured in Vega Baja, Puerto Rico. Comparison of the dissolution profiles show that the manufacturing site change from Vega Baja, Puerto Rico to did not have an effect on the release properties of the formulation. Therefore, differences in bioavailability between the formulations manufactured at the different sites are not expected. The dissolution profiles from the clinical formulations are shown below:

TABLE 2: Dissolution Profiles* of Bioequivalency Batches (from original submission)

Lot#	Strength Quin/HCTZ	15 min. (%)	30 min. (%)	45 min. (%)
CF 075099	20.0			
	12.5			
CF 070099	20.0			
	25.0			
CM 076040	10.0			
	12.5			
CM 075040	20.0			
	25.0			

* Mean dissolution n=12

The batch sizes for the demonstration batches above and the commercial batches to be marketed are identical. For the 10.0/12.5 tablets, the batch sizes will be tablets. For the 20.0/12.5 and 20.0/25.0 tablets, the batch sizes will be SUPAC-IR states that the **pilot scale batch sizes for solid oral dosage forms used in**

bio-studies should be, at a minimum, one-tenth that of full production, or [redacted] **tablets, whichever is larger**. The bio-batches used in the bio-studies (955-3 and 955-4) in the original submission, consisted of lot sizes equal to [redacted] tablets of 20/25 mg and 20/12.5 mg formulations. This is not one-tenth the production sizes listed above for the to-be-marketed formulations. This would constitute a level 2 (> 10x) scale-up as defined in the SUPAC-IR document. Such a change requires a Case B dissolution profile (i.e. multipoint dissolution profile in one medium at 15, 30, 45, 60, 120 minutes or until an asymptote is reached). The sponsor has submitted the dissolution profile for the production batches and thus satisfies this requirement.

RESULTS

For the food-effect study, mean quinaprilat Cmax was decreased 14% and Tmax was prolonged 54% following a high-fat meal as compared to the fasted state. This is possibly due to decreased absorption of quinapril after administration with food. Differences in mean quinaprilat AUC (0-inf), T1/2, and Ae% values for quinaprilat were 10% or less.

Mean HCTZ plasma concentration-time profiles were similar between treatments. Differences between the fed and fasted states for pharmacokinetic parameters were less than 20%. The rate and extent of absorption of HCTZ was similar between treatments.

COMMENTS

1) This food-effect study was performed before the current guidance document was drafted. The confidence intervals for AUC and Cmax for the difference between treatments would result in equivalence given the most current division recommendations.

2) The sponsor had submitted previous dissolution data at time points of 15, 30, and 45 minutes. For the current submission, and the sponsor has changed the time points for the new batches to 10, 20, and 30 minutes in the hopes of obtaining a more informative dissolution profile. For the previous submission, the interim specifications agreed to by both the division and sponsor was Q not less than [redacted] minutes. This specification resulted from the dissolution testing of only one production batch. The sponsor was supposed to obtain data from at least three more production lots, with the eventual specification target goal of Q not less than [redacted] minutes. With the submission of the demonstration batches, and this previous information, the proposed dissolution specification of Q not less than [redacted] minutes is **not acceptable**.

LABELING COMMENTS

1) The sponsor has proposed the following under the Pharmacokinetics and Metabolism section:

The above should be amended to the following:

> "The rate of quinapril absorption was reduced when ACCURETIC tablets were administered with a high-fat meal as compared to fasting. In a single study involving 12 healthy subjects, mean quinaprilat Cmax was decreased 14% and Tmax was prolonged 54% following a high-fat meal as compared to the fasted state. Mean hydrochlorothiazide Cmax was decreased 12% and Tmax was prolonged 19% following a high-fat meal as compared to the fasted state. The extent of absorption of quinaprilat and hydrochlorothiazide was not significantly affected by the administration of a high-fat meal. Therefore, ACCURETIC may be administered without regard to food."

2) The sponsor has complied with the request of the original reviewer that the labeling in the pharmacokinetics and metabolism section of quinapril be the same as the labeling for the quinapril product.

RECOMMENDATIONS

The food-effect study is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. The above comments should 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 20-125 meets the Office of Clinical Pharmacology and Biopharmaceutics requirements and is approvable.

/S/

Thomas A. Parmelee, Pharm.D. 5/21/99

–RD/FT by Patrick Marroum, Ph.D.

5/21/99

CC: NDA 20-125, HFD-110, HFD-860 (Mehta, Parmelee), CDER document room: Attn. BIOPHARM- CDR

APPENDIX I

Appendix 1

FEB 25 1992 DF

NDA: 20-125

SUBMISSION DATES: December 13, 1990
January 10, 1992
January 27, 1992

GENERIC NAME, DOSE AND FORMULATION: Quinapril/Hydrochlorothiazide
10 mg/12.5 mg, 20/12.5, and 20/25 tablets

BRAND NAME: Accuretic™

SPONSOR: Parke-Davis Pharmaceutical Research

REVIEWER: Ching-Leou C. Teng, Ph.D.

TYPE OF SUBMISSION: Combination Product

SYNOPSIS

The subject of this NDA is a combination tablet of quinapril and hydrochlorothiazide. Both quinapril and hydrochlorothiazide (HCTZ) products are on the market. The ADME of these two compounds have been well characterized and have not been included in this NDA. Bioequivalency studies comparing the bioavailability of clinical and to-be-marketed formulations were done on all tablet strengths. The drug interaction between quinapril and HCTZ was studied in the quinapril NDA and was adapted for this NDA as a supportive study.

RECOMMENDATION

The Division of Biopharmaceutics recommends that the Biopharmaceutic/Pharmacokinetics section of NDA 20-125 be accepted. General comment #1 (page 5) should be brought to the attention of medical reviewer in HFD-110.

APPEARS THIS WAY
ON ORIGINAL

TABLE OF CONTENTS

Note: Appendix II contains more detailed data/information such as dosage formulation, dissolution and individual subject data. This information is being retained in the Division of Biopharmaceutics and can be obtained upon requested.

Abbreviations:

C.I. - Confidence Interval
HCTZ - hydrochlorothiazide

BACKGROUND

Quinapril is an angiotensin converting enzyme (ACE) inhibitor used for the treatment of essential hypertension. Following oral administration, quinapril (prodrug) is hydrolyzed to quinaprilat which is the active compound to inhibit ACE activity. Hydrochlorothiazide (HCTZ) is a thiazide diuretic with antihypertensive activity. The mechanism of the antihypertensive effect of thiazide is unknown. The combined use of quinapril and HCTZ is anticipated to enhance efficacy and to have a favorable safety profile.

I. PHARMACOKINETICS

A. Quinapril (extracted from quinapril NDA)

Following oral administration, peak plasma quinapril concentration is observed within one hour. The apparent half-life of quinapril is about one hour. Upon absorption, quinapril is hydrolyzed to its major active metabolite, quinaprilat, and other minor inactive metabolites. The peak plasma quinaprilat concentration is observed approximately two hours following oral administration of quinapril. Quinaprilat is eliminated primarily by renal excretion and has an effective accumulation half-life of about three hours. Based on the recovery of quinapril and its metabolites in urine, the extent of absorption of quinapril is at least 60 %. The rate and extent of quinapril absorption decrease about 25 to 30 % when quinapril tablets are administered with a high-fat meal. The pharmacokinetics of quinapril and quinaprilat are linear over a single-dose range of 5-80 mg and 40-160 mg in multiple daily doses. In patients with renal insufficiency, the elimination half-life of quinaprilat increases as creatinine clearance decreases. The elimination of quinaprilat is reduced in elderly patients due to decrease in renal function. Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired metabolism of quinapril.

B. Hydrochlorothiazide

The absorption of HCTZ is about 60-80 % of the oral dose. Maximum plasma concentrations of HCTZ are observed from 0.5 to 5 hours following oral administration. Hydrochlorothiazide is not metabolized and is eliminated rapidly from the kidney. The renal clearance of HCTZ is approximately 300 ml/min. The plasma-time profile of HCTZ shows a biexponential decline with a terminal apparent elimination half-life of 6 to 15 hours.

II. DRUG INTERACTION (extracted from quinapril NDA)

The pharmacokinetics of quinapril, quinaprilat, and HCTZ following the concomitant administration of 40 mg quinapril capsules and 25 mg HCTZ tablets were similar to those observed following the administration of 40 mg quinapril capsules and 25 mg HCTZ tablets separately.

III. BIOAVAILABILITY/BIOEQUIVALENCE

A. Bioequivalence

Three bioequivalence studies were conducted using quinapril/HCTZ combination market-image tablets. The results of the studies demonstrate that to-be-marketed formulations are bioequivalent to the corresponding clinical formulations of quinapril tablets and HCTZ tablets given simultaneously. In addition, two 10 mg quinapril/12.5 mg HCTZ tablets are bioequivalent to a 20 mg/quinapril/25 mg HCTZ combination tablet.

B. Food effect

The food effect study was not conducted in this NDA. The results from the quinapril tablet study indicated that the food would decrease the rate and extent of quinapril absorption. Food slowed down the absorption rate of HCTZ and led to the lower Cmax value. There are conflicting reports in the literature regarding the influence of food on the extent of HCTZ absorption[1,2].

[1.] Bjorn Beermann and Margaretha Groschinsky-Grind, Europ. J. Clin. Pharmacol. 13, 125-128 1978.

[2.] Rashmi H. Barbhaiya, et al. Pharm. Sci. 72, 245-248, 1982

IV. FORMULATION

The 10 mg quinapril/12.5 mg HCTZ and 20 mg/25 mg tablets are compositionally proportional. The 20 mg/12.5 mg and 20 mg/25 mg tablets are not compositionally proportional, however, they are similar. Lactose (12.5 mg) is used to supplement the variation in the active component (12.5 mg HCTZ) such that two tablet strengths have the same tablet core weight.

V. DISSOLUTION

The following dissolution method and Q specifications are recommended (please see general comment #2 for detail):

Method - USP apparatus I (basket), 100 rpm, 900 ml of water at 37°C
Q specifications - not less than [ ] min for both quinapril and HCTZ

VI. ASSAY

The assay methodology is acceptable.

GENERAL COMMENT (NEED NOT BE SENT TO THE FIRM)

1. The firm did not perform the bioequivalency study to compare the bioavailability of HCTZ in the combination product to that of the commercial available HCTZ product. The concern is the interchangeability between the separate dosage forms of quinapril and HCTZ and this combination product for patients who are currently under the combination therapy taking the quinapril tablet and HCTZ product and plan to switch to the combination product. Absolute assurance of bioequivalence would be given by an in vivo comparison study, however according to the following reasons, this bioequivalency study may not be necessary.

a. The formulation of 25 mg HCTZ tablet used in the bioequivalency study is similar to the commercial 50 mg HCTZ tablet manufactured by Parke-Davis. The 25 mg HCTZ is replaced by mg lactose, mg microcrystalline cellulose, and mg corn starch in the 25 mg tablet. In addition, the 25 mg tablet passed the USP dissolution test for HCTZ.

b. The 25 mg HCTZ tablet used in the drug interaction study (902-221) is the commercial product. A cross-study comparison shows that the PK data of HCTZ following the oral administration of combination product are similar to the data obtained from the drug interaction study especially the amount of urinary excretion of HCTZ which is a more meaningful PK parameter for a diuretic drug like HCTZ.

COMMENTS TO BE SENT TO THE FIRM

Labeling Comments:

1. The labeling in the pharmacokinetics and metabolism section of quinapril should be the same as the labeling for the quinapril product.

2. The food effect study was not conducted for the combination tablet. The food effect on the rate of absorption of quinapril obtained from Accuretic is addressed in the labeling. The food effect on the extent of absorption of HCTZ is contradictory from the literature and can't be used to support this NDA. In addition to the inherent drug property, the formulation may also be a factor in the food effect on the drug bioavailability. Consequently, the impact of the food effect upon the bioavailability of the combination tablet can't be ascertained without the in vivo study. The firm is asked to indicate in the labeling that food effect study has not been done for the combination product.

General Comments:

1. The proposed dissolution method is basket 100 rpm. The firm has tried the dissolution method of 50 rpm paddle and found that the dissolution data were variable because a mount of insoluble excipients accumulated at the bottom of the dissolution vessel. Although the dissolution data with paddle speed of 50 rpm is more variable than those with basket speed of 100 rpm, the reviewer feels that the 50 rpm paddle method would be more discriminatory than 100 rpm basket method if the firm can extend the sampling time to 45 min or even 60 min. The firm is recommended to perform these two methods for future production lots (at least 3 lots, dissolution time profiles with 12 tablets of each). The final dissolution method and Q specification will be determined upon receiving the data. In the interim the recommended dissolution method and Q specifications are:

Method - USP apparatus I (basket), 100 rpm, 900 ml of water at 37°C
Q specifications - not less than ____ min for both quinapril and HCTZ

/S/ 1-31-92

Ching-Leou C. Teng, Ph.D.

FT initialed by Nicholas M. Fleischer, Ph.D. /S/ 4/24/92
Biopharm Day 1-29-92
Attendances: Tom Ludden, Ph.D., Henry Malinowski, Ph.D., Nicholas Fleischer, Ph.D., Ameeta Parekh, Ph.D.

cc: NDA 20-125, HFD-110(2), HFD-426(Teng,Fleischer), Chron, Division, Drug, Review, and HFD-19(FOI) files

Study 906-211 (adopted from quinapril NDA 19-885)

Title: Single dose pharmacokinetic drug-drug interaction study of quinapril and hydrochlorothiazide in healthy volunteers

Objectives: To assess the potential pharmacokinetic drug-drug interaction of quinapril and HCTZ in healthy subjects.

Investigator/site:

Protocol: The study was conducted in 12 healthy subjects. Each overnight fasting subject received a single dose of 40 mg quinapril capsule and 25 mg HCTZ tablet dose alone or concomitantly according to the randomized three-way crossover design. Blood and urine samples were collected at appropriate times following each dose. The washout period was one week between treatments.

Results: Mean(% C.V.)

	Quinaprilat		HCTZ	
	Single	Combo	Single	Combo
Cmax(ng/ml)	1274(25)	1382(23)	210(27)	197(20)
Tmax(h)	1.6(33)	1.6(27)	2.2(28)	2.0(32)
AUC(0-∞,ng*h/ml)	4345(13)	4643(21)	1245(27)	1188(21)
Ae(% of dose)	31(33)	28(16)	56(23)	51(18)

Conclusion:

Concomitant administration of a single 40 mg quinapril capsule and a 25 mg HCTZ tablet to healthy volunteers does not alter the single-dose pharmacokinetics of quinapril and HCTZ.

Protocol 955-3

Title: A bioequivalence study of 20 mg quinapril hydrochloride/25 mg hydrochlorothiazide tablets in healthy volunteers

Objectives: To determine whether quinapril/HCTZ combination tablets are bioequivalent to quinapril and HCTZ tablets administered concomitantly as separate dosage formulations

Investigators/Site:

Protocol: This was a two-way crossover study. 20 healthy subjects participated in and completed the study (Nov. 8-18 1989). All doses were given with 200 ml of water following an 8-hour overnight fast. Lunch was provided following the collection of the 4 hour blood sample. Blood samples were collected before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours following each dose. Urine samples were collected before dosing and during the 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48, and 48-72 hour intervals. The washout period between treatments was 7 days.

Formulation:

20 mg quinapril/25 mg HCTZ Lot CF070099, Lot Size	to-be-marketed formulation
20 mg quinapril Lot 0001059, Lot Size	pivotal clinical formulation
25 mg HCTZ Lot CP031078A, Lot Size	pivotal clinical formulation

Analytical Methods:

Conclusion:

The to-be-marketed formulation of 20 mg quinapril/25 mg HCTZ combination tablet is bioequivalent to 20 mg quinapril and 25 mg HCTZ tablets administered concomitantly as separate dosage forms.

Protocol 955-4

Title: A bioequivalence study of 20 mg quinapril hydrochloride/12.5 mg hydrochlorothiazide tablets in healthy volunteers

Objectives: To determine whether quinapril/HCTZ combination tablets are bioequivalent to quinapril and HCTZ tablets administered concomitantly as separate dosage formulations.

Investigators/Site: [redacted]

Protocol: This was a two-way crossover study. 20 healthy subjects participated in and completed the study (Nov. 1-Dec. 11, 1989). All doses were given with 200 ml of water following an 8-hour overnight fast. Lunch was provided following the collection of the 4 hour blood sample. Blood samples were collected before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours following each dose. Urine samples were collected before dosing and during the 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48, and 48-72 hour intervals. The washout period between treatments was 7 days.

Formulation:

20 mg quinapril/12.5 mg HCTZ Lot CF 075099, Lot Size to-be-marketed-formulation
20 mg quinapril Lot CL 0001059, Lot Size pivotal clinical formulation
25 mg HCTZ Lot CP 031078A, Lot Size pivotal clinical formulation

Analytical Methods:

Results:

	Combination 2x(20 mg/12.5 mg)	Separate (2x20 mg+25 mg)	90 % C.I. (ref. combination)
Quinaprilat [Mean (% C.V.)]			
Cmax(ng/ml)	1260(28.9)	1150(24.3)	85-98(Sig,ANOVA)
Tmax(h)	1.53(37.6)	1.38(26.0)	
AUC(0-∞,ng*h/ml)	4120(21.6)	4010(19.8)	91-103
Ae(% of dose)	31.1(17.9)	32.0(19.9)	97-113
HCTZ [Mean(% C.V.)]			
Cmax(ng/ml)	141(29.7)	134(38.3)	83-107
Tmax(h)	1.75(44.0)	1.98(37.1)	
AUC(0-∞,ng*h/ml)	885(23.7)	831(23.9)	86-102
Ae(% of dose)	47.5(20.2)	49.9(26.6)	96-110

Conclusion:

Two 20 mg quinapril/12.5 mg HCTZ combination tablets are bioequivalent to two 20 mg quinapril tablets and one 25 mg HCTZ tablet administered concomitantly as separate dosage forms.

Protocol 955-7

Title: A study in healthy volunteers to determine whether 10 mg quinapril/12.5 mg HCTZ and 20 mg quinapril/25 mg HCTZ combination tablets are bioequivalent to concomitantly administered 20 mg quinapril and 25 mg HCTZ tablets

Objective: To determine whether 10 mg quinapril/12.5 mg HCTZ combination tablets and 20 mg quinapril/25 mg HCTZ combination tablets are bioequivalent to 20 mg quinapril and 25 mg HCTZ tablets administered concomitantly as separate dosage formulations.

Investigator/Site: [redacted]

Protocol: This was a single dose, three-way crossover design. 21 subjects participated in and 20 subjects completed the study (June 5-June 26, 1990). All doses were administered with 8 ounces of water following an 8-hour overnight fast. Lunch and dinner were provided following the collection of 4- and 10-hour blood samples on each dosing day. Blood samples were collected before, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours after dosing. Urine samples were collected immediately before dosing and during the 0-2, 2-4, 4-6, 6-8, 8-12,

12-24, 24-36, 36-48, and 48-72 hour intervals. There were 7 days between treatments.

Formulation:

10 mg quinapril/12.5 mg HCTZ Lot CM076040, Lot Size , Puerto Rico*
20 mg quinapril/25 mg HCTZ Lot CM075040, Lot Size Puerto Rico*
20 mg quinapril Lot CM227089 Germany, pivotal clinical formulation
25 mg HCTZ Lot CP031078A Germany, pivotal clinical formulation

* Future manufacturing site.

Analytical Method:

Statistical Analysis (90 % C.I.)

	ANOVA	2x(10/12.5) vs. 20 + 25	20/25 vs. 20 + 25	2x(10/12.5) vs. 20/25
Quinaprilat				
Cmax	Sig	102-113 %	101-112 %	96-106 %
Tmax	NS			
AUC(0-∞)	NS	101-108 %	100-107 %	98-105 %
Ae	NS	98-110 %	96-108 %	96-108 %
HCTZ				
Cmax	NS	94-117 %	86-109 %	94-117 %
Tmax	NS			
AUC(0-∞)	NS	99-110 %	95-107 %	95-106 %
Ae	Sig	102-114 %	104-116 %	95-106 %

Conclusion:

Both 10 mg quinapril/12.5 mg HCTZ and 20 mg quinapril/25 mg HCTZ combination tablets are bioequivalent to 20 mg quinapril and 25 mg HCTZ tablets administered concomitantly. Two 10 mg quinapril/12.5 mg HCTZ tablets are also bioequivalent to one 20 mg quinapril/25 mg HCTZ combination tablet.

DISSOLUTION

The firm proposed the following dissolution test method and Q specifications:

Method - USP apparatus I (basket), 100 rpm, 900 ml water at 37°C
Q specification - min for both quinapril and HCTZ

Discussion:

The dissolution data showed that more than 95 % of quinapril and HCTZ in the combination tablets were dissolved in the dissolution media 15 min (first sampling time) after the dissolution test was started. The firm claimed that they had tried the paddle method with stirring speed of 50 rpm and found that the dissolution data were variable because a mount of insoluble excipients accumulated at the bottom of the dissolution vessel (appendix II). Although the dissolution data with paddle speed of 50 rpm is more variable then those with basket speed of 100 rpm, the reviewer feels that the 50 rpm paddle method would be more discriminatory than 100 rpm basket method if the firm can extend the sampling time to 45 min or even 60 min. The firm is recommended to perform these two methods for future production lots (at least 3 lots, dissolution time profiles with 12 tablets each). The final dissolution method and Q specification will be determined upon receiving the data. In the interim the recommended dissolution method and

Q specifications are:

Method - USP apparatus I (basket), 100 rpm, 900 ml of water at 37°C
Q specifications - not less than min for both quinapril and HCTZ

APPENDIX II

TABLE 2. Composition of Commercial Quinapril/Hydrochlorothiazide 20/25-mg Tablet

Formula Number: 4 Label Claim: Quinapril (as base) Hydrochlorothiazide	20.0 mg 25.0 mg mg/tab	Excipient Variation ± mg/tab
Tablet Core Ingredients		
Quinapril Hydrochloride	mg[a]	
Hydrochlorothiazide USP	mg	
Lactose NF Hydrous	mg	mg
Magnesium Carbonate USP	mg	mg
Povidone USP	mg	mg
Magnesium Stearate NF	mg	mg
Crospovidone NF	mg	mg
Total Core Weight	mg	
Tablet Coating		
Color Coat Composed of	mg	mg
Tablet Polishing		
Candellilla Wax FCC	mg	mg
Total Coated Tablet Weight	mg	

[a] 21.70 mg of quinapril hydrochloride is equivalent to 20.00 mg of quinapril base. Weight of quinapril hydrochloride may be adjusted based on drug assay to provide label claim as indicated.
[b] Removed during the drying process and does not appear in final product.

TABLE 3. Composition of Commercial Quinapril/Hydrochlorothiazide 10/12.5-mg Tablet

Formula Number: 2 Label Claim: Quinapril (as base) Hydrochlorothiazide	10.0 mg 12.5 mg mg/tab	Excipient Variation ± mg/tab
Tablet Core Ingredients		
Quinapril Hydrochloride	mg[a]	
Hydrochlorothiazide USP	mg	
Lactose NF Hydrous	mg	mg
Magnesium Carbonate USP	mg	mg
Povidone USP	mg	mg
Magnesium Stearate NF	mg	mg
Crospovidone NF	mg	mg
Total Core Weight	mg	
Tablet Coating		
Color Coat Composed of	mg	mg
Tablet Polishing		
Candellilla Wax FCC	mg	mg
Total Coated Tablet Weight	mg	

[a] 10.85 mg of quinapril hydrochloride is equivalent to 10.00 mg of quinapril base. Weight of quinapril hydrochloride may be adjusted based on drug assay to provide label claim as indicated.
[b] Removed during the drying process and does not appear in final product.

TABLE 4. Composition of Commercial Quinapril/Hydrochlorothiazide 20/12.5-mg Tablet

Formula Number: 3 Label Claim: Quinapril (as base) Hydrochlorothiazide	20.0 mg 12.5 mg mg/tab	Excipient Variation ± mg/tab
Tablet Core Ingredients		
Quinapril Hydrochloride	mg[a]	
Hydrochlorothiazide USP	mg	
Lactose NF Hydrous	mg	mg
Magnesium Carbonate USP	mg	mg
Povidone USP	mg	mg
Magnesium Stearate NF	mg	mg
Crospovidone NF	mg	mg
Total Core Weight	mg	
Tablet Coating		
Color Coat Composed of	mg	mg
Tablet Polishing		
Candellilla Wax FCC	mg	mg
Total Coated Tablet Weight	mg	

[a] 21.70 mg of quinapril hydrochloride is equivalent to 20.00 mg of quinapril base. Weight of quinapril hydrochloride may be adjusted based on drug assay to provide label claim as indicated.
[b] Removed during the drying process and does not appear in final product.

FORMULA NUMBER: 24
STRENGTH: 25 mg
DOSAGE FORM: Tablets

Clinical formulation

COMPOSITION:

INGREDIENT	AMOUNT PER TABLET
Hydrochlorothiazide BP	mg
Lactose EP	mg
Microcrystalline Cellulose NF	mg
Corn Starch EP	mg
Hydroxypropyl Cellulose FCC	mg
Calcium Stearate NF	mg
Total Weight	mg

FORMULA NUMBER: 25
STRENGTH: 50 mg
DOSAGE FORM: Tablets

Clinical formulation ≡ Commercial formulation

COMPOSITION:

INGREDIENT	AMOUNT PER TABLET
Hydrochlorothiazide BP	mg
Lactose EP	mg
Microcrystalline Cellulose NF	mg
Corn Starch EP	mg
Hydroxypropyl Cellulose FCC	mg
Calcium Stearate NF	mg
Total Weight	0 mg

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confidential

commercial

information

Draft Labeling

Clinical Tablet

Product: Hydrochlorothiazide 25 mg Tablets
Formulation No.: 24
Batch No.: CP031078A

Dissolution Profile

Apparatus: USP 1 (Basket)
Medium: 900 mL of 0.1 N hydrochloric acid
Speed: 100 rpm

Sample No.	10 Minutes	20 Minutes	30 Minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	99.9	102.7	103.4
RSD	1.8	2.0	3.5

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Product: Quinapril/Hydrochlorothiazide 10/12.5 mg Tablets
Formulation No.: 2A1
Batch No.: CM076040

Dissolution Profile

Apparatus: USP 1 (Basket)
Medium: 900 mL of Water
Speed: 100 rpm

Quinapril

Sample No.	15 Minutes	30 Minutes	45 Minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	102.3	102.1	100.4
RSD	1.7	1.5	1.4

Hydrochlorothiazide

Sample No.	15 Minutes	30 Minutes	45 Minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	92.2	99.9	100.4
RSD	3.6	1.7	2.1

Product: Quinapril/Hydrochlorothiazide 20/12.5 mg Tablets
Formulation No.: 3
Batch No.: CF075099

Dissolution Profile

Apparatus: USP 1 (Basket)
Medium: 900 mL of Water
Speed: 100 rpm

Quinapril

Sample No.	15 Minutes	30 Minutes	45 Minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	104.7	103.3	103.0
RSD	1.7	1.7	1.9

Hydrochlorothiazide

Sample No.	15 Minutes	30 Minutes	45 Minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	99.5	101.4	102.0
RSD	1.3	2.9	2.1

Product: Quinapril/Hydrochlorothiazide 20/25 mg Tablets
Formulation No.: 4
Batch No.: CF070099

Dissolution Profile

Apparatus: USP 1 (Basket)
Medium: 900 mL of Water
Speed: 100 rpm

Quinapril

Sample No.	15 Minutes	30 Minutes	45 Minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	103.3	101.5	103.1
RSD	1.2	1.4	1.5

Hydrochlorothiazide

Sample No.	15 Minutes	30 Minutes	45 Minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	96.7	97.4	99.5
RSD	1.7	1.5	1.6

Product: Quinapril/Hydrochlorothiazide 20/25 mg Tablets
Formulation No.: 4A1
Batch No.: CM075040

Dissolution Profile

Apparatus: USP 1 (Basket)
Medium: 900 mL of Water
Speed: 100 rpm

Quinapril

Sample No.	15 Minutes	30 Minutes	45 Minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	100.2	99.13	99.0
RSD	2.1	1.9	1.9

Hydrochlorothiazide

Sample No.	15 Minutes	30 Minutes	45 Minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	96.3	100.1	101.4
RSD	2.6	1.9	3.2

ACCURETIC (CI-955) TABLETS

Dissolution Procedure Development

In the Accuretic Tablets NDA, the dissolution procedure calls for USP Apparatus 1 (baskets) at 100 rpm using 900 mL of water as the medium. In developing this procedure, USP Apparatus 2 (paddles) at 50 rpm and 100 rpm was evaluated also. The data presented below show that Apparatus 2 at 50 rpm yields variable results within each time point, and, therefore, would not be an adequate quality control test. Apparatus 1 and Apparatus 2 at 100 rpm yielded more consistent results. Apparatus 1 at 100 rpm was chosen.

TABLE 1: Dissolution profile of Accuretic Tablets Lot CM-075040 Using USP Apparatus 2 at 50 rpm

	% Dissolved					
	Quinapril			Hydrochlorothiazide		
Tablet	10 min	20 min	30 min	10 min	20 min	30 min
1						
2						
3						
4						
5						
6						
Average	66	76	80	47	57	65

TABLE 2: Dissolution profile of Accuretic Tablets Lot CM-075040 Using USP Apparatus 2 at 100 rpm

	% Dissolved					
	Quinapril			Hydrochlorothiazide		
Tablet	10 min	20 min	30 min	10 min	20 min	30 min
1						
2						
3						
4						
5						
6						
Average	89	96	97	86	98	102

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10. TABLES

TABLE 1. Demographic Data For Subjects Completing [redacted] Protocol 955-3

Subject	Weight (kg)	Height (cm)	Age (yr)	Gender
1	71.4	174	21	M
2	63.6	175	21	M
3	65.0	169	29	M
4	73.1	173	20	M
5	58.2	171	23	M
6	69.6	170	24	M
7	67.0	175	28	M
8	93.1	176	18	M
9	77.2	170	41	M
10	56.3	170	31	M
11	57.6	170	19	M
12	67.1	169	18	M
13	70.7	180	29	M
14	60.6	180	23	M
15	66.8	173	24	M
16	60.6	180	24	M
17	70.4	183	28	M
18	66.8	173	18	M
19	74.1	177	20	M
20	59.9	166	43	M
Mean	67.5	174	25	M
Range	(56.3-93.1)	(166-183)	(18-43)	-

Table 3.1. Individual and Mean Quinaprilat Pharmacokinetic Parameters Following Single-Dose Administration of One 20-mg Quinapril HCl/25-mg Hydrochlorothiazide Tablet (CI-955) (Treatment 1): Protocol 955-3

Subject	Cmax	tmax	AUC(0-tldc)	AUC(0-∞)	λz	t½	Ae%
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
Mean	744	1.3	2528	2551	0.345	2.01*	32.4
%RSD	25.4	27.5	25.3	25.1	12.3	12.4	20.3

* Harmonic mean

Cmax = Maximum observed plasma concentration (ng/mL)
tmax = Time of Cmax (hr)
AUC(0-tldc) = Area under the plasma concentration-time curve from time zero to the time of the last detectable concentration (ng•hr/mL)
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinity (ng•hr/mL)
λz = Apparent elimination-rate constant (1/hr)
t½ = Apparent elimination half-life (hr)
Ae% = Amount excreted in urine from 0 to 72 hours postdose (% of dose)

TABLE 3.2. Individual and Mean Quinaprilat Pharmacokinetic Parameters Following Single-Dose Administration of One 20-mg Quinapril HCl Tablet Coadministered With One 25-mg Hydrochlorothiazide Tablet (CI-955) (Treatment 2): Protocol 955-3

Subject	Cmax	tmax	AUC(0-tldc)	AUC(0-∞)	λz	t½	Ae%
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
Mean	718	1.4	2434	2457	0.338	2.05*	34.0
%RSD	23.9	24.9	24.4	24.2	12.4	12.4	19.6

* Harmonic mean

Cmax = Maximum observed plasma concentration (ng/mL)
tmax = Time of Cmax (hr)
AUC(0-tldc) = Area under the plasma concentration-time curve from time zero to the time of the last detectable concentration (ng•hr/mL)
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinity (ng•hr/mL)
λz = Apparent elimination-rate constant (1/hr)
t½ = Apparent elimination half-life (hr)
Ae% = Amount excreted in urine from 0 to 72 hours postdose (% of dose)

TABLE 3.3. Individual and Mean HCTZ Pharmacokinetic Parameters Following Single-Dose Administration of One 20-mg Quinapril HCl/25-mg Hydrochlorothiazide Tablet (CI-955) (Treatment 1): Protocol 955-3

Subject	Cmax	tmax	AUC(0-tldc)	AUC(0-∞)	λz	t½	Ae%
1							
2							
4							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
Mean	171	1.5	953	1049	0.091	7.58*	61.2
%RSD	28.7	24.9	23.0	23.1	11.6	11.6	19.4

* Harmonic mean

Cmax = Maximum observed plasma concentration (ng/mL)
tmax = Time of Cmax (hr)
AUC(0-tldc) = Area under the plasma concentration-time curve from time zero to the time of the last detectable concentration (ng•hr/mL)
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinity (ng•hr/mL)
λz = Apparent elimination-rate constant (1/hr)
t½ = Apparent elimination half-life (hr)
Ae% = Amount excreted in urine from 0 to 72 hours postdose (% of dose)

TABLE 3.4. Individual and Mean Hydrochlorothiazide Pharmacokinetic Parameters Following Single-Dose Administration of One 20-mg Quinapril HCl Tablet Coadministered With One 25-mg Hydrochlorothiazide Tablet (CI-955) (Treatment 2): Protocol

Subject	Cmax	tmax	AUC(0-tldc)	AUC(0-∞)	λz	t½	Ae%
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
Mean	167	1.6	947	1044	0.097	7.14*	60.6
%RSD	24.4	28.0	21.5	21.0	21.4	21.6	15.6

* Harmonic mean

Cmax = Maximum observed plasma concentration (ng/mL)
tmax = Time of Cmax (hr)
AUC(0-tldc) = Area under the plasma concentration-time curve from time zero to the time of the last detectable concentration (ng•hr/mL)
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinity (ng•hr/mL)
λz = Apparent elimination-rate constant (1/hr)
t½ = Apparent elimination half-life (hr)
Ae% = Amount excreted in urine from 0 to 72 hours postdose (% of dose)

Protocol 955-4

10. TABLES

TABLE 1. Demographic Data for Subjects Completing Protocol 955-004

Subject	Weight (kg)	Height (cm)	Age (yr)	Gender	Race
1	71	174	20	M	B
2	76	185	24	M	C
3	96	186	24	M	C
4	67	172	26	M	C
5	70	175	26	M	C
6	74	172	25	M	C
7	72	183	20	M	C
8	76	179	21	M	C
9	55	175	25	M	C
10	89	191	29	M	C
11	73	181	24	M	C
12	69	168	19	M	C
13	63	175	24	M	C
14	72	176	29	M	C
15	65	170	24	M	C
16	60	172	19	M	C
17	72	178	20	M	C
18	70	175	21	M	C
19	89	177	39	M	C
20	110	194	29	M	C
Mean	74	178	24	20M/0F	19C/1B
Range	(55-100)	(168-194)	(19-39)		

C = Caucasian
B = Black

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TABLE 3.1. Individual and Mean Quinaprilat Pharmacokinetic Parameters Following Single-Dose Administration of Two 20-mg Quinapril HCl/12.5-mg Hydrochlorothiazide Tablets (CI-955) (Treatment 1): Protocol 955-4

Subject	Cmax	tmax	AUC(0-tldc)	AUC(0-∞)	λz	$t_{\frac{1}{2}}$	Ae%
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
24							
Mean	1260	1.53	4030	4120	0.329	2.12*	31.1
%RSD	28.9	37.6	22.1	21.6	9.6	9.7	17.9

* Harmonic mean

Cmax = Maximum observed plasma concentration (ng/mL)
tmax = Time of Cmax (hr)
AUC(0-tldc) = Area under the plasma concentration-time curve from time zero to the time of the last detectable concentration (ng·hr/mL)
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinity (ng·hr/mL)
λz = Apparent elimination-rate constant (hr)
$t_{\frac{1}{2}}$ = Apparent elimination half-life (hr)
Ae% = Amount excreted in urine from 0 to 72 hours postdose (% of dose)

044

TABLE 3.2. Individual and Mean Quinaprilat Pharmacokinetic Parameters Following Single-Dose Administration of Two 20-mg Quinapril HCl Tablets Administered Concomitantly With One 25-mg Hydrochlorothiazide Tablet (Treatment 2): Protocol 955-4

Subject	Cmax	tmax	AUC(0-tldc)	AUC(0-∞)	λz	$t_{\frac{1}{2}}$	Ae%
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
24							
Mean	1150	1.38	3930	4010	0.340	2.07*	32.0
%RSD	24.3	26.0	19.4	19.8	11.5	11.9	19.9

*. Harmonic mean

Cmax = Maximum observed plasma concentration (ng/mL)
tmax = Time of Cmax (hr)
AUC(0-tldc) = Area under the plasma concentration-time curve from time zero to the time of the last detectable concentration (ng·hr/mL)
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinity (ng·hr/mL)
λz = Apparent elimination-rate constant (hr)
$t_{\frac{1}{2}}$ = Apparent elimination half-life (hr)
Ae% = Amount excreted in urine from 0 to 72 hours postdose (% of dose)

045

TABLE 3.3. Individual and Mean Hydrochlorothiazide Pharmacokinetic Parameters Following Single-Dose Administration of Two 20-mg Quinapril HCl/12.5-mg Hydrochlorothiazide (CI-955) Tablets (Treatment 1): Protocol 955-4

Subject	Cmax	tmax	AUC(0-tldc)	AUC(0-∞)	λz	t½	Ae%
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
Mean	141	1.75	788	885	0.089	8.76*	47.5
%RSD	29.7	44.0	25.2	23.7	41.8	43.2	20.2

* Harmonic mean

Cmax = Maximum observed plasma concentration (ng/mL)
tmax = Time of Cmax (hr)
AUC(0-tldc) = Area under the plasma concentration-time curve from time zero to the time of the last detectable concentration (ng·hr/mL)
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinity (ng·hr/mL)
λz = Apparent elimination-rate constant (hr)
t½ = Apparent elimination half-life (hr)
Ae% = Amount excreted in urine from 0 to 72 hours postdose (% of dose)

TABLE 3.4. Individual and Mean Hydrochlorothiazide Pharmacokinetic Parameters Following Single-Dose Administration of Two 20-mg Quinapril HCl Tablets Administered Concomitantly With One 25-mg Hydrochlorothiazide Tablet (Treatment 2): Protocol 955-4

Subject	Cmax	tmax	AUC(0-tldc)	AUC(0-∞)	λz	t½	Ae%
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
Mean	134	1.98	746	831	0.092	7.53*	49.9
%RSD	38.3	37.1	23.7	23.9	41.2	43.0	26.6

* Harmonic mean

Cmax = Maximum observed plasma concentration (ng/mL)
tmax = Time of Cmax (hr)
AUC(0-tldc) = Area under the plasma concentration-time curve from time zero to the time of the last detectable concentration (ng·hr/mL)
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinity (ng·hr/mL)
λz = Apparent elimination-rate constant (hr)
t½ = Apparent elimination half-life (hr)
Ae% = Amount excreted in urine from 0 to 72 hours postdose (% of dose)

10. TABLES

TABLE 1. Demographic Data for Subjects Completing Protocol 955-7

Subject	Weight (kg)	Height (cm)	Age (yr)	Gender
1	105.1	175	41	F
2	75.5	173	29	M
3	52.5	166	41	F
4	55.0	159	38	F
5	65.0	169	31	F
7	62.7	169	39	F
8	72.3	176	37	F
9	105.4	182	44	M
10	66.3	182	24	M
11	85.9	176	29	M
12	102.0	186	36	M
13	89.9	185	38	M
14	90.3	175	34	M
15	63.4	179	36	M
16	92.4	191	30	M
17	79.8	180	29	M
18	67.3	170	31	M
19	79.8	184	21	M
20	76.5	191	21	M
21	77.4	183	31	M
Mean	77.6	177	33	
Range	52.5-105.4	159-191	(21-44)	

058

Table 3.1. Individual and Mean Quinaprilat Pharmacokinetic Parameters Following Single-Dose Administration of Two 10-mg Quinapril HCl/12.5-mg Hydrochlorothiazide Tablets (CI-955) (Treatment 1): Protocol 955-7

Subject	Cmax	tmax	AUC(0-tldc)	AUC(0-∞)	λz	t½	Ae%
1							
2							
3							
4							
5							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
Mean	637	1.6	2248	2300	0.308	2.25*	30.4
%RSD	19.0	25.4	18.8	18.6	7.12	7.11	18.7

* Harmonic mean

Cmax = Maximum observed plasma concentration (ng/mL)
tmax = Time of Cmax (hr)
AUC(0-tldc) = Area under the plasma concentration-time curve from time zero to the time of the last detectable concentration (ng•hr/mL)
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinity (ng•hr/mL)
λz = Apparent elimination-rate constant (1/hr)
t½ = Apparent elimination half-life (hr)
Ae% = Amount excreted in urine from 0 to 72 hours postdose (% of dose)

059

TABLE 3.2. Individual and Mean Quinaprilat Pharmacokinetic Parameters Following Single-Dose Administration of One 20-mg Quinapril HCl/25-mg Hydrochlorothiazide Combination Tablet (Treatment 2): [redacted]

Subject	Cmax	tmax	AUC(0-tldc)	AUC(0-∞)	λz	t½	Ae%
1							
2							
3							
4							
5							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
Mean	629	1.4	2204	2262	0.320	2.17*	29.8
%RSD	17.2	23.2	17.7	18.0	7.25	7.19	14.7

* Harmonic mean

Cmax = Maximum observed plasma concentration (ng/mL)
tmax = Time of Cmax (hr)
AUC(0-tldc) = Area under the plasma concentration-time curve from time zero to the time of the last detectable concentration (ng•hr/mL)
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinity (ng•hr/mL)
λz = Apparent elimination-rate constant (1/hr)
t½ = Apparent elimination half-life (hr)
Ae% = Amount excreted in urine from 0 to 72 hours postdose (% of dose)

TABLE 3.3. Individual and Mean Quinaprilat Pharmacokinetic Parameters Following Single-Dose Administration of One 20-mg Quinapril HCl Tablet Administered With One 25-mg Hydrochlorothiazide Tablet (Treatment 3): Protocol 955-7

Subject	Cmax	tmax	AUC(0-tldc)	AUC(0-∞)	λz	t½	Ae%
1							
2							
3							
4							
5							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
10							
21							
Mean	594	1.6	2140	2194	0.317	2.19*	29.2
%RSD	19.1	31.4	19.7	19.5	8.27	8.22	17.2

* Harmonic mean

Cmax = Maximum observed plasma concentration (ng/mL)
tmax = Time of Cmax (hr)
AUC(0-tldc) = Area under the plasma concentration-time curve from time zero to the time of the last detectable concentration (ng•hr/mL)
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinity (ng•hr/mL)
λz = Apparent elimination-rate constant (1/hr)
t½ = Apparent elimination half-life (hr)
Ae% = Amount excreted in urine from 0 to 72 hours postdose (% of dose)

TABLE 3.4. Individual and Mean HCTZ Pharmacokinetic Parameters Following Single-Dose Administration of Two 10-mg Quinapril HCl/12.5-mg Hydrochlorothiazide Tablets (CI-955) (Treatment 1): Protocol 955-7

Subject	Cmax	tmax	AUC(0-tldc)	AUC(0-∞)	λz	t½	Ae%
1							
2							
3							
4							
5							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
Mean	143	1.9	875	970	0.090	7.72*	63.1
%RSD	33.4	41.5	20.5	19.4	11.1	11.2	9.07

* Harmonic mean

Cmax = Maximum observed plasma concentration (ng/mL)
tmax = Time of Cmax (hr)
AUC(0-tldc) = Area under the plasma concentration-time curve from time zero to the time of the last detectable concentration (ng•hr/mL)
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinity (ng•hr/mL)
λz = Apparent elimination-rate constant (1/hr)
t½ = Apparent elimination half-life (hr)
Ae% = Amount excreted in urine from 0 to 72 hours postdose (% of dose)

062

TABLE 3.5. Individual and Mean HCTZ Pharmacokinetic Parameters Following Single-Dose Administration of One 20-mg Quinapril HCl/25-mg Hydrochlorothiazide Combination Tablet (Treatment 2): Protocol 955-7

Subject	Cmax	tmax	AUC(0-tldc)	AUC(0-∞)	λz	t½	Ae%
1							
2							
3							
4							
5							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
Mean	131	1.8	842	933	0.093	7.49*	64.0
%RSD	26.3	31.4	16.1	15.7	15.9	15.9	15.6

* Harmonic mean

Cmax = Maximum observed plasma concentration (ng/mL)
tmax = Time of Cmax (hr)
AUC(0-tldc) = Area under the plasma concentration-time curve from time zero to the time of the last detectable concentration (ng•hr/mL)
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinity (ng•hr/mL)
λz = Apparent elimination-rate constant (1/hr)
t½ = Apparent elimination half-life (hr)
Ae% = Amount excreted in urine from 0 to 72 hours postdose (% of dose)

063

TABLE 3.6. Individual and Mean Hydrochlorothiazide Pharmacokinetic Parameters Following Single-Dose Administration of One 20-mg Quinapril HCl Tablet Administered Concomitantly with One 25-mg Hydrochlorothiazide Tablet (Treatment 3):

Protocol 955-7

Subject	Cmax	tmax	AUC(0-tldc)	AUC(0-∞)	λz	t½	Ae%
1							
2							
3							
4							
5							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
Mean	135	2.1	831	925	0.089	7.82*	58.3
%RSD	32.7	42.7	23.2	23.2	12.2	12.3	12.6

* Harmonic mean

Cmax = Maximum observed plasma concentration (ng/mL)
tmax = Time of Cmax (hr)
AUC(0-tldc) = Area under the plasma concentration-time curve from time zero to the time of the last detectable concentration (ng•hr/mL)
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinity (ng•hr/mL)
λz = Apparent elimination-rate constant (1/hr)
t½ = Apparent elimination half-life (hr)
Ae% = Amount excreted in urine from 0 to 72 hours postdose (% of dose)

K.BONGIOVANNI

AUG 27 1992

NDA:20-125 Submission Date: July 30, 1992.

Quinapril/Hydrochlorothiazide
Tablets(10/12.5, 20/12.5, 20/25)
Accuretic®
Parke-Davis Reviewer: Patrick J Marroum

Type of submission: Change in dissolution specification.

Background:

This is in response to Dr.Teng's recommendation in her Biopharmaceutics review (dated 2/25/1992) to set the dissolution specification for both quinapril and hydrochlorothiazide to not less than minutes. The firm requested that the specification be set at not less than minutes.

RECOMMENDATION:

After reviewing the initial dissolution data presented in the original NDA, and after discussion with Dr.Wolters (HFD 110 supervisory chemist) and Dr.Cunningham (HFD 110 chemistry reviewer), it was learnt that this dissolution specification was set based on the results from one production lot. Moreover, the firm is in the process to put at least 3 more productions lots under stability testing and that they would collect dissolution data from theselots. This is why it was agreed to set the interim specification at not less than minutes with the understanding that the firm is also going to sample also at 15 minutes. This additional data will be presented to the Agency and if there are no problems at the 15 minute time point the specification of not less than minutes will be adopted.
In the event that the additional stability lots do not meet the 15 minutes specification, either the shelf-life of the product will have to be shortened; or the sponsor may have to prove that the changes in the dissolution characteristics of the product have no impact on the bioavailability.

Patrick J Marroum Ph.D

/S/

RD initialed by A.Parekh /S/ 8/27/92
FT initialed by Nicholas Fleischer /S/ 8/27/92

cc: NDA 20-125, HFD 110, HFD 426 (Marroum, Fleischer), Chron, Drug.

JUN 4 1993

OF

NDA:20-125

Submission Date: September 2, 1992.

Quinapril/Hydrochlorothiazide
Tablets(10/12.5, 20/12.5, 20/25)
Accuretic[R]
Parke-Davis

Reviewer: Patrick J Marroum

Type of submission: Change in dissolution specification.

Background:

In the review of Dr Marroum dated August 24, 1992, it was agreed to set the interim dissolution specifications for Accuretic to not less than ____ minutes for both quinapril and hydrochlorothiazide with the understanding that the firm is also going to sample at the 15 minute time point. This additional data will be presented to the Agency and if there are no problems at the 15 minute time point, the specification of not less than ____ minutes will be adopted. Included also in this letter is the final printed labelling for Accuretic (in which there are no biopharmaceutics issues pending).
This submission is an acknowledgment of the sponsor of this recommendation and thus does not need to be reviewed.

/S/

Patrick J Marroum Ph.D

RD initialed by A Parekh /S/
FT initialed by ~~Nicholas Fleischer~~ /S/ 6/1/93

cc: NDA 20-125 HFD 110, HFD 426 (Marroum, Fleischer), Chron, Drug.

APPENDIX 2

"A SINGLE-DOSE PHARMACOKINETIC STUDY TO DETERMINE THE EFFECT OF A HIGH-FAT MEAL ON THE BIOAVAILABILITY OF CI-955 MARKET-IMAGE TABLETS (20-MG QUINAPRIL HCL/25-MG— HYDROCHLOROTHIAZIDE) IN HEALTHY VOLUNTEERS (PROTOCOL 955-8)"

PROTOCOL: 955-8

SPONSOR: Parke-Davis Pharmaceutical Limited
2800 Plymouth Road
Ann Arbor, MI 48105

INVESTIGATOR AND STUDY SITE:

T.M deVries, E.L. Posvar, A.B. Vassos, A.J. Sedman, and S.C. Olson
Parke-Davis Pharmaceutical Research Division
Warner-Lambert Company
Ann Arbor, Michigan 48105

Wisconsin Analytical and Research Services LTD
Madison, Wisconsin 53713

OBJECTIVES:

To determine the effect of a high-fat meal on the bioavailability of CI-955 market-image tablets (20-mg quinapril HCl/25-mg HCTZ).

FORMULATIONS:

1) 20-mg quinapril HCl/25-mg HCTZ tablets, Lot # CM075040, Formulation W15241-4 Amendment 1, manufactured at Vega Baja, Puerto Rico.

STUDY DESIGN:

This study was a single-dose, non-blind, randomized, two-way crossover design conducted in 12 healthy subjects aged 18 to 55 years. Each subject received the following treatments according to a randomized schedule:

1) One 20-mg quinapril HCl/25-mg HCTZ CI-955 tablet administered orally under fasting conditions (FASTED)
2) One 20-mg quinapril HCl/25-mg HCTZ CI-955 tablet administered orally 15 minutes after beginning a high-fat breakfast (FOOD)

The washout period between treatments was seven days. The high-fat breakfast consisted of the following: two scrambled eggs, two slices white toast with two teaspoons margarine, two strips bacon, two ounces hash brown potatoes, and 8 ounces whole white milk.

Blood samples (10mL) were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours after dosing. Urine was collected during the 0-12, 12-24, 24-48, and 48-72 hour time intervals. Both plasma and urine were assayed for quinapril, quinaprilat, and HCTZ.

ASSAY:

DATA ANALYSIS:

Plasma and urine quinapril concentrations were recorded, but not statistically analyzed. Pharmacokinetic parameters were determined for the pharmacologically active compounds, quinaprilat and HCTZ. These parameters included Cmax, Tmax, AUC (0-t), AUC (0-inf), and T1/2. Sequence, subject within sequence, period, and treatment effects were evaluated by analysis of variance (ANOVA), and 90% confidence intervals for differences between least square mean parameters were determined.

RESULTS:

The results of the study are summarized in the following tables and figure:

TABLE 1: Mean Quinaprilat and HCTZ Pharmacokinetic Parameters

Parameter	Arithmetic Means (%RSD) FASTED	FOOD	FOOD/FASTED
Quinaprilat			
Cmax (ng/mL)	642 (20.8)	554 (24.6)	0.86
Tmax (hr)	1.46 (17.7)	2.25 (39.6)	1.54
AUC (0-inf) (ng.hr/mL)	2297 (26.3)	2154 (21.2)	0.94
T1/2 (hr)	2.24 (13.7)	2.12 (12.1)	0.95
Ae% (% of dose)	34.6 (18.5)	31.1 (17.9)	0.90
HCTZ			
Cmax (ng/mL)	170 (36.7)	150 (29.7)	0.88
Tmax (hr)	1.71 (29.2)	2.04 (38.3)	1.19
AUC (0-inf) (ng.hr/mL)	1122 (24.9)	1170 (33.3)	1.04
T1/2 (hr)	8.06 (12.4)	8.09 (12.9)	1.00
Ae% (% of dose)	14.5 (26.0)	13.8 (19.3)	0.95

TABLE 2: Summary of Statistical Evaluation of Quinaprilat and HCTZ Pharmacokinetic Parameters

Parameter	ANOVA Results Observed Difference (%)	P value	90% Shortest CI
Quinaprilat			
Cmax	13.7	0.016	77.7-94.9
Tmax	54.1	0.017	120-189
AUC (0-inf)	6.2	0.268	84.1-103
Ae%	10.1	0.105	79.5-100
HCTZ			
Cmax	11.8	0.119	75.5-101
Tmax	19.3	0.337	84.3-154
AUC (0-inf)	4.3	0.310	97-112
Ae%	4.8	0.510	82.8-108

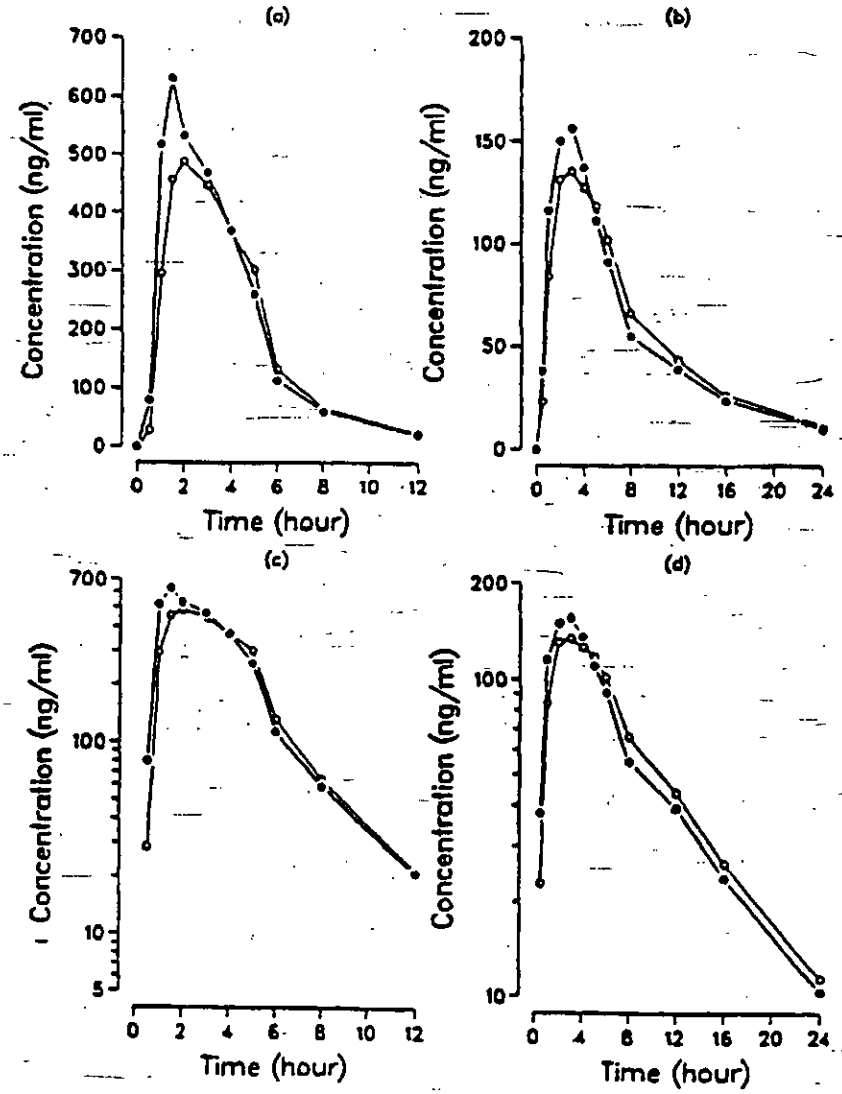

Figure 1. Mean (a) Rectilinear and (c) Semilogarithmic Quinaprilat Plasma Concentration-time Profiles and mean (b) Rectilinear and (d) Semilogarithmic HCTZ Plasma Concentration-time Profiles Following One 20-mg Quinapril/25-mg HCTZ Combination Tablet While Fasting (-●-) and With a High-Fat Meal (-○-): Protocol 955-8