CENTER FOR DRUG EVALUATION AND RESEARCH

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Z-McDonald

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CARDIO-RENAL DRUG PRODUCT DIVISION
HFD 110
QUINAPRIL/HCTZ
MEDICAL REVIEW
NDA 20-125

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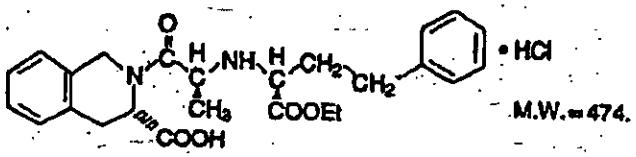
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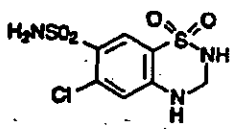
Introduction

1.0 The structure of the components of the drug "Accuretic" (Quinapril and Hydrochlorothiazide) are as follows:

Quinapril



Hydrochlorothiazide



1.1 Rationale for indication

Combination therapy with quinapril and HCTZ is based on the enhancement of blood pressure reduction by diuretic-induced dependence of BP regulation of the renin-angiotensin-system (RAS). The expectation is that quinapril will produce an increase in the response from 50-60% to 70-80% on addition of the thiazide diuretic, hydrochlorothiazide.

2.0 Prior approvability by FDA

The original NDA (20-125) for Accuretic was submitted in December 1990. FDA issued an approvable letter in May 1992 which culminated in submission of labeling by sponsor in September of 1992. The approvable letter was subsequently withdrawn by the FDA in October 1992 due to "unavailability" of a manufacturing facility acceptable to the Agency for the final product. This withdrawal was without prejudice to resubmission at such time as the sponsor decided to manufacture and market in the US. Since 1993, Accupril has been approved in 31 countries worldwide and no country has ever refused or withdrawn marketing approval (See Appendix C of this review). The sponsor has now decided to resubmit NDA 20-125 for approval for the treatment of mild to moderate hypertension in those patients for whom combination therapy is appropriate.

2.1 Resubmission of NDA

The proposed format for a new NDA was received from the sponsor and agreed to by a medical reviewer in January 1999 subject to the following two conditions:

- ISS to be amended and SAEs summarized in the post-approval database.
- Update the labeling to reflect changes made to the original package insert.

2.2 Safety database

The current submission includes cross-references to Item 8 of the original NDA 20-125 for all clinical and statistical information (vols 1.16 -1.52), and also includes the final report for Protocol 955-8 which was ongoing at the time of the original NDA submission. The latter has an impact on current labeling.
The current document submitted as NDA 20-125 N-RS is an abbreviated Safety supplement to the original NDA. It is in 3 parts:

- Summaries of serious adverse events derived from 2 databases spanning over 7.5 years;
- Reported deaths and non-fatal, serious adverse events, and
- Results of a search of published literature for specific serious adverse events and deaths.

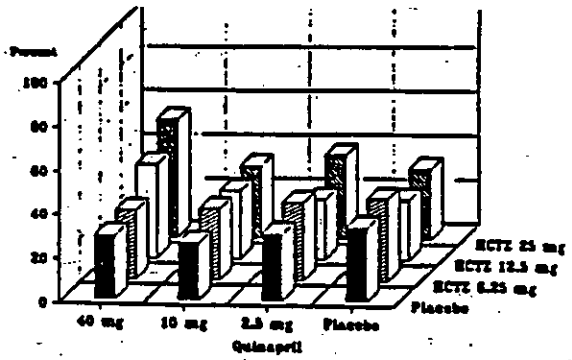
3.0 Efficacy data from original NDA

Two major controlled trials, a factorial design with dose response and a parallel design trial among specific doses of combination versus monotherapy, were carried out in 31 centers (26 were non-US). The medical reviewer of the original NDA concluded that there was statistically significant difference between the combination therapy versus diuretic or quinapril monotherapy ($p=0.020$ and $p=0.008$ respectively for the low dose, and $p=0.025$ and $p=0.023$ respectively for the high dose). Other studies carried out included positive-controlled trial of quinapril versus propranolol, and positive-controlled trial of quinapril versus captopril, and positive controlled studies of quinapril versus captopril and HCTZ background . The results of these studies showed efficacy of quinapril therapy, and also showed that additional reducing effects of BP were observed on addition of HCTZ. Quinapril10/HCTZ12.5 was more effective than monotherapy (Quinapril/HCTZ -14.4; Quinapril -11.8; HCTZ -12.2). Doubling the doses gave rise to the following BP reductions -18.7, -16.5, -16.5, respectively.

4.0 Overview of Safety in D-B controlled trials in Protocol 906-241 of original NDA medical review

Figure 1 , extracted from the original review, shows a positive dose response for adverse drug events at 40mg quinapril, and to a lesser extent at the 10mg dose level with increasing dose of HCTZ .

Figure 1: Dose-response for adverse drug events.



4.1 The table below (51) lists most frequently reported adverse drug events in the original NDA.

TABLE 51. Most Frequently Reported Adverse Events (Percent of Patients)

Adverse Event	Placebo (N = 27)	Quinapril Monotherapy (N = 86)	HCTZ Monotherapy (N = 88)	Quinapril + HCTZ (N = 259)	Total (N = 460)
Headache	14.8	4.7	13.6	4.6	7.0
Dizziness	0.0	2.3	2.3	5.0	3.7
Fatigue	0.0	2.3	1.1	3.1	2.4
Myalgia	0.0	3.5	2.3	2.3	2.4
Abdominal Pain	7.4	1.2	1.1	1.9	2.0
Vertigo	3.7	2.3	1.1	1.9	2.0
Rhinitis	0.0	1.2	1.1	2.7	2.0
Coughing	0.0	0.0	2.3	2.3	1.7
Nausea and/or Vomiting	3.7	1.2	2.3	1.5	1.7
Viral Infection	0.0	1.2	1.1	1.9	1.5
Asthenia	0.0	1.2	1.1	1.5	1.3
Pharyngitis	0.0	3.5	1.1	0.8	1.3
Sinusitis	3.7	2.3	2.3	0.4	1.3

The table below (48) is a a summary of first occurrences of ADEs, total adverse events and also by age and severity from the original NDA.

TABLE 48. Summary of Adverse Events (AEs)

	Placebo (N = 27)	Quinapril Monotherapy (N = 86)	HCTZ Monotherapy (N = 88)	Quinapril + HCTZ (N = 259)
Number of Patients with Adverse Events (%)				
All AEs	9 (33)	24 (28)	28 (32)	83 (36)
Associated[a] AEs	5 (19)	11 (13)	13 (15)	46 (18)
Number of First Occurrences and Total Reports				
All AEs				
First Occurrences	14	44	41	171
Total Reports	15	47	61	174
Associated AEs				
First Occurrences	6	15	17	70
Total Reports	6	15	17	70
Number of Patients with Adverse Events by Age				
All AEs				
<65 years (N = 397)	8 (32)	22 (28)	25 (32)	78 (35)
≥65 years (N = 63)	1 (50)	1 (7)	3 (30)	5 (38)
Associated AEs				
<65 years	5 (19)	11 (13)	11 (14)	37 (17)
≥65 years	0 (0)	0 (0)	2 (20)	9 (23)
Number of Total Reports by Severity				
All AEs				
Mild	8	21	21	93
Moderate	7	16	15	64
Severe	0	0	5	13
Not Specified	0	0	0	14
Associated AEs				
Mild	5	12	12	33
Moderate	1	3	3	23
Severe	0	0	2	9
Not Specified	0	0	0	5
Number of Patients with Clinically Important Adverse Events (%)	0 (0)	0 (0)	2 (2)	8 (3)
Number of Deaths	0	0	0	0
Number of Patients Withdrawn for Adverse Events (%)				
All AEs	1 (4)	1 (1)	0 (0)	12 (5)
Associated AEs	1 (4)	1 (1)	0 (0)	6 (3)

[a] Considered by the investigator possibly, probably, or definitely related to study drug.

The table below (52) lists withdrawals considered to be adverse drug events in the original NDA

TABLE 52. Withdrawals Due to Adverse Events

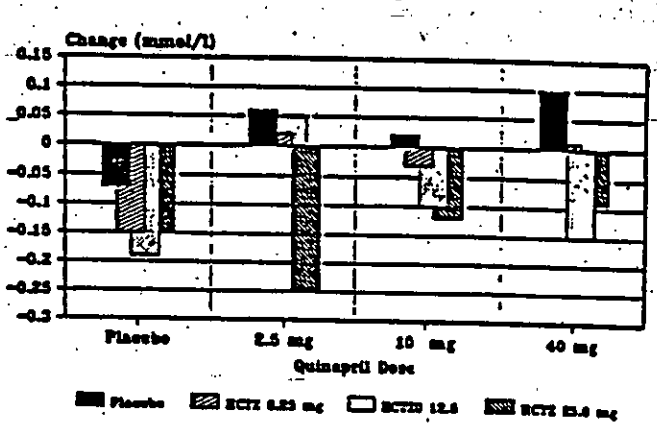
Treatment		Center	Patient	Age Sex	Study Day Began	Adverse Event	Attributable to Study Drug by Investigator
Quinapril	HCTZ						
0	0	21	3	58 F	3	Vasodilation	Probably
2.5	6.25	11	7	61 M	2	Headache, Malaise	Possibly
2.5	6.25	12	4	54 F	10	Palpitation, Insomnia	Possibly
2.5	12.5	25	14	67 M	2	Nausea/Vomiting, Tremor, Abdominal Pain	Possibly
2.5	25	14	6	48 F	45	Fracture	Definitely Not
10	12.5	21	11	40 F	19	Dizziness	Unlikely
10	25	12	21	41 F	1	Facial Paralysis	Unlikely
40	0	8	3	56 M	4	Nausea/Vomiting	Possibly
40	6.25	22	24	51 M	2	Chest Pain	Possibly
40	12.5	6	5	61 F	23	Transischaemic Attack	Unlikely
40	12.5	12	29	42 M	2	Angina Pectoris	Probably
40	12.5	27	8	59 M	10	Hypotension	Possibly
40	25	8	1	59 F	11	Fatigue, Vertigo	Probably
40	25	23	4	49 M	6	Somnolence, Dizziness, Sweating, Tachycardia	Probably

The table below (53) is a summary of patients with changes in serum potassium-baseline to the last visit.

TABLE 53. Mean Change in Serum Potassium (mmol/L) from Baseline to the Last Visit (N = 422)

HCTZ (mg)	Quinapril (mg)			
	0	2.5	10	40
0	-0.07	0.06	0.02	0.10
6.25	-0.15	0.02	-0.03	0.01
12.50	-0.19	0.05	-0.10	-0.15
25.00	-0.15	-0.25	-0.12	-0.09

The graph below shows greater serum potassium reduction in patients on lower doses of quinapril compared to higher doses of quinapril and HCTZ, and to placebo.



The table below (66) is a summary of patients with changes in platelets < normal range.

TABLE 66. Patients with a Possibly Clinically Important Decrease in Platelets Below Normal Range at Final Value

Treatment		Center	Patient	Platelets ($\times 10^3/mm^3$)	
Quinapril	HCTZ			Baseline	Final Value
0	0	4	1	233	172
0	25	15	9	153	122
2.5	6.25	32	11	102	70
10	6.25	12	14	265	130
40	6.25	15	3	211	108

5.0 Summary of ADEs - original NDA (Quinapril/HCTZ)
Out of 6/1457 (0.4%) deaths on Quinapril/HCTZ, which occurred >150 days of treatment, 4 patients were > 60 years old and had MI, 2 died of squamous cell carcinoma and cerbrovascular accident and hypertension, respectively. The percentage of patients with first occurrence of ADEs and the total number of ADEs reported in the original NDA are in Table 48 (See page 3).

5.1 Dosing Recommended dosing regimen by Sponsor considered "reasonable" by Medical Reviewer of original NDA is as follows: 12.5HCTZ/Quinapril 10 and 12.5HCTZ/Quinapril20mg. Approvable letter : Dosing approved in label (See Appendix E)

5.2 Drug exposure Cumulative sales of Quinapril/HCTZ from market launch in 1993 to 1998 was tablets. Patient exposure assuming each patient received 1 tablet per day for 365 days approximates patient-years. Assuming only 50% of the tablets sold were taken by patients, patient exposure to date approximates patient years (Table 6, page 27).

5.3 Integrated Safety Summary
Since the original NDA received an approvable letter the following safety data have been reported: Deaths and non-fatal SAEs (Tables 1-3).

*Deaths: Table 1: Cumulative listing of Reported Deaths through February 1999

Study	Center	Patient ID	Age/ Sex	Study Day	Cause of Death
Quinapril/HCTZ (Cutoff date:9/28/90)					
906-82	83	1	62/M	446	MI
906-82	84	15	62/M	365	MI
906-82	90	9	60/M	747	Cancer
906-114	116	20	73/M	421	MI
906-114	126	4	42/M	497	MI
906-238	15	3	34/F	237	CVA
Non-HCTZ patients					
906-114	122	9	62/M	203	Neoplasm
906-258	6	47	96/F	75	Bronchitis
9003-4	16	345	66/F	34	CVA
9003-4	16	348	68/F	16	Suicide
Enalapril					
9-003-4	16	341	50/M	197	Ruptured Abdomial Aneurysm
Quinapril/H451C1Z (Cutoff Date: 10/10/91)					
906-241	12	19	59/M	176	Neoplasm
Quinapril/HCTZ (Cutoff Date: 2/08/99)					
033-0955-910003-00	25	1	79/F	451	Neoplasm
033-0955-970010			75/M	Unk	Viral Enceph.
033-0955-940005			73/M	Unk	Neoplasm
049-0955-980005			73/M	63	Unk
049-0955-960007			71/F	116	MI
049-0955-960011			58/F	Unk	Unk
049-0955-980012			85/F	Unk	Unk

*See narratives of patients who died in Appendix A.

5.4 In the safety data of the original NDA the most frequently reported serious adverse events are in table 2, inclusive of 69 patients in SU1 and 1571 patients in SU2 (See Appendix B).

Table 2 showing serious adverse events* SU1/SU2

Adverse event (Disease)	Number of patients
Gout	15/1457
Syncope	11
Cancer or neoplasm	11
Myocardial Infarction	5
Diabetes	2
Bladder tumor	2
Bone neoplasm	1

5.5 Since the last safety update (SU), a total of 62 patients were reported to have experienced non-fatal serious adverse events over a period of 7.5 years. These were derived from ongoing clinical studies at the last SU and the remainder from postmarketing reports (Table 3). The most frequently occurring adverse events include bradycardia and syncope, malaise, angioedema, pneumonia, hyponatremia, hypokalemia and dehydration.

The most frequently affected body systems (10 patients) and most frequently occurring adverse events (3 patients) within each body system were: cardiovascular system—bradycardia, syncope; body as a whole—malaise; skin and appendages—angioedema; respiratory system—pneumonia and metabolic and nutritional—hyponatremia, hypokalemia, and dehydration.

The most commonly reported postmarketing serious adverse events were angioedema in 7 patients, and hyponatremia in 6 patients. Of the 7 occurrences of angioedema, all were considered related to treatment and the patients recovered after discontinuation of treatment. Only 1 of the 6 patients with hyponatremia, was considered possibly related to treatment and 4 of the 6 patients discontinued medication. The fate of the remaining 2 patients was not known. Two additional rare serious adverse events were patients with Stevens Johnson syndrome and erythema multiforme. There were also 2 patients with thrombocytopenia both of which were considered related to treatment.

The summary of the 62 patients with nonfatal serious adverse events by body system is presented in Table 3 and the narratives are in Appendix B.

Table 3: Nonfatal, Serious Adverse events by Body System

System	Number
Body as a whole	15
Cardiovascular System	15
Digestive System	8
Hemic System	4
Metabolic and Nutritional Disorders	11
Musculo-Skeletal System	4
Nervous System	7
Respiratory System	7
Skin and Appendages	13
Special Senses	1
Urogenital System	9
Total number of patients with an event	62

Among the nonfatal serious adverse events observed among patients who had received Quinapril/HCTZ, three events that were possibly related to drug intake and were life threatening included angioedema, renal failure/chronic renal diseases, and Agranulocytosis (Table 4). Pulmonary infiltrates have been reported with other ACE inhibitors and they were encountered in patients on Accupril therapy. None of these events occurred with greater frequency in the combined therapy compared to monotherapy. Hyponatremia, and hypokalemia were not uncommon laboratory abnormalities and these may be due to the added diuretic, HCTZ.

Table 4: Serious adverse events of note in the post-approval database

Patient ID/Age/Sex/Race	Nonfatal Serious Adverse event	*Causality/Relatedness
033-973001/49/F/C	Skin lesion with IgA deposit and Renal Failure	Not related
033-980004/68/M/C	Acute renal failure	Possibly related
049-980016/76/F/C	Agranulocytosis	Possibly related
049-99000172/F/C	Stevens Johnson's Syndrome/Toxic epidermal necrolysis	Possibly related
046-940003/no info.	Erythema multiforme	Possibly related
046-960002/65/M/C 046-980002/71/M/C 033-950001/69/M/C 033-960003/75/F/? 033-970002/45/M/C 039-970005/57/M/C	Angioedema " " " " "	Possibly related
046-980001/56/M/C	Myositis, Pulmonary infiltrates	Unknown
049-970005/60/F/C	Alveolitis	Possibly related
033-970009/65/F/B	Granulocytopenia	Possibly related
033-960001/54/M/?B	Cholestatic hepatitis (G-6-P-D def. patient)	Possibly related
046-980003/56/M/C	Lung infiltrates	Possibly related
049-960004/64/M/C	Rhabdomyolysis with increased creatine kinase.Renal failure with increased Creatinine kinase	Not determinable

* =Investigators/Sponsors assessment; C=Caucasian, B=Black, M=Males, F=Females
In addition to patients with renal failure, several patients with renal diseases had nephrotic syndrome, and focal glomerulonephritis,

5.6 Literature search for adverse events associated with Quinapril and HCTZ intake revealed 5 patients with relatively rare serious adverse events:

Table 5 List of publications relating to relatively rare adverse events in patients exposed to accuretic

Dose (mg)	Study(N)	Adverse event(N)	Reference
Quinapril2.5 /HCTZ25	Quinapril on hypertensives 60-90yr old. (179)	Angioedema (1)	Howes et al., J Am Geratr Soc 44; 1135, 1996
Quinapril/HCTZ12.5	5 step titration open label Quinapril in ↑ BP. (981)	Deaths (2); Stroke and MI-1 each	Jaillon et al., J Cardiovasc Pharm S39, 1992
Quinapril 20/HCTZ	Quinapril in LVH - open label.Efficacy and Safety (98)	Angioedema(1)	Lavezzaro et al., Lab Invest 8, 38-48, 1994
Quinapril10	Quinapril for 4 months(1)	Pulmonary edema and hypotension(1)	Leser et al., Monaldi Arch Chest Dis 49;308-310, 1994
Quinapril10-30/HCTZ25	Quinapril for 18 months (1)	Angioedema (1)	Maier C., Anesthetist 44; 875-879, 1995
Search was restricted to Angioedema, eosinophilic pneumonitis or death associated with Quinapril and HCTZ.			

5.7 Deaths

The narratives for patients who died are in Appendix A. Over the 7.5 years since the last safety update (SU), which included up to 6 years of clinical practice experience in up to 30 countries, an additional 7 Quinapril/HCTZ-treated patients were reported to have died and 62 patients experienced nonfatal, serious adverse events (For narratives see Appendix B, pp.10-26). The types and occurrences of serious adverse events summarized in this SS did not reveal any unexpected safety trends or clinically significant changes in the serious adverse event profile from that reported in the ISS and 2 SUs. In the last SU (SU2), a cumulative total of 12 deaths were reported for the entire Quinapril/HCTZ drug development program. Seven of these 12 patients had received Quinapril/HCTZ and 5 had not. Causes of death among the 7 Quinapril/HCTZ-treated patients were myocardial infarction (4 patients), cancer (1), cerebrovascular accident (1), and neoplasm (1).

5.8 Database

The total number of treated patients in the clinical pharmacology studies and in clinical studies submitted in NDA, SU1 and SU2 are summarized in Table 7, page 28 (Appendix D).

6.0 CONCLUSIONS

- The safety profile of Accuretic is based on the assumption that if only 50% of tablets prescribed had been taken by patients over the past 7.5 years in those 31 countries where it has been approved (Table 6, page 27), patient exposure, by now, would approximate 566,000 patient years.
- The safety profile from the postmarketing period of 7.5 years including 6 years of worldwide postmarketing clinical experience has not revealed any unexpected findings or any clinically significant changes from the original NDA.
- The additional data in the resubmission support the conclusions in the original NDA that Quinapril/HCTZ is safe and well tolerated by patients with mild to moderate hypertension.
- Accuretic should be approved for the treatment of mild-to-moderate hypertension.

7.0 Recommendation

Considering that Accupril (the combined drug) has demonstrated efficacy in mild-to-moderate hypertension (Original NDA 20-125) and in view of the drug's tolerability and safety over a 7.5years of postmarketing in more than 30 countries, Quniapril and Hydrochlorothiazide (Accuretic) should be approved for the treatment of mild-to-moderate hypertension subject to the agency specifications and requirements for manufacture.

8.0 Labeling

The package insert currently submitted and the 1992 previously submitted package insert are similar to those of other ACE inhibitors except in the data relating to relative frequencies of adverse events. The data on adverse events table in the 1992 approvable PI does not reflect postmarketing experience up to February 8, 1999 because the Number of subjects is the same. However if the 1992 table is correct, which is doubtful, there is no significant difference between the relative percent frequencies in adverse events among patients, receiving accuretic compared to placebo except in the frequencies of coughing which had apparently increased in Accuretic-treated patients from 1.6% (1992) to 3.2% (1999) compared to 0.0 (1992) to 2%(1999) in placebo group. Diarrhea was also slightly increased in the accuretic group (1.4%) compared to placebo (1.0%). In general, there are more symptoms observed in the currently proposed changes compared to those listed in the 1992 approvable labeling even though the N is similar. However, disorders of sleep, are not significantly different between the two groups (Table 8, page 38- insomnia and somnolence). Other changes in the current package insert are acceptable. The single study on food-effect shows a 14% reduction in the rate of accuretic tablet absorption when administered with a high-fat meal as compared to fasting (Biopharm review). The AUC was reduced by about 6% in subjects administered high-fat meal compared to fasting. For suggested changes in labeling See pages 29 and 38 of this review.

9.0 APPENDIX A

Narratives for 7 Patients Who Died

033-0955-910003-00, Study 955-005, Center 025, was a 79-year-old female who had neoplastic nodules in lungs with associated fever and tiredness resulting in death. The patient had been receiving quinapril/HCTZ on a compassionate use basis for treatment of hypertension from May 12, 1990 to August 5, 1991, for a total of 451 days. The patient saw her physician on the day quinapril/HCTZ was discontinued, which was Study Day 86, for tiredness, fever (38.7°C), and hypotension. Radiography of lungs and blood analysis were performed on Study Day 87. Patient was hospitalized on Study Day 91 at which time diagnosis of neoplastic lung nodules was made and she was treated with cisplastin. Patient died on Study Day 113. Origin of the cancer is not known.

033-0955-970010, A 75-year-old man with a history of thrombopenia (platelets 90,000/mm 3) was switched from Loxen (nicardipine) to Acuilix (quinapril and hydrochlorothiazide) and experienced an aggravation of thrombopenia, his platelets dropped to 45,000/mm 3 . The physician considered the event was probably related to quinapril/hydrochlorothiazide. This case was reported by a physician in France, local reference number 19970259.
Additional information received from the physician on September 25, 1997, related that the patient was a 75-year-old man with hypertension, who has had thrombopenia for an unknown number of years, and who had had a platelet count of 120,000/mm 3 since 1995. He started taking Acuilix (quinapril and hydrochlorothiazide) in May 1997, and experienced an aggravation of his thrombopenia. Work-up included anti-platelet antibody which was positive and a thoracoabdominal scan which was also normal as well as "all other laboratory and exams were normal." At the end of August 1997, the patient experienced abnormal gait, akinesia, tremor, muscle weakness; and voice, speech, and respiratory disturbances. A few weeks later, in September 97, the patient died. The physician considered the events were related to a viral encephalopathy worsened by corticotherapy and definitely not related to quinapril hydrochlorothiazide.

039-0955-940005-01, A 73-year-old male with history of hypertension and diabetes mellitus developed mediastinal neoplasm on Day 229 of treatment with Acuprel plus HCTZ (quinapril 20 mg plus hydrochlorothiazide 6.25 mg). Patient was also taking chloropropamide and phenformin. Accuprel was initiated on January 29, 1994. During the summer of 1994, patient experienced anorexia, articular pain, and decrease in walking. On September 13, 1994, during the night, patient developed sweating, palpitations, and thoracalgia; on same day, patient was hospitalized and an ECG and thoracic X-ray were performed. ECG revealed atrial fibrillation which disappeared spontaneously after 6 hours. Patient was moved to the pneumology division where arterial catheterizations, bronchoscopy, and spirometry examinations were performed. On September 23, 1993, patient was discharged on quinapril 20 mg/HCTZ 6.25 mg daily, chlorpropamide 250 mg daily, phenformin 60 mg daily, ranitidine 150 mg daily, digoxin 0.25 mg daily, and bromazepam 15 drops daily. Patient has not yet recovered and the adverse event was considered to be severe in intensity and definitely not related to the study medication. This case was reported in a patient enrolled in a Phase 3 study.
Follow up information received May 5, 1995, from the physician revealed that the patient died. The cause of death was listed as neoplasm.

049-0955-960007, Patient Protocol 0955-423-006-1-OS, a 71-year-old woman taking Accuzide (quinapril and hydrochlorothiazide) 20/12.5 mg daily for hypertension as part of Phase 4 study since April 9, 1996, died on August 2, 1996, due to a myocardial infarction. The patient's medical history was remarkable for coronary artery disease, hyperlipidemia, and hyperuricemia. The investigator considered the event was definitely

not related to the study drug. This case was reported by a physician in Germany.

049-0955-960011, Patient , Protocol 0955-423-006-1-OS, a 58-year-old female taking Accuzide (quinapril and hydrochlorothiazide) one daily since September 29, 1996, for hypertension as part of a Phase 4 study died on October 3, 1996. Her blood pressure prior to starting Accuzide therapy was 210/105, pulse rate was 72/min. Concomitant medications included Molsidomine and Glycerol Trinitrate. The patient's medical history was remarkable for cardiac insufficiency, coronary heart disease, and renal insufficiency. The physician determined the death to be definitely not related to the Accuzide. This case was reported by a physician from Germany.

049-0955-980005, A health care professional reported on July 7, 1998, that a 73-year-old Caucasian female patient experienced death after taking Accuzide (quinapril hydrochlorothiazide) for 42 days as a participant in a Phase 4 clinical study (Protocol 0955-423-004). Quinapril therapy was initiated on September 4, 1995, for the treatment of hypertension. The patient was hospitalized and took lab tests on September 4, 1995, her blood pressure (BP) was 200/120 mmHg and pulse was 96/min, the patient's glucose level was 108 mg/dL, total cholesterol was 349 mg/dL, and uric acid was 6.0 mg/dL. On October 16, 1995, the patient's BP was 180/100 mmHg and pulse was 92/min. Quinapril therapy was discontinued on October 16, 1995. The patient died on November 5, 1995. The patient's medical history is remarkable for lipometabolic disease. Concomitant medication includes Mevinacor. The investigator determined that the event is not related to quinapril. This case was reported by a physician in Germany.

049-0955-980012, A health care professional reported on July 7, 1998, that a 85-year-old female patient, developed fatal condition leading to death after taking Accuzide (quinapril hydrochlorothiazide) 1 tablet by mouth, daily as a participant in clinical study (Protocol 0955-423-004-1-OS). Quinapril therapy was initiated on July 24, 1995, for the treatment of hypertension. On November 20, 1995, the patient died. Medical history is remarkable for hypertension, lipometabolic disturbance, diabetes mellitus, hyperuricemia, cardiac insufficiency, coronary heart disease, and arrhythmia. Concomitant medications include Ca-antagonist and diuretic. The reporter determined the event was definitely not related to quinapril. This case was reported by a physician in Germany via the Federal Drug Institute (BfArM), Local Reference number 1998-7-166.

APPENDIX B
Narratives for Patients Who Experienced Nonfatal Serious Adverse Events

027-0955-940001, Patient receiving Accuretic (quinapril/thiazide) 10/12.5 mg developed nephrotic syndrome. Patient was taking thiazide from February 1994 to May 1994 for hypertension. On June 5, 1994, patient initiated Amiloride 5 mg plus HCTZ 50 mg. On June 15, 1994, Amiloride was switched to Accuretic. On June 20, 1994, proteinuria = 3 plus. On June 30, 1994, proteinuria = 2 plus. On July 12, 1994, proteinuria = 3 plus and serum albumin = 32 gm/L. On July 17, 1994, creatinine clearance = 152.3 (normal = 80 to 120). On July 18, 1994 urinary protein = 7.5 gm/24 hours. On July 19, 1994, Accuretic was discontinued and Prazosin was initiated. On July 27, 1994, urinary protein = 9.5 gm/24 hrs, hepatitis B and antinuclear factor = negative, complement 3 = 112.8 (high), complement 4 = normal, ESR = 58, and full blood count and kidney ultrasound = normal. Subsequent (date unknown) renal ultrasound revealed idiopathic focal glomerulosclerosis (a rare disease) with no connection to Accuretic therapy. Patient has a history of hypertension and previous thiazide use for approximately 3 months, and NSAID use for several months on and off during 1994. No known sulfonamide allergy.

031-0955-960001, Patient is a 74-year-old woman with hypertension. She was taking Accuzide (quinapril/HCTZ) 1 tablet daily and was started on Accuzide on

January 7, 1995. She was also using timolol eye drops. On July 5, 1995, she developed dehydration. She was hospitalized and was rehydrated. The Accuzide was discontinued on July 12, 1995. The patient has recovered. The reporter has determined that the event is probably related to the Accuzide.

032-0955-960001, Patient — , Protocol 955-418-001-200, is a 36-year-old man taking Accuretic (hydrochlorothiazide 12.5 mg, quinapril hydrochloride 10 mg) once daily as part of a Phase 4 study, was hospitalized on December 21, 1994, for an asthma crisis. Accuretic was discontinued and the patient was withdrawn from the study. Concomitant medications included Beclomethasone Dipropionate® and salbutamol. Follow-up information received from the physician on July 22, 1996, indicates the patient was taking Accuretic for hypertension and states the asthma crisis started on December 20, 1994. It also provides additional past history including eczema, allergic rhinitis, and prior hospitalizations in 1980 and 1982 for status epilepticus and rhythm disturbances; CPR was performed during one of these hospitalizations. The patient recovered on December 24, 1994. The investigator determined the adverse event was severe in intensity and was unlikely related to Accuretic.

032-0955-960003, Patient — No. 164, Protocol 0955-418-001, a 77-year-old woman, taking Accuretic (hydrochlorothiazide, quinapril hydrochloride) 12.5 and 10 mg, respectively, per day for high blood pressure as part of a Phase 4 study, was hospitalized on August 28, 1994, due to a cerebrovascular accident with right hemiparesis. The hydrochlorothiazide/quinapril hydrochloride was discontinued on August 29, 1994, and the patient was withdrawn from the study. The patient has recovered with sequelae. Concomitant medications included fenofibrate and co-dergocrine. The patient's medical history was significant for dyslipidemia type IIa, cerebrovascular sclerosis, and renal insufficiency. The physician determined the events were moderate in intensity and unlikely related to the study drug. This case was reported by a physician in Belgium.

032-0955-960004, Patient — No. 62, Protocol 0955-418-001, a 71-year-old man, taking Accuretic (hydrochlorothiazide, quinapril hydrochloride) 12.5 and 10 mg, respectively, per day for hypertension as part of a Phase 4 study, was hospitalized on June 3, 1994, due to septic shock and pneumonia. His bronchial aspirate revealed pneumococcus. The hydrochlorothiazide/quinapril hydrochloride was discontinued on June 3, 1994, and the patient was withdrawn from the study. He has recovered. Concomitant medications included fenoterol bromhydrate, and ipratropium bromure inhalations. The patient's medical history was significant for chronic obstructive pulmonary disease. The physician determined the events were moderate in intensity and unlikely related to the study drug.

032-0955-960005, Patient — No. 9605, Protocol 955-418-001-200, a 69-year-old woman taking Accuretic (quinapril) 10 and 12.5 mg daily for hypertension as part of Phase 4 study, was hospitalized on October 7, 1994, with an acute myocardial infarction. The patient started the study on August 30, 1994. The patient's medical history is remarkable for type II diabetes, Paget's disease, mammary carcinoma with mammectomy, and arthritis. The investigator determined that the adverse event was definitely not related to the study drug. This case was reported by a physician in Belgium. Additional information received on July 15, 1996. Accuretic discontinued on October 7, 1994. Concomitant medications included Glibenclamid and Aspirin.

033-0955-910-01-00, Study 955-005, Center 023, a 55-year-old male, was hospitalized for surgery on inguinal hernia on study Day 187. The patient entered the study on September 29, 1990, for placebo phase, then began double-blind phase on study Day 17 and started open label phase on study Day 70. He first received 1 tablet a day of quinapril 20 mg + hydrochlorothiazide 12.5 mg for 1 month, then switched to 2 tablets a

day of quinapril 20 mg + hydrochlorothiazide 12.5 mg beginning study Day 103, which was continuing at the time this event was reported. Other medications were domperidone, ranitidine, pancreas powder, roxithromycin, fusa-fungine, pholcodine, and biclotymol. Patient has had hypertension since 1986 and dyspepsia for several months. He required surgery because of a worsening of the pre-existing hernia. Surgery was successful and the patient recovered.

033-0955-910002-00, Study 955-005, Center 023, a 38-year-old male receiving quinapril/HCTZ, experienced acute renal failure, dehydration, vomiting, and diarrhea. The patient went to his physician on study Day 169 for treatment of diarrhea, vomiting, and fever for which he was given domperidone, loperamide, amoxicillin, carbasalate calcium, and paracetamol. He was hospitalized on study Day 173, where labs were: WBC = 14,300/mm 3 , blood urea = 45 Mmol/L, creatinine = 1070 mmol/L. Diagnosis of acute renal failure secondary to dehydration was made. Patient was treated for dehydration and study medication was discontinued; total exposure to study medication was 172 days. Patient recovered and was discharged from intensive care on study Day 176.

033-0955-950001-00, A 69-year-old male began receiving Koretic (quinapril + hydrochlorothiazide) on December 14, 1994. Two or 3 who noted facial edema without glottis edema. The patient was not hospitalized, but received IV Betamethasone and recovered the next day. The reporting physician felt the facial edema was related to Koretic.

033-0955-960001, Patient is a 54-year-old man with arterial hypertension. He has a history of glucose-6-phosphate dehydrogenase deficiency, paludism in childhood and urinary schistosomiasis. He was taking Acuilix (quinapril and hydrochlorothiazide) 20 mg daily and was started in 1996. On July 6, 1996, he was hospitalized for headache, fever, and abdominal pain. On July 12, 1996, he developed cholestatic hepatitis. Acuilix was discontinued on July 13, 1996. He was treated with Loxen. Liver enzymes returned to normal. He recovered from the headache, fever, and abdominal pain on July 17, 1996. The cholestatic hepatitis is ongoing. The reporter determined the events were moderate in intensity and definitely related to Acuilix.

033-0955-960002, An 85-year-old woman patient was taking Acuilix (quinapril and hydrochlorothiazide). She was also taking Celectol and Kardegic. On June 10, 1996, she was hospitalized for hyponatremia. She recovered within 2 weeks. The investigator determined the adverse event was unlikely related to Acuilix.

033-0955-960003, Patient is a 75-year-old woman with arterial hypertension. The patient has a history of psoriasis arthropathica, subcapital fracture, pulmonary embolism, and hernia. The patient was taking Acuilix (quinapril-hydrochlorothiazide) one-half tablet daily starting April 30, 1996. The patient was also taking Avlocardyl, naftazone, Athymil, and Sectral. The patient developed angioedema on May 1, 1996. Acuilix was discontinued on May 2, 1996. The patient recovered. The physician determined the adverse event was severe in intensity and definitely related to the Acuilix.

033-0955-960004, A 92-year-old woman developed bradycardia, acute renal failure, and malaise on April 20, 1995, while taking Acuilix (quinapril/hydrochlorothiazide) 10 mg daily. Concomitant medications included Profenid, Sectral, and digoxine. Acuilix was discontinued. The patient has recovered.

033-0955-960005, Patient is a 59-year-old woman with mild essential hypertension. She was taking Acuilix (quinapril and hydrochlorothiazide) "for months." On November 17,

1996, she was hospitalized for malaise, loss of consciousness, and hypokalemia. While hospitalized, she developed auricular fibrillation which decreased with treatment of the hypokalemia. The Acuilix was discontinued and the patient recovered from the malaise, loss of consciousness, and hypokalemia.

033-0955-970002, A 45-year-old man with a history of combined hyperlipidemia and hypertension started taking Acuilix (quinapril/hydrochlorothiazide) on July 1, 1996, for hypertension. He was also taking Tenordate and Zocor since July 1, 1994. On August 15, 1996, he developed Quincke's edema and urticaria. He had been stung by a wasp 15 days earlier. The patient also experienced the adverse events in September 1996 and November 1996. It is unknown whether Acuilix therapy was stopped and reintroduced during these months. Acuilix was discontinued on December 10, 1996, and the patient recovered. Therapy with Tenordate and Zocor continues. The physician determined the adverse events were unlikely related to Acuilix, Tenordate, or Zocor.

033-0955-970003, Patient is a 73-year-old woman with hypertension. She started taking Acuilix (hydrochlorothiazide, quinapril hydrochloride) on June 20, 1996. She was also taking Hyperium 1 mg, Alpress LP, and Soprol 10 mg. On July 13, 1996, the patient was hospitalized after experiencing convulsions due to hyponatremia (sodium level was 133 mmol/L) and she fell. She also experienced a fracture, but it is unknown whether this is a consequence of the fall. The patient was treated with sodium chloride infusion and water restriction. The patient recovered with sequalae. The medications were stopped. The hypertension was treated with Tenordate.

033-0955-970004, An 86-year-old woman patient with mild essential hypertension was taking Acuilix (hydrochlorothiazide, quinapril HCl). She has a history of left heart failure and colic diverticulum. Concomitant medications include Fumafer (ferrous fumarate), Discotrine (glonoinum, trinitrine), and Corbionax (amiodarone HCl). On April 25, 1996, she was nospitalized for chest pain and coughing. Cough treatment was not successful. Acuilix and Fumafer were discontinued on April 29, 1996. The patient recovered. The physician determined the adverse event is possibly related to Acuilix.

033-0955-970005, An 83-year-old woman patient with essential hypertension was taking Acuilix (quinapril HCl ± hydrochlorothiazide) 1 capsule daily. She has a history of diseases of the circulatory system, joint prosthesis, and familial hypercholesterolemia. Concomitant medications include Tenormine (atenolol), Temesta (lorazepam), Cervoxan (vinburnine), Zylorix (allopurinol), and Xanax (alprazolam). The patient was hospitalized on January 8, 1996, for severe bradycardia, hypotension, and malaise followed by syncope. Acuilix and atenolol were discontinued on January 15, 1996. The patient recovered and was started on Losartan. The physician determined the bradycardia and hypotension were severe in intensity and that the adverse events were possibly related to Acuilix or atenolol.

033-0955-970007, An 83-year-old man started taking Acuilix (quinapril/HCTZ) 30 mg/18.75 mg daily on an unknown date for an unknown reason. He was also taking Aspirine UPSA (acetylsalicylic acid, ascorbic acid), Debridat (trimebutine maleate), Duphalac (lactulose), Mogadon (nitrazepam), Tinset (oxatomide), and Zyloric (allopurinol). On March 1, 1997, the patient was hospitalized for cytolitic and cholestatic hepatitis. That day his bilirubin, transaminase, and GGT were increased. On March 2, 1997, all medications were discontinued. The following day the patient experienced no pain but was jaundiced. On March 4, 1997, he experienced sensitivity to palpation and had decreased jaundice. On March 5, 1997, he had a normal abdominal echography. According to the physician, a drug-induced hepatitis was suspected. The physician determined the adverse event was unlikely related to Acuilix as well as the other drugs.

033-0955-970009, A 65-year-old black African woman patient with hypertension, started taking 20 mg of Acuilix (quinapril hydrochlorothiazide) daily in May 1997 after unspecified ACE and spironolactone were discontinued. She has a history of abnormal vision, secondary to "Nivaquine." One month later, in June 1997 the patient experienced granulocytopenia. Her "white blood cell count was 3900/mm 3 , neutrophils—1014/mm 3 , and lymphocytes were 2496/mm 3 ." Quinapril HCL + hydrochlorothiazide was discontinued and the outcome of this case is unknown. The medical reviewer of Sanofi -Winthrop determined that granulocytopenia was medically serious. The reporting physician determined that the "relationship to Koretic [quinapril HCL + hydrochlorothiazide is not yet specified." This case was reported by a physician via Sanofi - Winthrop in France, local reference No. 19970193. Additional information received on July 9, 1997, related that quinapril HCL + hydrochlorothiazide was discontinued on June 27, 1997. On July 3, 1997, the patient's "neutrophils were 1465/mm 3 , lymphocytes - 1624/mm3, and monocytes were 475/mm 3 " the values of which where equivalent to those before Acuilix therapy.

033-0955-973001, A health care professional reported on December 22, 1997, that a 49-year-old woman patient developed arthralgia, vascular purpura, and proteinuria on October 3, 1997, while taking Acuilix (quinapril + hydrochlorothiazide) for arterial hypertension. Acuilix had been started on January 1, 1995. A histological examination of the skin revealed "vasculitis." Direct immunofluorescence revealed deposits of IgA C3 "spreading in profound derm." Acuilix was discontinued on October 8, 1997. On October 20, 1997, the patient developed renal insufficiency with proteinuria, leukocyturia, and hematuria which led to the patient's hospitalization on October 28, 1997. Immunological testing was negative for antinuclear antibodies, cryoglobulinemia, Hepatitis B and C serology, and rheumatoid factor. Urine analysis was normal. Renal ultrasound exam was normal, but a Doppler study revealed stenosis of the left renal artery. The patient improved progressively. The renal function normalized within 24 hours except for proteinuria at 1.24 g. The patient was also taking Lipanthyl (fenofibrate) for hyperlipidemia. The reporting health care professional and the Parke-Davis (France) medical reviewer considered the events were unlikely related to Acuilix. Follow-up information received from the healthcare professional on January 23, 1998, via the Agence du Medicament, confirmed the previous report and revealed that on January 6, 1998, a scintigraphy with captopril test eliminated a renal stenosis. On January 12, 1998, laboratory tests revealed the result of "CH50 (complement dosage by hemolyse)" test was normal, and research of ANCA (anticytoplasm polynuclear neutrophil) was negative. "The patient recovered (clinic and biologic)." Causality assessment for the notifies as well as for the Parke-Davis (France) medical reviewer is unlikely.

033-0955-973002, A health care professional reported on December 22, 1997, that a 50-year-old woman patient was hospitalized on March 14, 1997, for hyponatremia (sodium—122), diffuse edema, and decreased plasma osmolality while taking Acuilix (quinapril + hydrochlorothiazide). Acuilix was discontinued (exact date unknown), and the edema persisted but the serum sodium normalized. By March 20, 1997, sodium was 134; on March 28, 1997, sodium was 139. Concomitant medications included Athymil (mianserin hydrochloride), Eupressyl (urapidil), Lysanxia (prazepam), and Sotalex (sotalol). The patient's Athymil was increased to 45 mg daily on March 26, 1997, and to 60 mg daily on April 5, 1997. The edema decreased but was still present in the legs in November 1997. The clinical outcome was "favorable." The patient has a history of heart insufficiency. The reporting health care professional and the Parke-Davis (France) medical reviewer considered the events were unlikely related to Acuilix. This case was reported by a health care professional in France via Agence Du Medicament (No. AG970306).

033-0955-973003, A health care professional reported on December 22, 1997, that an 82-year-old woman patient experienced hypokalemia while receiving Acuilix (hydrochlorothiazide, quinapril hydrochloride) orally. The patient was treated on July 4, 1997, with Rocefin (ceftriaxone sodium) 1 g for a urinary infection. The following day, she experienced vomiting, abdominal pain, fever (39.8°C), and coughing. Laboratory testing on July 5; 1997, revealed her potassium was 3.1 mmol/L. The patient was hospitalized. Hydrochlorothiazide/quinapril hydrochloride was discontinued on July 6, 1997. On July 7, 1997, her potassium was 4.4 mmol/L and on July 10, 1997, her potassium was 4.3 mmol/L. The patient recovered from the event. According to the reporting health care professional and the Parke-Davis (France) medical reviewer, the event was unlikely related to hydrochlorothiazide/quinapril hydrochloride. The patient's medical history is remarkable for diabetes mellitus, arterial hypertension, heart insufficiency, and chronic bronchitis. Concomitant medications included: Corvasal (molsidomine), Daonil (glibenclamide), Aspegic (acetylsalicylate lysine), and Amlor (amlodipine besilate). This case was reported by a health care professional in France via Agence Du Medicament.

033-0955-980004, A health care professional reported on May 29, 1998, that a 68-year-old man experienced diarrhea and acute renal failure leading to hospitalization after receiving Acuilix (quinapril + hydrochlorothiazide) 20 mg daily by mouth for approximately 1 year. Quinapril + hydrochlorothiazide was started April 15, 1997. In March 1998, he experienced diarrhea. On April 8, 1998, he was hospitalized for acute renal insufficiency. Quinapril + hydrochlorothiazide was discontinued April 8, 1998, intravenous rehydration was performed. The patient recovered. The patient had a history of smoking and arteritis. This case was reported by a physician in France. The French Medicine Agency and the Parke-Davis medical reviewer assessed the event as possibly related to Acuilix.

033-0955-980006, A health care professional reported on July 9, 1998, that a 71-year-old man experienced confusion and hyponatremia, leading to hospitalization, starting on April 2, 1998, while receiving Acuilix (quinapril, hydrochlorothiazide) 20 mg by mouth daily for 95 days. The patient started taking quinapril on January 15, 1998, for benign essential hypertension. The patient was hospitalized on April 20, 1998, and quinapril therapy was discontinued. The patient recovered. Concomitant medication included Tegretol LP (carbamazepine). The patient's medical history is remarkable for chronic alcoholism, hepatocarcinoma, parotid tumor, malaria, and cerebral vascular accident with epilepsy in 1994. The investigator and the Parke-Davis (France) medical reviewer determined that the adverse events were possibly related to quinapril.

033-0955-980007, A health care professional reported on July 28, 1998, that a 77-year-old man experienced pruritus and a maculopapular rash on February 10, 1998, leading to hospitalization while receiving Acuilix (quinapril hydrochloride) 22.5 mg by mouth daily for 1 month and Detensiel (bisoprolol) for 3 weeks. The patient started taking quinapril hydrochloride and bisoprolol in January 1998. The patient was treated with antihistamines, and systemic and topical corticosteroids without relief. Quinapril and bisoprolol were discontinued on February 10, 1998, and within 5 days his pruritus improved. However, "a patch test with Acuilix was negative." Within 2 months all events were resolved and the patient has recovered without sequelae. The French Medical Agency and the Parke-Davis (France) medical reviewer determined the events were possibly related to quinapril.

033-0955-980008, A health care professional reported on August 28, 1998, that a 59-year-old man developed varicose ulcerations leading to hospitalization while

receiving an unknown dose of Acuilix (quinapril hydrochloride), Zyloric (allopurinol), and Amlor (amlodipine besilate). The patient was treated with interferon until April 1996 and Hydrea (hydroxycarbamide) until November 1996 for chronic myeloid leukemia. In November 1996 , the patient developed a varicose ulceration, and he was treated with Vercyte (pipobroman). Over a year later, the patient developed "ischemic and necrotic lesions of the tiptoes." The patient was hospitalized on January 2, 1998, and was treated with Ilomedine (iloprost). The patient's clinical outcome is unknown. Quinapril, Amlor, Zycloric, and Vercyte therapy statuses are unknown. The patient's medical history is remarkable for chronic myeloid leukemia. The reporter and the Parke-Davis (France) medical reviewer considered the event was unlikely related to quinapril.

033-0955-980013, A health care professional reported on October 14, 1998, that an 86-year-old woman patient experienced hyponatremia, hypokalemia, an increase in thyroid stimulating hormone (TSH), a decrease in triiodothyronine (T3), and thyroxine (T4) leading to hospitalization on April 7, 1998, for bilateral basal pneumopathy while receiving oral Acuilix (quinapril hydrochloride and hydrochlorothiazide) one-half of 1 tablet daily. Laboratory studies revealed leucocytosis - 26,000 WBC/mm 3 , hyponatremia 104 mmol/L, hypokalemia - 3 mmol/L, TSH - 4.35, and a decreased T3 and T4. On April 9, 1998, Acuilix was discontinued, hydration was restricted and salt was progressively given. Antibiotic therapy and thyroid treatment were also administered. The patient's clinical state improved progressively. Her laboratory values were normal when she was discharged. The patient's medical history is remarkable for hypothyroidism, hypertension, and a myocardial infarction. The reporter determined the events were unlikely related to Acuilix and "accordingly her hyponatremia seemed likely to be multifactorial." The Parke-Davis (France) medical reviewer determined the events were unlikely related to Acuilix.

033-0955-980014, A health care professional reported on October 15, 1998, that a 76-year-old woman patient developed painful acute pancreatitis leading to hospitalization on September 1, 1998, while receiving Koretic (quinapril hydrochlorothiazide) 32.5 mg by mouth daily, Diovenor (diosomin) 300 mg by mouth daily, Lipanthyl (fenofibrate) 200 mg by mouth daily, Peridys (domperidone) 20 mg by mouth daily, Loxen (nicardipine) 40 mg by mouth daily, and Zoltum (omeprazole) 20 mg by mouth daily. The patient started taking quinapril in 1995 for hypertension. Laboratory tests revealed amylase - 1760 U/l, lipase—1000 U/l. A scan revealed: edema and duodeno-jejunal ileus. Koretic, fenofibrate, domperidone, nicardipine, and omeprazole therapies were discontinued on September 1, 1998. Diosomin therapy status in unknown. The patient recovered without sequelae within 5 days. On September 6, 1998, enzymes returned to normal. A scan done on September 22, 1998, revealed a pancreatic pseudo-cyst. She did not have a medical history of hypercalcemia, alcohol, or cholelithiusis, normal lipid levels.

033-0955-980016, A health care professional reported on November 30, 1998, that an 83-year-old woman patient experienced falls and malaise on February 12, 1998, leading to hospitalization while receiving Acuilix (quinapril hydrochlorothiazide) 20 mg by mouth daily. The patient was taking quinapril + HCTZ for benign hypertension. Quinapril + HCTZ therapy was decreased to 5 mg daily on February 14, 1998. The patient recovered without sequella. The patient was discharged from the hospital with the treatment Ac...tel (quinapril) 5 mg daily. The patient's medical history is remarkable for Parkinson's disease. Concomitant medications included Dogmatil (sulpiride) and Havlane (loprazolam). The reporter and the Parke-Davis (France) medical reviewer determined that the events were possibly related to quinapril. This case was reported by the Agence Du Medicament.

033-0955-990001, A health care professional reported on January 8, 1999, that a 66-year-old woman patient developed bradycardia, hypotension, acute renal insufficiency, hypokalemia, hyponatremia, and dehydration starting on December 7, 1998, leading to hospitalization while receiving Acuilix (quinapril hydrochlorothiazide) orally. The patient was taking quinapril + hydrochlorothiazide (HCTZ) for arterial hypertension. The patient "suffered of her arm" due to a fall in the beginning of December 1998; this led to an "aggravation of her depression, anorexia, and an elevated medication." The patient's pulse was 40 beats per minute and blood pressure at 60/35. The patient was treated by gastric wash and atropine. Quinapril therapy status is unknown. The patient has recovered without sequelae. The patient's medical history is remarkable for hypercholesterolemia and neurotic depression. Concomitant medications include Hyperium (rilmenidine), Vasten (pravastatin sodium), Havlane (loprazolam mesilate), and Xanax (alprazolam). The reporter and the Parke-Davis (France) medical reviewer determined the events to be unlikely related to quinapril + HCTZ. This case was reported by a physician in France via Agence Du Medicament.

039-0955-970002, Patient , is a 44-year-old man with hypertension. He has a history of glaucoma. The patient was taking Enalapril without clinical effect. On March 7, 1997, he was started on Accuretic (20 mg of quinapril plus 12.5 mg of hydrochlorthiazide). Concomitant medications included timolol maleate. Approximately 1 month after starting Accuretic, on April 9, 1997, the patient experienced impotence. Accuretic was discontinued on April 8, 1997, and the patient recovered. The physician determined the adverse event to be moderate in intensity and possibly related to Accuretic. This case was reported by a physician in Italy.

039-0955-970005, A health care professional reported on November 13, 1997, that a 57-year-old man, experienced facial edema and pruritis on October 3, 1997, after receiving Quinizide (quinapril + hydrochlorothiazide) 20 + 12.5 mg by mouth daily for approximately 4 to 6 months (start date is not available). On October 3, 1997, the patient complained of moderate face edema and pruritis which was treated with antihistamines and interruption of quinapril + hydrochlorothiazide. After a few days, the treatment was reintroduced and the reaction reappeared. Quinapril + hydrochlorothiazide was discontinued and the patient completely recovered. Concomitant medication included carvedilol. The patient has a history of being intolerant to other antihypertensive treatments. The adverse events were moderate in intensity and considered by the physician as possibly related to quinapril + hydrochlorothiazide.

046-0955-940001, A patient receiving Accupro comp (quinapril + hydrochlororthiazide) for 1 month for mild hypertension experienced petechiae of the legs. The patient's thrombocyte cell count was 6 ´ 10 9 . Hemoglobin and LPK were normal, as was a bone marrow examination. The patient was hospitalized, and hospitalization was prolonged. Patient was treated with prednisolone and recovered. This case was reported by a physician in Sweden.

046-0955-940002, Patient initiated Accupril (quinapril) in January 1994 for hypertonia. Patient has a history of hypertension for 20 years. Accupril reportedly reduced patient's weight 7 kg in 8 weeks. On 5 different occasions, patient drank 5 glasses of wine and the next day experienced total loss of memory of the night before. Patient did not consider herself drunk on these occasions.

046-0955-940003, Accupril (quinapril) was initiated in May 1993 for hypertension. In June 1994 it was changed into quinapril combined with hydrochlorothiazide (Accupro comp 10/12.5). After 6 weeks exanthema, according to the report (like erythema

multiforme) disappeared at time of discontinuation of quinapril. This case was reported by a health care professional in Sweden.

046-0955-940004, Patient taking Accupril (quinapril) for hypertonia for approximately one month experienced arthritis and exanthema. Patient experienced the same reaction years earlier while taking moduretic. This case was reported by a physician in Sweden.

046-0955-960001, A 43-year-old man with hypertension, was hospitalized on February 29, 1996, with a swollen tongue while taking Accupro Comp (quinapril/hydrochlorothiazide) 10/12.5 mg daily. The patient has a medical history of psoriasis. The patient is also taking metoprolol. The patient had no problems swallowing or breathing. He was treated with steroids and his symptoms regressed. The patient later returned to the hospital with increasing swollen tongue and swollen lips. At this time, he had difficulty swallowing but no breathing difficulty. He again received steroids and clemastine. Accupro Comp was discontinued and the patient recovered. The physician determined that the adverse event was severe in intensity and possibly related to Accupro Comp.

046-0955-960002, A 65-year-old man with hypertension, was hospitalized with a swollen tongue and throat on April 3, 1995, while taking Accupro Comp (quinapril/hydrochlorothiazide) 10/12.5 mg. He was treated with betamethasone and IV hydrocortisone. Accupro Comp treatment was continued and on October 10, 1995, the patient again developed angioedema and was hospitalized. Accupro Comp was then discontinued. The patient recovered. The physician determined that the adverse event was severe in intensity and probably related to Accupro Comp. This case was reported by an unknown source in Sweden.

046-0955-970002, A 60-year-old woman patient with essential hypertension, started taking Accupro (quinapril HCl + hydrochlorothiazide) on October 23, 1996. Concomitant medications included calcium gluconate, Panodil (paracetamol), Behepan (cyanocobalamin), Mucomyst (acetylcysteine), Calciopen (phenoximethylpenicillin calcium), Toilax (bisacodyl), Bricanyl (terbutaline sulfate), Doloxene (dextropropoxyphene HCl), Pulmicort (budesonide), Lopid (gemfibrozil), and Lomir (isradipine). On January 16, 1997, the patient developed angioedema and was hospitalized. Accupro was discontinued on January 28, 1997. The patient recovered. The patient was rechallenged (date unknown) and symptoms reappeared. The investigator determined the adverse event was severe in intensity and probably related to Accupro.

046-0955-980001, An unidentified Swedish source reported on January 7, 1998, that an unidentified 56-year-old man experienced pulmonary infiltration and myositis beginning in June 1997 while taking Accupro Comp 20 (quinapril hydrochlorothiazide) 12.5 mg during the last 18 months for hypertension. The patient was also taking Pravachol (pravastatin sodium). In June 1997 he had developed a cough and a low-grade fever. An x-ray of the heart and lungs revealed left-sided infiltrates. He was treated with amoxicillin which was subsequently discontinued and replaced with loracarbef. On June 25, 1997, he also experienced myalgia and Pravachol (pravastatin) was discontinued as a possible causal drug per the reporter. A pulmonary x-ray was performed 2 weeks later which showed pleural liquid and remaining infiltrates. He also developed weight increase, edema, and breathlessness which was treated with diuretics. His condition improved. During July 10, 1997, to July 14, 1997, the patient was hospitalized because of his impaired general condition, muscle weakness, and tiredness. He was subsequently diagnosed with possible pneumonia and myositis. The patient was treated with phenoxymethylpenicillin. His general condition improved, but his lung x-rays continued to show unchanged infiltrates. In October 1997, he continued to have myalgia and lung

symptoms. He was treated with steroids which resulted in an improvement in his pulmonary symptoms. Laboratory data performed on June 25, 1997, showed elevated CK (creatine kinase) at 5.9 (nl <3.3 ukat/L). On June 30, 1997, lab values were: CK-13.6, "CRP"-44, and LD (lactic dehydrogenase) - 12.2 (nl 3.9-8.0 ukat/L). On July 4, 1997, a lab result for CRP was 38. On July 7, 1997, a lab result for CRP was 31. On July 10, 1997, the lab values were: CK-26.0 and CRP-29. The patient's clinical outcome is unknown. His medical history is remarkable for atrial fibrillation, hypothyroidism, and diet-treated diabetes. Concomitant medications include Levaxin (levothyroxine sodium), Waran (warfarin sodium), Plendil (felodipine), and Sotacor (sotalol HCl).

046-0955-980002, A health care professional reported on February 9, 1998, that a 71-year-old man patient (identified as No. 973022) experienced angioedema while taking Accupro Comp (quinapril HCl/hydrochlorothiazide). The patient was started on quinapril HCl, hydrochlorothiazide 1 tablet daily orally in 1997 for essential benign hypertension. On November 16, 1997, he developed breathing difficulties and a severe swelling of the tongue. The patient was hospitalized and treated with hydrocortisone and prednisolone. He did not improve and was transferred to the intensive care unit, where betamethasone was administered intravenously. Quinapril HCl/hydrochlorothiazide was discontinued on November 16, 1997, and Lasix retard (furosemide) was started. The patient recovered and was discharged 2 days later. Reportedly, the patient had developed a swelling of the tongue in the beginning of November 1997, but the symptoms had resolved spontaneously. Concomitant medication included Plendil (felodipine). The reporter determined the event was severe in intensity and probably related to quinapril HCl, hydrochlorothiazide.

046-0955-980003, A health care professional reported on April 17, 1998, that a 56-year-old man experienced pneumonia, myositis, weight increased, and edema while receiving Accupro Comp (hydrochlorothiazide, quinapril HCl) 20/12.5 mg daily, orally for 18 months. Pravachol (pravastatin sodium) 40 mg daily was also considered a cosuspect. Hydrochlorothiazide, quinapril HCl was started in 1996 for hypertension. Pravastatin sodium was started on June 28, 1996, for hyperlipidemia and hyperglyceridemia. In June 1997, the patient developed a cough and a low-grade fever. A chest x-ray revealed left sided infiltrates. He started treatment with amoxicillin, which was discontinued and loracarbef was instituted. He also experienced myalgia. Pravastatin sodium was discontinued on June 25, 1997. A pulmonary x-ray performed 2 weeks later (July 1997) showed pleural liquid and remaining infiltrates. The patient also experienced an increase in weight, edema, and breathlessness, which was treated with diuretics withclinical improvement. During July 10, 1997, and July 14, 1997, because of muscle weakness, tiredness, and impaired general condition he was referred to the hospital, where possible pneumonia and myositis were diagnosed. He was treated with phenoxymethylpenicillin and his general condition improved, but an x-ray of the lungs showed unchanged infiltrates. In October, the patient still had myalgia and lung symptoms. Laboratory values provided as follows: June 25, 1997: creatine kinase -5.9 mckat/L (normal <3.3 ukat/L); June 30, 1997: C-reactive protein (CRP)—44 (units unk), CK—13.6 mckat/L (normal <3.3 ukat/L), lactic dehydrogenase (LDH)—12.2 mckat/L (normal 3.9—8.0 mckat/L); July 4, 1997: CRP—38 (units unk); July 7, 1997: CRP—31 (units unk); July 10, 1997: CRP—29 (units unk), CK—26.0 mckat/L (normal <3.3 ukat/L); August 5, 1997: CRP—52 (units unk), CK—48.5 mckat/L (normal <3.3 ukat/L), erythrocyte sedimentation rate (ESR)—34 (units unk); August 12, 1997: CRP—27 (units unk), CK—28 mckat/L (normal <3.3 ukat/L), (ESR)—28 (units unk); September 16, 1997: CRP—<10 (units unk), CK—6.4 mckat/L) (normal <3.3 ukat/L), ESR—24 (units unk); October 2, 1997: 4.9 mckat/L (<3.3 ukat/L), ESR—22 (units unk); and October 14, 1997: CK—6.1 mckat/L (normal <3.3 ukat/L), and ESR—6.1 (units unk). Hydrochlorothiazide, quinapril HCl therapy continues. The patient has not

recovered from the myositis, he continues to experience myalgia. He also has not recovered from the pneumonia. The patient has a history of hypertension, atrial fibrillation, metabolic syndrome (diet treated diabetes), and hypothyroidism. Concomitant medications included Levaxin (levothyroxine sodium), Waran (warfarin sodium), Kalitabs (potassium chloride), Furix (furosemide), Plendil (felodipine), and Sotacor (sotalol HCl). The reporting physician determined the events were severe in intensity and possibly related to Accupro (quinapril HCl) and pravastatin. This case was reported by an unknown physician via the Swedish Medical Products Agency, Local Reference No. 971996.

049-0955-940001, Patient receiving Accuzide (quinapril 10 mg plus hydrochlorothiazide 12.5 mg) daily since April 1, 1993, developed toxic hepatitis on April 11, 1994, elevated liver function tests were noted: SGOT = 42 U/L, SGPT = 106 U/L, GGT = 193 U/L, and alkaline phosphatase = 355 U/L. On April 18, 1994, SGOT = 42 U/L, SGPT = 188 U/L, GGT = 198 U/L, and alkaline phosphatase = 402 U/L. Patient was hospitalized on April 20, 1994; liver biopsy results corresponded to toxic hepatitis. Patient was discharged from the hospital on May 6, 1994; Accuzide therapy was discontinued on May 7, 1994. One month following discontinuation of Accuzide, patient's SGOT = 27 U/L, SGPT = 42 U/L, GGT = 198 U/L, and alkaline phosphatase = 396 U/L. Patient also takes atenolol. Patient has a history of arterial hypertension, aortic stenosis grade 1, status post nephrectomy, status post surgical/radiological treatment of breast cancer, chronic face neuralgia of unknown origin, euthyroid goiter, osteoporosis, hypercholesterolemia, and hyperuricemia. This case was reported to us by a physician via our affiliate in Germany.

049-0955-940002, A male patient with a history of hypertension and diabetes mellitus receiving Accuzide (quinapril + hydrochlorothiazide) for 3 months experienced abdominal cramps. Accuzide was discontinued and the symptoms abated, but reappeared after the drug was given again. Concomitant medications were Antagonil (Nicardipin HCl) and insulin. This case was reported by a physician.

049-0955-960001, Patient , protocol 0955-423-004-1, a 49-year-old man taking Accuzide (quinapril + hydrochlorothiazide) 20 mg daily for hypertension since October 26, 1995, as part of Phase 4 study collapsed and was subsequently hospitalized on November 27, 1995. Accuzide was discontinued and treatment with a Beta-Blocker initiated. The patient recovered and was discharged approximately 1 week later. Concomitant medications included (Cocculus, Conium, and Ambra and petroleum combination), Silymarin and diazepam. The patient's medical history is remarkable for coronary artery disease and alcoholism. There was insufficient information to determine relationship to study drug. This case was reported by a physician in Germany. Additional information received from the physician on July 7, 1998, related that on October 26, 1995, baseline laboratory studies revealed a sitting blood pressure (BP) of 150/110 mm/Hg. His pulse was 84/min, triglycerides were 180 mg/dL, total cholesterol was 240 mg/dL, and uric acid was 3.5 mg/dL. Quinapril therapy was discontinued on November 27, 1995. The patient has recovered. Concomitant medications included Vertigoheel (homepathics nos). The investigator determined the event was probably related to quinapril; however, he stated that the, "causality of the adverse event was not quite clear."

049-0955-960002, Patient No. 1-OS, Protocol 955-423-004, a 75-year-old woman taking Accuzide (quinapril + HCTZ) for hypertension since March 2, 1995, as part of Phase 4 study, developed generalized dermatitis with itching, rash, and transitory nail disturbed maturation. The patient's medical history is remarkable for diabetes mellitus, hyperlipidemia, and coronary artery disease. Concomitant medications included nifedipine retard, comb-insulin, Corvator, isosorbide mononitrate, and Bezafibrat. The

patient was hospitalized. Accuzide was discontinued. The patient recovered. The investigator determined the adverse event was severe in intensity and possibly related to study drug. This case was reported by a physician in Germany. Additional information received from the patient on August 7, 1998, indicated that the patient's dermatitis spread from head over the trunk to the legs, with itching redness and temporary disturbances of nail development. It was also associated with "severe physical and psychic impairment." The condition improved slowly after the discontinuation of Accuzide (quinapril + HCTZ).

049-0955-960004, Patient , is a 64-year-old man with hypertension. He was taking Accuzide (hydrochlorothiazide 12.5 mg, quinapril hydrochloride 10 mg) daily and atenolol 100 mg daily. On May 23, 1996, he was hospitalized due to rhabdomyolysis with an increased creatine kinase of 52,300 m/L. He also developed paralysis and renal failure with an increased creatinine. The patient has recovered with sequelae. Thephysician determined the rhabdomyolysis was immediately life threatening and the relationship to the hydrochlorothiazide, quinapril hydrochloride, and atenolol was undeterminable.

049-0955-960006, Patient is a 66-year-old woman with hypertension. She has a history of depression and anxiety. She was taking Accuzide (quinapril HCl and hydrochlorothiazide) 20 mg daily and was started on Accuzide on November 10, 1994. She was also taking oxazepam and fluspirilen. In April 1996, the patient developed thrombocytopenia and anemia and was hospitalized. On admission, thrombocytes were low at 16,000 and Hgb at 10.5. Accuzide and fluspirilen were discontinued. The patient was placed on Cortison and Imurek. She was discharged from the hospital and now is being followed by a hematologist. She has been switched to Celiprolol HCl and amlodipine for hypertension. The patient has not yet recovered. The physician determined the events were severe in intensity and possibly related to Accuzide.

049-0955-960009, Patient Protocol 0955-423-006-1-OS, a 68-year-old woman taking Accuzide (quinapril, hydrochlorothiazide) for hypertension as part of an observational study was hospitalized on November 19, 1996, due to a posterior myocardial infarction. Quinapril/hydrochlorothiazide was started on August 26, 1996, and was continued. The patient has not yet recovered. Concomitant medications included diltiazem, aspirin, glibenclamide, and cisapride. The patient's history is significant for diabetes mellitus and coronary heart disease. The physician determined the event was severe in intensity and definitely not related to the study drug.

049-0955-960010, Patient , Protocol 0955-423-006-1-OS, a 75-year-old man taking Accuzide (quinapril and hydrochlorothiazide) since November 6, 1996, as part of a Phase 4 study, was hospitalized on December 4, 1996, for worsening of cor pulmonale. The Accuzide dose was maintained and the outcome of the event is unknown. Concomitant medication included theophylline. The patient's history is remarkable for cardiac insufficiency, coronary heart disease, cor pulmonale, hypertension for 40 years, and previous treatment with digitalis. The reporter determined the event to be life threatening and definitely not related to the Accuzide.

049-0955-970002, Patient is a 48-year-old man with hypertension. He has a history of coronary artery disease, lipid metabolism disorder, and hyperuricemia. He was taking Accuzide (quinapril, hydrochlorothiazide) 2 tablets daily and had started Accuzide on September 25, 1996. He was also taking a beta blocker (unspecified). The patient was hospitalized for an unspecified reaction. Accuzide was discontinued due to "administrative" reasons. According to the reporting physician, the patient had good

results from Accuzide. The causality assessment is indeterminable at this time. Additional information received from the physician on April 29, 1997, related the patient experienced speech disorder and dizziness in November 1, 1996. The patient has recovered. The patient's past medical history is also remarkable for obesity and atrial fibrillation. The reporting physician determined the adverse events were moderate in intensity and definitely not related to Accuzide.

049-0955-970003, Patient is a 55-year-old man with hypertension. He has a history of diabetes mellitus, liver cirrhosis with portal hypertension, and hypertension since 1994. He was taking Accuzide (quinapril and hydrochlorothiazide) 1.5 tablets from November 25, 1996, to December 17, 1996, and 2 tablets from December 18, 1996, to an unspecified date. He was also taking "Maniuil" for treatment of his diabetes. Accuzide was discontinued because of esophageal cancer and metastases with ascites. Other antihypertensive agent and diuretics were started. The reporting physician did not consider the treatment discontinuation to be related to an adverse event.
Follow-up information was received from the physician on November 5, 1997, indicating that the patient, who was participating in an observational study (Protocol 0955-423-006-1-05) was hospitalized (date unknown) for the events and has not yet recovered. Quinapril and hydrochlorothiazide "1.5 tablets" was started November 25, 1996. On December 18, 1996, the dose was increased to "2 tablets" daily and later discontinued. The stop date is unknown. The reporter indicated that the relationship of the adverse events to the study drug was unlikely.

049-0955-970005, Patient a 60-year-old woman with hypertension and a 3-year history of exercise dyspnea, "adipose individual condition," esophagitis, pneumonia a year ago, retrosternal pain radiating to the back, complains of becoming asthmatic around canaries, cough, and migraine since 1984, gastrointestinal complaints since 1996 (all year round and independent of location or activity), and varicosities in both lower legs, started taking Accuzide (quinapril hydrochloride and hydrochlorothiazide) 10 to 20 mg orally and Nifehexal (nifedipine—dose unknown) on an unknown date. On February 24, 1997, the patient was hospitalized for retrosternal/left thoracic pain and was diagnosed with suspected alveolitis due to ACE inhibitors and ulcerous reflux esophagitis. She was in good general condition, with no signs of cardiopulmonary decompensation, clear "crackling" over basal lung segments on both sides, and otherwise had an unremarkable status. "The ECG revealed excessive left type, normofrequent sinus rhythm, flat end segment, and no dynamics over course." Infarction was ruled out. An exercise ECG was performed later and was stopped after 100 watts, 10 minutes at capacity. The patient had a maximum pulse rate of 168/min and blood pressure of 230/120 mmHg which indicated exercise hypertension. Also, the patient had no symptoms of angina pectoris, no relevant ST decrease, and no sign of relevant coronary heart disease. Echocardiography showed small, concentric, hypertrophied, left ventricle with good LV function. X-ray examination of the thorax at 2 levels revealed numerous reticular signs over both lower fields. On March 3, 1997, an esophagogastroscopy revealed ulcerous reflux esophagitis with slidinghiatus hernia and mild bulbitis which, according to the physician, "very likely explained the 'patient's' complaints." The patient reported "increasing freedom from complaints" under H2 blocker, prokinetics, and proton pump inhibitors. Control esophagogastroscopy on March 12, 1997, showed healing. A bronchoscopy with bronchoalveolar lavage was unremarkable for morphological findings. Pulmonary function examination revealed mild to moderate restriction, also similar degree of obstruction, and the beginning of emphysematous lung expansion. The patient also had the following laboratory values: pANCA and cANCA were negative, "ANA 1:80 (positive), >1:40," and DNS antibodies were negative. Bronchoalveolar lavage showed elevated neutrophils and eosinophils. Differential cytology found elevated polymorphonuclear and eosinophilic cell proportions and also a greatly reduced cell-mediated immunodefense. "ESR was

20/30 mm W (36/62) and all other values were normal." Alveolitis was suspected because the patient has had exercise dyspnea over the past 3 years. Extensive allergy tests were performed to rule out other possible etiology. The patient had "no reaction to the intracutaneous test of inhalative antigens with normal skin reactivity. In splintering, the patient had a discrete reaction to Aspergillus and Pullularia, RAST classes O in each case. Nasal testing was negative for both. RAST for Dermatophagoides pteronyssius and farinae indicated RAST classes O and total IgE was 37.2 kU/L. IgG values were negative with respect to various canaries, budgies, and parakeet antigens, weakly positive for Aspergillus fumigatus and Pullularia, Cephalosporium acremonium and Trichoderma viride above 40%." Allergic genesis of alveolitis was ruled out and the physician suspects that alveolitis developed under treatment with ACE inhibitor medication. Accuzide was discontinued in February 1997, and the patient was switched to another antihypertensive medication and released from the hospital on March 14, 1997. Clinical outcome is unknown. The physician requested that the patient be readmitted to the hospital 3 months later for "control examination." Recommended medication therapy is a follows: Lorzaar (losartan potassium) 50 mg 1 ´ 1 and pantozol 1 ´ 1 for another 3 weeks. Reportedly, the physician determined that the "suspicion of alveolitis" was possibly related to Accuzide. This case was reported by a unknown physician in Germany via BfArM, Local DRA No. 97004273.

049-0955-980006, A health care professional reported on July 7, 1998, that a 69-year-old woman patient, experienced vasculitis and developed an infection leading to hospitalization after taking quinapril hydrochlorothiazide 1.0 mg daily per oral as a participant in a Phase 4 clinical study (Protocol 0909-423-123-1-OS). The patient started taking quinapril/hydrochlorothiazide on November 2, 1995, for the treatment of hypertension. The patient experienced the event on December 27, 1995. The patient recovered in February 1996. Quinapril hydrochlorothiazide therapy was discontinued. The patient's medical history is remarkable for hypertension, lipometabolic disturbance, hyperuricemia, subclinical neurogenic muscular atrophy, and adiposity. Concomitant medications included Godamed (acetylsalicylic acid, aminoacetic acid), Trepress, and Uripurinol 300 (allopurinol). The investigator determined the adverse events were moderate in intensity and unlikely related to quinapril/hydrochlorothiazide. This case was reported by a physician in Germany, Local Reference No. FR 1998-7-169.

049-0955-980009, A health care professional reported on July 7, 1998, that a 53-year-old man, , developed angina pectoris on approximately August 25, 1995, leading to hospitalization while receiving Accuzide (quinapril hydrochloride, hydrochlorothiazide) orally, as a participant in an observational study (Protocol 0955-423-004-1-OS). The patient started taking quinapril on August 25, 1995, for hypertension. That day, his sitting blood pressure (BP) was 200/105 mmHg and pulse was 76/min, and the patient experienced angina pectoris. Quinapril therapy was discontinued and the patient has recovered. The patient's medical history is remarkable for hypertension (1992) and lipometabolic disease. The investigator determined the event was moderate in intensity and was "unclear" regarding the relationship of the event to the study drug.

049-0955-980010, A health care professional reported on July 7, 1998, that a 44-year-old man, experienced severe visual disturbance, unstable gait, lateral headache, dyspnea, meningeal irritation, dizziness, and suspected alcohol breath leading to hospitalization, while taking Accuzide (quinapril + hydrochlorothiazide(HCTZ)) one-half dose per oral, for 7 days as a participant in the OPUS clinical study (Protocol 0955-423-004-1-OS). The patient started taking quinapril + HCTZ on January 11, 1996, for the treatment of hypertension. In January 1996, the patient experienced the event. Laboratory tests on January 11, 1996, revealed a blood pressure (BP) of 165/95 mm Hg, pulse 120/min, and glucose 59 mg/dL; similar tests on January 18, 1996, showed a BP of 150/110 mm Hg,

pulse 104/min, and a glucose value reported as "normal". Quinapril + HCTZ therapy was discontinued. The patient has recovered. The patient's medical history is remarkable for hypertension, lipometabolic disturbance, increased liver values, and suspected alcohol abuse. The reporter determined the adverse events were severe in intensity and unlikely related to quinapril + HCTZ. This case was reported by a physician in Germany, Local Reference No. FR 1998-7-170.

049-0955-980011, A health care professional reported on July 7, 1998, that a 65-year-old man, developed cellulitis, connective tissue knots, and vasculitis on June 10, 1995, while receiving Accuzide (quinapril hydrochloride, hydrochlorothiazide) 20 mg by mouth daily for 3 weeks as a participant in an observational study (0955-423-004-1-OS). The patient started taking quinapril on May 20, 1995, for hypertension. On June 10, 1995, the patient developed cellulitis, connective tissue knots, and vasculitis causing "permanent damage". Subsequently, quinapril therapy was decreased to 10 mg daily on June 20, 1995. The patient has not yet recovered. The patient's medical history is remarkable for lipid metabolism disorder, hyperuricemia, cardiac surgery (mitral valve in 1980 and 1991), cardiac insufficiency, hypertension and atrial fibrillation since 1993. Concomitant medications include digitoxin, Marcoumar (phenprocoumon), rauwolfia, and a calcium antagonist. The investigator determined the adverse events were moderate in intensity and possibly related to quinapril.

049-0955-980013, A health care professional reported on September 21, 1998, that 47-year-old man developed pancreatitis on December 29, 1997, leading to hospitalization while receiving an unknown dose of Accuzide (hydrochlorothiazide, quinapril hydrochloride) by mouth. The patient started taking quinapril on February 17, 1995, for hypertension. Laboratory studies (on unknown date) revealed an elevated lipase up to 2751. An endoscopic retrograde cholangiopancreatography (ERCP) found no cause twice. In April 1998, the patient's lipase level was 361. Quinapril therapy was discontinued on June 25, 1998. A repeat ERCP in July 1998 again found no cause. Reportedly, the patient has recovered, but still complains of a "strange sensation in abdomen." There is no history of alcohol abuse.

049-0955-980015, A health care professional reported on November 24, 1998, that a 57-year-old woman patient, experienced larynx edema considered to be life threatening and deep venous thrombosis considered to be medically significant while receiving an unknown dose of Accuzide (quinapril hydrochlorothiazide) orally. The patient was taking quinapril for hypertension. Treatment included a tracheotomy, intrasurgical resuscitation, and ventilation-therapy. Quinapril therapy status is unknown. The patient recovered from the larynx edema with sequelae, and the clinical outcome of the deep venous thrombosis is unknown. The patient's medical history is remarkable for depression. The reporting physician determined the event was possibly related to quinapril. Follow-up information received from the physician on February 23, 1998, indicated that the patient was diagnosed with right deep leg-pelvic venous thrombosis, angioneurotic edema, and tachyarrhythmia while receiving quinapril. The patient had angioneuroticedema instead of larynx edema as previously reported. The patient was in the hospital for intensive medial care in status after emergency tracheotomy and cardiopulmonary reanimation after administration of an ACE inhibitor (quinapril). The patient was transferred from the Ear Nose and Throat (ENT) department to another department in the hospital. The patient was in chronically reduced general condition, adipose, nutritional conditions with normal vigilance and orientation. There was no cyanosis or dyspnea. The right leg was livid, swollen, and increased in circumference, the foot pulses could be felt on all sides. Lungs auscultatory free with vesicular respiratory sounds. In status after tracheotomy, deep, well-granulating, nearly closed tracheostoma. Laboratory studies revealed on October 18, 1998, that hemoglobin—12.8 g/dL, leukocytes—14,000/mL, thrombocytes—361000/mL, creatinine (CREAT)—0.9 mg/dL, sodium (NA)—

137 mmol/L, potassium (K)—4.7 mmol/L, glutamic-oxaloacetic transaminase (GOT)—10 U/L, glutamic pyruvic transaminase (GPT)—18 U/L, gamma-glutamyl transferase (GGT)—94 U/L, alkaline phosphatase (ALK-P)—189 U/L, C-reactive protein (CRP)—17.2 mg/dL, partial prothrombin time (PTT)—26 seconds, electrocardiogram (ECG) showed continued arrhythmia with rate of 110/min, left type, and preterminal negative Ts in I, aVL, and V4 to V6. The same day, a duplex sonography revealed complete deepleg venous thrombosis starting in the popliteal area extending to external iliac vein; whereby, the thrombus cannot be delineated proximal. Therefore, PTT heparinization was started, followed by an abdominal-pelvic computed tomography (Pelvic CT), on October 20, 1998, which found right pelvic venous thrombosis with cavathrombosis. The thrombic clot extended approximately 5 cm below the renal veins. Secondary findings included a slight spleen infarction and pleural effusion. A transthoracic echocardiography found the left atrium enlarged and the right cardiac dimensions were borderline enlarged. No signs of thromboses were found in the transthoracic examination. On October 20, 1998, a carotid Doppler revealed slight arteriosclerotic changes on the left side. There is semicircumferent calcified plaque high in the area of the right bulbous. This makes the outflow area of the internal communicating carotid artery impossible to evaluate. However, the flow profile in the further course is normal. A pulmonary perfusion scintigraphy was performed on October 22, 1998, in mild dyspnea to rule out pulmonary embolism. There was no scintigraphic evidence of segmental perfusion defect in the sense of pulmonary embolism. On October 22, 1998, the long-term blood pressure measurement revealed increased systolic and diastolic blood pressure values over the course of the day (96% above 140 mmHg, and 96% over 90 mmHg) with nearly obliterated circadian rhythm. Several blood pressure controls on subsequent days until discharge showed normotensive values. On October 23, 1998, marcumarization depending on Quick was applied. The patient received prior medication with Novodigal 0.2 1 ´ 1/day and Isoptin 80 3 ´ 1/day for continued arrhythmia. A chest x-ray on October 28, 1998, indicated left type, enlarged heart with no signs of congestion, no infiltrates, and no effusions. A consultation with ENT, on October 29, 1998, showed no acute indication for surgical tracheostoma closure in light of continuing granulation. On October 30, 1998, a course control duplex sonography revealed complete deep right leg venous thrombosis with nearly complete organization around the external iliac vein with lack of cranial limitability. On November 2, 1998, a pelvic CT showed a slight decrease in size of the thrombus in the inferior vena cava. This extends towards cranial 4 cm after the communicating iliac vein junction. On November 6, 1998, a duplex sonographic course control revealed recanalized popliteal vein and superficial femoral vein with slight residual thrombi in the organization, completely occluded communicating femoral vein due to organized thrombus. The external iliac vein appeared partially canalized, the communicating and caudal iliac vein. The same day, Hb—12.8 g/dL, leukocytes 7,400/mL, thrombocytes 342000/mL, creatinine 0.4 mg/dL, NA—139 mmol/L, K—4.8 mmol/L, Bilirubin—0.5 mg/dL, GGT—decreasing 36 U/L, ALK—P—121 U/L, CRP—3.3 mg/dL. The patient has recovered. The patient's medical history is remarkable for an arrhythmia.

049-0955-980016, A health care professional reported on December 3, 1998, that a 76-year-old woman patient, , developed agranulocytosis on November 1998 leading to hospitalization while receiving Accuzide (quinapril hydrochlorothiazide) 10 mg by mouth daily. The patient was taking quinapril hydrochlorothiazide (HCTZ) for hypertension. Laboratory studies revealed white blood cell count (WBC) at 400, hemoglobin at 108, and granulocytes at 70. The patient was treated with Neupogen. Laboratory results revealed WBC at 2000. Quinapril + HCTZ therapy was discontinued on approximately November 25, 1998. The patient has not yet recovered. The reporter determined that the event was possibly related to quinapril ∓ HCTZ. The patient's medical history is remarkable for coronary heart disease, reduced cardiac contractility,

left cardiac insufficiency, and reduced renal function. Concomitant medications included Nitrendipin (nitrendipine), allopurinol, and ASA (acetylsalicylic acid). Follow-up information received from the physician on January 14, 1999, indicated that the "AE [agranulocytosis] is a systemic condition and not related to Accuzide." No further information was reported.

049-0955-990001, A health care professional reported on December 10, 1998, that a 72-year-old woman patient experienced mucolysis, a cough, hyperuricemia, and a febrile infection on March 14, 1997, while receiving Accuzide (quinapril and hydrochlorothiazide) by mouth for arterial hypertension. The patient was treated with ACC200 (acetylcyteine) from March 14, 1997, to March 23, 1997, for mucolysis, Capval (noscapine resin) from March 14, 1997, to March 23, 1997, for cough, and allopurinol since March 14, 1997, for hyperuricemia, and Cotrimoxazol (sulfamethoxazole trimethoprim) from March 14, 1997, to March 19, 1997, for the febrile infection. On March 20, 1997, the patient complained of a headache and was treated with aspirin (acetylsalicylic acid). On March 28, 1997, the patient developed blisters in the inside of the right cheek, vaginal erosion, chills, fever of 40°C, and red eyes. On March 31, 1997, she was hospitalized and diagnosed with Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN). On April 4, 1997, she was diagnosed with conjunctivitis. The clinical outcome of the SJS/TEN, hyperuricemia, headaches, mucolysis, cough, febrile infections, and, conjunctivitis are unknown. The patient's medical history is remarkable for insulin-dependent diabetes mellitus, staphylococcus aureus sepsis, radiation therapy to ovaries for dysmenorrhea, thrombosis, and a metabolic disorder. Concomitant medications included Depot-H-Insulin (insulin human), Modip (felodipine), and Falithrom (phenprocoumon). The reporting physician determined SJS/TEN was possibly related to quinapril.

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APPENDIX C

Table 6: Countries and dates when Accupril received approval for therapy

Country	Trade Name	Date of Marketing Authorization	Date of Market Introduction
United Kingdom	Accuretic	Mar 12, 1992	Jan 1993
Ireland	Accuretic	Apr 16, 1992	Jan 1996
Germany	Accuzide	Jan 28, 1993	Mar 1993
Italy	Accuretic	Feb 01, 1993	Oct 1993
Switzerland	Accuretic	Apr 08, 1993	Jun 1993
South Africa	Accuretic	Apr 14, 1993	Jan 1994
Sweden	Accupro Comp	Jun 29, 1993	Oct 1993
Greece	Accuretic	Jul 19, 1993	Sep 1994
France	Acuilix	Jul 27, 1993	Aug 1994
Austria	Accuzide	Oct 13, 1993	Apr 1994
Belgium	Accuretic	Dec 08, 1993	Feb 1995
Luxembourg	Accuretic	Apr 1994 –	
Netherlands	Accuzide	Jun 14, 1994	Oct 1994
Czech Republic	Accuzide	Oct 26, 1994 –	
Finland	Accupro Comp	Nov 28, 1994	Jan 1996
Spain	Accuretic	Nov 29, 1994	Jan 1995
Colombia	Accuretic	May 17, 1995	Sep 1996
Morocco	Acuilix	Jun 26, 1995	May 1997
Tunisia	Acuilix	Jul 07, 1995	Jan 1996
Mauritius	Acuilix	Sep 05, 1995	1997
Portugal	Accuretic	Feb 16, 1996	Sep 1996
Malawi	Accuretic	Apr 15, 1996 –	
Zambia	Accuretic	Apr 15, 1996 –	
Indian Ocean Islands	Acuilix	Apr 20, 1996 –	
Middle East	Accuzide	Apr 26, 1996 –	
Saudi Arabia	Accuzide	Apr 26, 1996 –	
SR Yugoslavia	Hemovkin Plus	Jul 11, 1996 –	
Peru	Accuretic	Apr 29, 1997	May 1997
Algeria	Acuilix	Mar 27, 1997	Sep 1997
Ivory Coast	Acuilix	Sep 29, 1997 –	
Canada	Accuretic	Sep 1998 –	

♦ = Data not available.

Appendix D

Table 7a

Listing of Completed Clinical Pharmacology and Clinical Studies Submitted in NDA, SU1, and SU2

Study	No. of Quinapril/HCTZ-Treated Patients
Uncontrolled Studies Added in SU1	
906-327X, 906-333X	69
Uncontrolled Studies Added in SU2	
None	
Cumulative Total Patients Summarized For Controlled/Uncontrolled Studies in Second Safety Update	1571
CUMULATIVE TOTAL OF ALL HEALTHY VOLUNTEERS AND PATIENTS IN THE NDA, SU1, AND SU2	1656

The sum of the participants in each study is greater than the actual number in this application because 5 of the 6 open-label extensions included patients who were also in double-blind studies. Each participant is counted only once.

* The NDA summarized safety data from 825 Quinapril/HCTZ-treated patients. Five patients were subsequently found to have received HCTZ only after completing the studies and are no longer included in safety summaries.
* Clinical report not available

Table 7b

Table 1. Cutoff Dates for Serious Adverse Events and Cumulative Number of Participants Treated With Quinapril/HCTZ Included in Safety Summaries to the Quinapril/HCTZ NDA

Safety Summary	Cutoff Date	Cumulative No. of Studies	Cumulative No. of Participants
NDA ISS (RR-REG 720-02780)[1]	9/28/90		
Clinical Pharmacology	–	4	73
Clinical	–	20	1384[a]
Total	–	24	1457[a]
SU1 (RR-REG 720-02955)[2]	4/1/91		
Clinical Pharmacology	–	5	85
Clinical Studies	–	23	1463
Total	–	28	1548
SU2 (RR-REG 720-03014)[3]	10/10/91		
Clinical Pharmacology	–	5	85
Clinical Studies	–	24	1571
Total	–	29	1656

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pages of trade

secret and/or

confidential

commercial

information

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cc:
HFD-110
HFD-110/A.O.Williams
HFD-110/Z.Mcdonald
HFD-110/S.Chen

/S/
A.O.Williams,M.D.

K BONAPARTE

MAR 12 1992

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICERS NDA REVIEW

NDA#: 20- 125

DRUG: Accuretic(tm) (quinapril HCL/hydrochlorothiazide)

SPONSOR: Parke- Davis

TYPE SUBMISSION: NDA Amendment

DATE SUBMISSION: Jan 9, 1992

DATE REVIEW: Feb 7, 1992

REVIEWER: P.L. Dern M.D.

RESUME:

This submission contains RESEARCH REPORT RR 4301- 00150, which provides results of Study 906- 340, an 8- week, randomized, actively- controlled, 26- center (foreign), parallel, 3- group trial of 20mgm quinapril(Q) combined with 12.5mgm HCTZ versus each component. The Sponsor's analysis showed Q+HCTZ more effective than Q and H with a level of safety to be described.

TABLE 3 shows the schedule of observations. The primarary efficacy criterion was trough sup diastolic BP (SDBP) at 20- 28 hrs. Randomization was stratified on center in blocks of 6. The statistical null hypothesis was that the efficacy of the combination was not superior to the effect of Q and of HCTZ (n.b. not in the form of two separate tests).

Observation/Procedure	End of Study Week							
	Screening	Placebo-Baseline[a]				Double-Blind			
		-4	-3	-2	-1[b]	1	2	4	8
Medical History	X								
Physical Examination	X								X
12-Lead Electrocardiogram	X				X				X
Clinical Laboratory	X				X		X[c]	X[c]	X
Vital Signs	X	X	X	X	X[d]	X	X	X	X
Medication Dispensing	X	X	X	X	X	X	X	X	
Patient Compliance		X	X	X	X	X	X	X	X
Concurrent Medication		X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X

[a] Patients were to be off antihypertensive medication for a minimum of 14 days and on placebo for at least 14 days before entering the double-blind period. Therefore, some placebo-baseline visits were optional to allow time for blood pressure stabilization.

[b] After the last placebo-baseline measurements and qualifying of patients for the double-blind period, the first double-blind dose was given at the same visit.

[c] Determination of sodium and potassium only.

[d] Measurements were to be made at trough and hourly-up to 4 hours after the first dose-(Day 1).

BASELINE VALUES: Table 5 (not attached) showed that the distributions of treatment groups by sex, age, median duration of history of hypertension, and percentage of black subjects (n=3 cases per Rx group) were similar. Baseline mean SDBP was Q: 109.1; Q+HCTZ: 108.8; H:108.6. The percentage of cases with AGE >= 65years was 14/108(13%) for Q+HCTZ vs 21/106(20%) for Q, these being the extremes.

Thus, with possible exception of the number of older subjects being lower in the Q+HCTZ group, baseline values were acceptably similar among treatments (n.b fewer older subjects might bias the Q+HCTZ group toward smaller responses to the HCTZ component but this would support the finding of Q+HCTZ >HCTZ so the bias is probably favorable. The contracted plasma volume of older subjects, among other factors, favors an increased response to diuretics.

CONCURRENT Rx: Individual center data was checked for numbers of cases on non- steroidal anti-inflammatory drugs due to the possibility of these agents causing resistance to hypotensive effects. N=4 cases were noted in the Q group;2 in the HCTZ group; and 2 in the Q+HCTZ group.

PATIENT DISPOSITION: Table 10 shows the numbers randomized, about 108 per group, with very much fewer withdrawals (total) in the Q+HCTZ group, only N=2 cases, and the largest number occurring in the Q group. Most withdrawals in all Rx groups occurred after the 4th week of the trial.

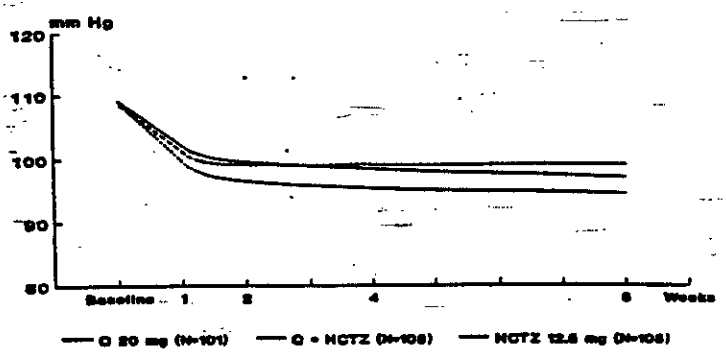
EFFICACY RESULTS: The Sponsor notes that, for the "Evaluable" patient analysis (n.b. or what we would call "per- protocol"), n= 12 cases were excluded on a priori grounds due to withdrawal prior to day 26 as therapy duration was short. n.b. The apriori designation of this would not necessarily eliminate bias due to, say, the disturbance of the randomization consequent to this exclusion, thus the use of "evaluable" cases on this ground of a priori designation is untenable. A priori designation is not a cure-all.

Cases excluded from all efficacy analyses, including intent-to- treat ones, were Q: N=5 (no double-blind data); Q+HCTZ (none); HCTZ:n=1 (no baseline data. Thus very few such exclusions were made. All randomized cases received safety evaluations including "evaluable" ones.

The last available data were used for cases not completing the full trial period.

Effect of time on treatment: The Sponsor tabulated the raw changes from baseline for SDBP by Rx group and time from baseline. For times >= to 4 weeks of therapy the treatment responses were , on average, similar. Very few patients withdrew prior to 4 wks so this source of bias would be negligeable.

The following plot due to the Sponsor shows the time course of the average Rx response expressed as the SDBP itself rather than the change. There is, visually, a tendency for the Q monotherapy slope to be steeper than those from the other agents but BP in the Q group started slightly higher and its activity slightly delayed.



Adjusted mean treatment response: The mean response in change of SDBP, adjusted by analysis of covariance , -14.1mmHg (SE 0.8), was significantly different from Q, which gave -11.8mmHg (SE 0.9), and from HCTZ, -9.5mmHg(SE 0.8). The respective one- sided p values for these contrasts were 0.024 and <0.001.

Comment on statistical analysis: This Reviewer sees the Sponsor's procedure as 1) providing a mean response adjusted for baseline status and, 2) providing contrasts among those adjusted mean responses according to a special null hypothesis deemed by the Sponsor as more appropriate to combination testing than the usual one. Most commonly, two separate tests would be made, one between the combination and each component, separately, with the "nominal" p value from each presented as if one had done n=2 independent tests. Since the Sponsor is interested in only whether the combination is better than both components, the superiority over any one is not an issue for him. His method for testing his null hypothesis confirms superiority of the combination if the larger one- sided p value from the two contrasts is <= 0.05. Those p values shown in the previous paragraph meet that standard.

The interaction of center x treatment group is not significant as seen in APP C vol 1/3.

TABLE 10. Patient Disposition
[Number (%) of Patients]

	Quinapril 20 mg	Quinapril + HCTZ	HCTZ 12.5 mg	Total
Randomized to Treatment	106	108	109	323
Withdrawals				
Adverse Events	6 (5.7)	0 (0.0)	2 (1.8)	8 (2.5)
Lack of Efficacy	2 (1.9)	2 (1.9)	3 (2.8)	7 (2.2)
Lost to Follow-up	2 (1.9)	0 (0.0)	2 (1.8)	4 (1.2)
Personal Reasons	0 (0.0)	0 (0.0)	2 (1.8)	2 (0.6)
Noncompliance	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.3)
Other[a]	3 (2.8)	0 (0.0)	1 (0.9)	4 (1.2)
Total	13 (12.3)	2 (1.9)	11 (10.1)	26 (8.0)
Completed[b]	93 (87.7)	106 (98.1)	98 (89.9)	297 (92.0)
Time in Study				
2 Weeks (≥12 Days)	101 (95.3)	108 (100)	106 (97.2)	315 (97.5)
4 Weeks (≥26 Days)	100 (94.3)	108 (100)	103 (94.5)	311 (96.3)
8 Weeks (≥54 Days)	92 (86.8)	101 (93.5)	94 (86.2)	287 (88.9)

[a] Two patients withdrew due to a medication dispensing error (see Section 5.2.); one was withdrawn to treat frequent episodes of tachycardia (which were already present at screening); one was withdrawn due to abnormal clinical laboratory results (granulocytopenia) from the end of placebo-baseline which were were not known until after the initiation of double-blind therapy..

[b] According to the investigators

RESPONSES BY SUBGROUP: One is not totally at the mercy of those who worry about being misled by subgroup analysis since, for example, we would, from other experience, expect older patients to be more suceptible to diuretics (see above discussion of bias due to fewer older subjects in the Q+HCTZ group) by virtue of,at least, their contracted blood volumes. The following table (18) shows larger responses in the >= year old group. For example, for HCTZ, older subjects have a 6.2mmH greater mean fall in supine SBP and this represents a 67% increase in response. For the Q group the response is 4.6mmHg larger in older subjects, a 38% increase. So, while the effect of age is not limited to effects of diuretics, it is prominant for them. This Reviewer suggests that the effects of HCTZ or Q+HCTZ in old vs young subjects may be tested directly without regard for multiple comparisons in view of the pre-existing experience cited above. If this is done for Q+HCTZ, using under an assumption of a pooled SE= 4.454, t= -1.39, df= 97,.05<p<.10, a very nearly "significant" value. If one is concerned about the borderline significance level, then reflect on the fact that the confidence limits would certainly include values of an "old- young" difference of clear interest for safety purposes.

A second subgroup examined by the Sponsor consisted of cases with and without a baseline SDBP of 110mm SDBP. A result unanticipated by the Sponsor was the finding of a greater response in diastolic, but not systolic BP, for subjects with lower baseline values in all Rx groups. The Reviewer suggests that one possibility, among others, is that subjects with lower baseline pressures might have been more likely to show placebo effects in addition to Rx effects -that is that more labile cases may have been included in those with low baselines. The size of this effect in the Q+HCTZ group was BL <110 BP change -17.7; BL >=110 BP change -13.5. Note that the adjustments for BL BP presumably would have dealt with this phenomenon in the key efficacy analysis.

The last subgroup looked at was that of sex. Women had larger responses than men for all Rx groups.

All of the subgroup evaluations appear to have been done in "evaluable" cases.

Standing BP: Standing DBP and SBP changes from baseline were , on average, Q: -10.8, -11.9; Q+HCTZ: -12.8, -16.2, H: -8.8, -9.4. Thus, overall, orthostatic decreases were not characteristic. For individual effects related to safety see "first- dose" and other effects under Adverse Effects.

SAFETY: Table 22 shows that a larger percentage, 23.6%, of patient reporting all ADE occurred in the Q ttreatment group (23.6% vs Q+HCTZ 13.9%, H 11.0%). A larger number were reported in old (28.6%) than in young (8.5%) in the Q+HCTZ treatment group, although it should be noted that ther numbers of older patients is quite small (N=14 >=65yrs; N=85 <65yrs.
The table shows that almost all withdrawals "for ADEs" occurred in the Q Rx group; that there were no deaths.

TABLE 22. Summary of Adverse Events (AEs)

	Quinapril 20 mg (N=106)	Quinapril + HCTZ (N=108)	HCTZ 12.5 mg (N=109)
Number of Patients Reporting Adverse Events (%)			
All AEs	25 (23.6)	15 (13.9)	12 (11.0)
Associated[a] AEs	16 (15.1)	10 (9.3)	5 (4.6)
Number of First Occurrences and Total Reports			
All AEs			
First Occurrences	40	20	16
Total Reports	41	20	17
Associated[a] AEs			
First Occurrences	24	12	7
Total Reports	24	12	7
Number of Patients Reporting Adverse Events by Age (%)			
All AEs			
<65 Years	21 (24.7)	11 (11.7)	11 (12.5)
≥65 Years	4 (19.0)	4 (28.6)	1 (4.8)
Associated[a] AEs			
<65 Years	14 (16.5)	8 (8.5)	5 (5.7)
≥65 Years	2 (9.5)	2 (14.3)	0 (0.0)
Number of Total Reports by Severity			
All AEs			
Mild	21	9	10
Moderate	19	8	4
Severe	1	3	3
Associated[a] AEs			
Mild	8	7	5
Moderate	15	3	1
Severe	1	2	1
Number of Patients With Clinically Important AEs (%)	3 (2.8)	1 (0.9)	1 (0.9)
Number of Deaths	0	0	0
Number of Patients Withdrawn for Adverse Events			
All AEs	6	0	2
Associated[a] AEs	5	0	1

[a] Considered by the investigator possibly, probably, or definitely related to study drug.

Table 23, shows "number of patients (%)" with the first occurrence of particular ADEs and "total reports", which include multiple events in one case. On the first page of the table ADE involving the cardiovascualr system, including hypotension, were very uncommon though one episode of the latter is recorded in the Q+HCTZ group, described in the Sponsor's text as "severe", and in the Q group. On page 2 of the table cough is noted in 3.7% of the Q+H cases;2.8% of the Q cases and none of the HCTZ ones.

TABLE 23. All Adverse Events by Body System and Treatment Group
(Page 1 of 2)

BODY SYSTEM/ Adverse Events	Quinapril 20 mg (N=106)			Quinapril + HCTZ (N=108)			HCTZ 12.5 mg (N=109)		
	Number of Pts	(%)	Total Reports	Number of Pts	(%)	Total Reports	Number of Pts	(%)	Total Reports
BODY AS A WHOLE[a]	9	(8.5)	12	3	(2.8)	3	3	(2.8)	4
Chill	1	(0.9)	1	0	(0.0)	0	0	(0.0)	0
Fatigue	1	(0.9)	1	2	(1.9)	2	1	(0.9)	1
Headache	5	(4.7)	5	0	(0.0)	0	2	(1.8)	3
Malaise	1	(0.9)	1	0	(0.0)	0	0	(0.0)	0
Back Pain	1	(0.9)	2	1	(0.9)	1	0	(0.0)	0
Chest Pain	1	(0.9)	1	0	(0.0)	0	0	(0.0)	0
Viral Infection	1	(0.9)	1	0	(0.0)	0	0	(0.0)	0
CARDIOVASCULAR SYSTEM[a]	7	(6.6)	7	1	(0.9)	1	1	(0.9)	1
Hypotension	1	(0.9)	1	1	(0.9)	1	0	(0.0)	0
Heart Failure	0	(0.0)	0	0	(0.0)	0	1	(0.9)	1
Cardiovascular Disord.	1	(0.9)	1	0	(0.0)	0	0	(0.0)	0
Vasodilatation	1	(0.9)	1	0	(0.0)	0	0	(0.0)	0
Palpitation	2	(1.9)	2	0	(0.0)	0	0	(0.0)	0
Extrasystoles Ventr.	1	(0.9)	1	0	(0.0)	0	0	(0.0)	0
Ventr. Hypertrophy	1	(0.9)	1	0	(0.0)	0	0	(0.0)	0
DIGESTIVE SYSTEM[a]	6	(5.7)	7	3	(2.8)	3	2	(1.8)	3
Dental Abnormalities	1	(0.9)	1	0	(0.0)	0	0	(0.0)	0
Mouth or Throat Dry	1	(0.9)	1	1	(0.9)	1	0	(0.0)	0
Nausea &/Or Vomiting	2	(1.9)	2	0	(0.0)	0	1	(0.9)	1
Diarrhea	0	(0.0)	0	1	(0.9)	1	0	(0.0)	0
Flatulence	1	(0.9)	1	0	(0.0)	0	1	(0.9)	1
Hepatocell. Pathology	0	(0.0)	0	0	(0.0)	0	1	(0.9)	1
Abdominal Pain	2	(1.9)	2	1	(0.9)	1	0	(0.0)	0
MUSCULOSKELETAL SYSTEM[a]	2	(1.9)	2	2	(1.9)	2	0	(0.0)	0
Arthralgia	2	(1.9)	2	0	(0.0)	0	0	(0.0)	0
Joint Disorder	0	(0.0)	0	1	(0.9)	1	0	(0.0)	0
Myalgia	0	(0.0)	0	1	(0.9)	1	0	(0.0)	0

"Clinically Important ADE", according to Sponsor's evaluation:

The Sponsor considered that N=1 serious ADEs occurred, hypotension, occurred in the Q monotherapy group; 3 (joint disorder, cough, diarrhea) in the combination group, and 3 (syncope, headache, and heart failure) in the H monotherapy group.

Pt 2, Center 2 withdrew after 5 weeks of Q therapy due to "malaise","right abdominal pain", and " dark urine"thought to be consistant with gall bladder disease. This patients laboratory listing shows no abnormalities of hepato- biliary function. Recovery is said to have occurred "in four days'.

Pt 2 Center 22,age 86, had severe diarrhea after 4wks combination Rx and recovered in 4 days after completing the study. Laboratory listings were unremarkable.

Pt 13 Center 7, age 41, had syncope and hypotension (SupSystBP 86mmHg) 3hrs after the first dose of quinapril.

Pt 4 Center 22, age 73, had diffuse rash, abdominal pain, and nausea after 17 days of Q monotherapy.Treatment was withdrawn and the rash cleared "in half a year". There were multiple other medications. Only the screening and DAY 1 laboratory values are present.

Pt 8 Center 21, age 58, had baseline granulocytopenia but started Q Rx since lab data were not available was started on Rx but discontinued one day later. Examination of laboratory listings confirms that granulocytopenia was present before Rx.

The Reviewer examined the laboratory listings and Investigator comments for withdrawn cases in the Q and Q+HCTZ treatment groups whether or not they were considered related to treatment by the Investigator. The Investigator comments were in tabular form and not every withdrawn case had comments.

Withdrawals "due to adverse events": N= 8 q monotherapy cases, N= 2 HCTZ cases, and no combination cases were withdrawn due to ADEs, according to the Sponsor. N= 3 of the Q monotherapy ADE- withfdrawals and the N= 1 HCTZ one have been discussed under "serious ADE" and the remaining ones are noted now.

Patient 8 Center 9 had a first- dose fall in 1- hour BP from 136 to 114mmHg on Q monotherapy that was without associated symptoms but led to withdrawal.

Patient 1 Center 26 had cough on Q monotherapy and was withdrawn. Cough ceased.

Patient 3 Center 28 was withdrawn from Q therapy for headache and nausea. Recovery occurred in one day.

Patient 7 Center 16 had fatigue on HCTZ and withdrew with recovery.

SERUM POTASSIUM:

The following table (27) shows that on Q 20mgm and Q+HCTZ the mean changes in serum K were always of positive sign (K increase) but were all negative on HCTZ. However in Q and Q+HCTZ the number of subjects with a decrease of >5% increased progressively with time on treatment between weeks 2 and 8.

TABLE 27. Mean and Discrete Changes (≥0.5 mmol/L) in Serum Potassium From Baseline (mmol/L)

	Quinapril 20 mg	Quinapril + HCTZ	HCTZ 12.5 mg
Baseline	(N=100)	(N=106)	(N=101)
Mean	4.16	4.13	4.21
Week 2	(N=87)	(N=94)	(N=93)
Mean Change From Baseline	0.12	0.04	-0.05
Increase/Decrease ≥0.5(%)	16/2	13/6	15/23
Week 4	(N=95)	(N=95)	(N=92)
Mean Change From Baseline	0.12	0.01	-0.19
Increase/Decrease ≥0.5(%)	19/4	14/12	8/24
Week 8	(N=91)	(N=99)	(N=94)
Mean Change From Baseline	0.10	0.01	-0.11
Increase/Decrease ≥0.5(%)	19/8	18/17	11/22
Last Visit	(N=100)	(N=106)	(N=101)
Mean Change From Baseline	0.09	0.01	-0.11
Increase/Decrease ≥0.5(%)	17/9	19/17	12/23

HYPOTENSION AND ORTHOSTATIC HYPOTENSION AFTER FIRST DOSE: The Sponsor defined "orthostatic hypotension" as a decrease in systolic BP of >20mmHg on standing if accompanied with clinical symptoms. "Hypotension" was defined as a standing systolic BP <100mmHg with symptoms. In addition the Sponsor examined all cases with the BP requirements with or without symptoms and provided a brief summary on those with symptoms.

Supine and standing BP were recorded for up to 4 hours post dose and for at least 2 hours in N=311 patients which were nearly equally divided among the N=3 Rx groups- about N=104 in each. N= 8, 7, 6 cases, respectively, in the Q, Q+HCTZ, and H groups had an orthostatic fall of >20mm after the first dose. N= 3 cases were considerted to have symptoms related to these postrural falls in BP.

Patient 2, Center 15, age 63 is reported to have had symptoms on Q+HCTZ although the lowest BP, that at 2hrs, was rather high, 140/110. The patient continued in the study.

Patient 13 Center 17, age 41, previously noted under "clinically- important ADE", had a postural fall from 124mmHg to 86mmHg with collapse 3 hrs after the first dose of Q 20mgm.

Patient 8, Center 9, noted under "withdrawals due to ADE", had first dose hypotension without specified symptoms on Q monotherapy. The fall in BP seems minimal, to 114mH systolic.

N= 2 other patients had orthostatic falls in BP, but without symptoms. Patient 7, Center 3, age 64, had a standing SBP of 98mmHg 1 hr after ther first dose of the combination. Patient 4, Center 19, age 51, had a standing SBP of 90mm Hg at 2hrs after first dose of Q monotherapy.

HYPOTENSION AND ORTHOSTATIC HYPOTENSION AT TROUGH: Almost equal numbers of cases in each Rx group,(Q: N=11; Q+HCTZ: N=10; H: N=13) had orthostatic falls in BP of >20mm systolic at trough. n.b. clinical experience indicates that symptomatology of orthostatic hypotension may occur by history with only modest observed falls noted in the clinic. Patient 12 Center 9, age 53, had definite orthostatic changes of SBP from 150 to 114, a rather high level, yet reported dizziness starting on day 8 of HCTZ monotherapy.

Patient 10 Center 11, age 52, had an asymptomatic supine trough SBP of 95mmHg on day 8 of combination Rx.

N=2 other patients were reported to have had clinical symptoms consistant with hypotension, syncope and dizziness on HCTZ monotherapy but without recorded low BP levels.

In conclusion, one notes that hypotension or first- dose hypotension with or without symptoms occurred in all Rx groups though the more severe or symptomatic examples had received Q mono or combination Rx.

CLINICAL LABORATORY DATA: Table 33 shows median changes in units.

TABLE 33. Summary of Median Differences Between Baseline and Final Value

Parameter	Unit	Quinapril 20 mg (N=79-100)	Quinapril + HCTZ (N=81-106)	HCTZ 12.5 mg (N=76-101)
Hemoglobin	g/L	0	-1	-1
Hematocrit	%	0	0	0
Platelets	$X10^9/L$	5.5	-2	6
Erythrocytes	$X10^{12}/L$	-0.01	0	0.02
White Blood Count	$X10^9/L$	-0.1	-0.1	-0.2
Polymorphs (Neutroph.)	%	-1.9	-1.6	1.6
Lymphocytes	%	1	1	-1
Monocytes	%	0	0	0
Eosinophils	%	0	0	0
Basophils	%	0	0	0
Fasting Glucose	mmol/L	-0.05	0	0.2
Blood Urea Nitrogen	mmol/L	0.3	0.4	0.13
Creatinine	µmol/L	-1	0	1
Creatinine Phosphokinase	U/L	-4	-4	1
Alkaline Phosphatase	U/L	0	-2	0
Bilirubin (Total)	µmol/L	0	0	1
LDH	U/L	-5	-2	0
SGOT	U/L	0	0.5	0
SGPT	U/L	0	0	0
Cholesterol (Total)	mmol/L	-0.1	-0.01	0
Uric Acid	µmol/L	-6.5	0	10.5
Sodium	mmol/L	0	0	0
Potassium	mmol/L	0.1	0	-0.2
Calcium	mmol/L	0.01	0	0.02
Chloride	mmol/L	0	-1	-1
Protein (Total)	g/L	0	1	0
Albumin	g/L	0	0.45	0
Urine pH		0	0	0
Urine Spec. Gravity[a]	g/mL	0	0	0

[a] N=43-45

The median changes which differ in sign or magnitude for Q+ HCTZ versus the components are platelets(-), alk phosp (-), sgot (+), total protein and albumen (+). All the items tabulated are those suceptible to analysis as continuous variates.

Table 34, next page, adds the variables more readily quantified by discrete measures and shows those changing to "low" or "high" values, essentially one row of a "shift table".Taking account of the clinical importance of a shift to "adverse" or "neutral". Laboratory values showing a larger percent of cases moving to "adverse" in the Q+ HCTZ (vs the other Rxs) are: hematocrit, wbc,eosinophils,bun,creatinine, urine wbc.

Table 35, unattached, shows cases that were considered by the Sponsor to have possibly clinically important decreases in hematologic variables. For hematocrit one case on Q monotherapy had a fall from 38 at screening to a final value of 37 after a baseline value of 45. It is not clear that this case actually had a fall in hematocrit since only the second measurement was above the final one. One case had a final wbc count of 3.7 x 10 E9/L after previous values of 5.8 and 5.9.

Serum creatinine showed a median change of 0 micromol/l for Q+HCTZ and a fall of 0.1 in the Q monotherapy group. In discrete terms, n= 4 cases changed from neutral to adverse in the combination group versus 2 in each monotherapy one.

Table 37, below, shows cases with deviations of levels of hepatic function tests.

TABLE 37. Patients With Deviations of Final Laboratory Values Reflecting Hepatic Function Larger Than 50% of the Normal Range Interval

Treatment (mg)		Center-	Normal	Screening	Baseline	Final
Quinapril	HCTZ	Patient	Range	Value	Value	Value
Alkaline Phosphatase (U/L)						
20	12.5	7-17	25-115	77	414	310
20	12.5	14-7	20-100	101	112	144
Total Bilirubin (μmol/L)						
20	--	21-11	0-17	12	8	26
20	12.5	13-22	4-17	11	-	25
20	12.5	21-18	0-17	14	17	28
SGOT (U/L)						
--	12.5	7-4	5-45	18	21	246
SGPT (U/L)						
--	12.5	7-2	5-40	8	15	137
--	12.5	7-4	5-40	15	27	531
Albumin (g/L)						
20	--	21-11	37-42	28.7	33.5	21.7
20	--	21-17	37-42	32.7	39.5	27.9

TABLE 34. Percent of Patients Changing to "Low" or "High" Values at the End of the Study

Parameter	(Adv/ Neu)	Quinapril 20 mg Adv/Neu	Quinapril + HCTZ Adv/Neu	HCTZ 12.5 mg Adv/Neu
Hemoglobin	(L/H)	4/ 3	2/ 4	3/ 2
Hematocrit	(L/H)	6/ 0	9/ 3	5/ 4
Platelets	(L/H)	1/ 3	2/ 4	0/ 3
Erythrocytes	(L/H)	3/ 1	2/ 0	4/ 1
White Blood Count	(L/H)	2/ 1	3/ 1	1/ 2
Polymorphs	(L/H)	7/ 3	8/ 2	1/ 8
Eosinophils	(H/L)	8/ 2	13/ 1	7/ 8
Basophils	(L/H)	0/ 3	0/ 3	0/ 8
Monocytes	(L/H)	11/ 5	11/ 3	15/ 4
Lymphocytes	(L/H)	1/15	4/17	5/ 8
Fasting Glucose	(H/L)	9/ 2	9/ 2	10/ 2
Blood Urea Nitrogen	(H/L)	9/ 1	12/ 2	8/ 3
Creatinine	(H/L)	2/ 2	4/ 0	2/ 0
Creatinine Phosphokinase	(H/L)	4/ 1	8/ 1	13/ 0
Alkaline Phosphatase	(H/L)	0/ 2	1/ 1	4/ 1
Bilirubin	(H/L)	2/ 0	4/ 0	7/ 0
Total Cholesterol	(H/L)	15/ 0	14/ 0	21/ 1
LDH	(H/L)	7/ 4	10/ 4	10/ 1
SGOT (AST)	(H/L)	7/ 1	3/ 0	7/ 0
SGPT (ALT)	(H/L)	10/ 1	6/ 0	11/ 1
Uric Acid	(H/L)	4/ 0	5/ 1	7/ 1
Sodium	(L/H)	0/ 8	5/ 1	6/ 0
Potassium	(L/H)	2/ 4	8/ 1	9/ 3
Calcium	(L/H)	4/ 4	6/ 3	4/ 3
Chloride	(L/H)	5/ 7	9/ 7	5/ 5
Total Protein	(L/H)	6/ 5	1/ 2	2/ 5
Albumin	(L/H)	3/ 2	0/ 2	3/ 3
Urine pH	(H/L)	0/11	3/13	5/ 9
Urine Spec. Weight	(H/L)	18/12	15/20	19/24
Urine Protein	(H/L)	6/ -	7/ -	13/ -
Urine Glucose	(H/L)	0/ -	0/ -	1/ -
Ketones	(H/L)	0/ -	0/ -	1/ -
Urine Blood	(H/L)	0/ -	8/ -	2/ -
WBC/hpf	(H/L)	11/ -	13/ -	8/ -
Urine Bilirubin	(H/L)	3/ -	0/ -	0/ -

Definition of adv/neu for each parameter:
Adv = potentially adverse change
Neu = change of minimal clinical significance or possibly beneficial change

Uric Acid, see table of median changes from baseline, tended to increase on HCTZ as expected but to be diminished or not elevated on Q and Q+ HCTZ, respectively suggesting a definite amelioration of the hyperurecemic effect of HCTZ.

Urine sediment: Pyuria was a prominant finding in the previous submission of Protocol 906-241, a factorial experiment but not in Protocol 906- 303, a parallel study similar in design to the present one. The Reviewer shows the Sponsor's shift tables below:

	QUIN		Q+HCTZ		HCTZ	
BL\LV	NORM	HIGH	NORM	HIGH	NORM	HIGH
NORM	49	6	49	7	47	4
HIGH	7	21	8	21	6	20
Chi Sq	0ns		0ns		0.1ns	

There is an insufficient excess of cases in the cells row 1 col 2, those that show N cases shifting from normal to high values of pyuria. The Chi sq statistics at the bottom of the tables are those for the McNemar test of shift; all are non- significant.

Conclusions:

1. The Q+HCTZ treatment effect in study 906- 303 (previous submission) was -14.4 for Q10/HCTZ 12.5, and -18.7mmHg for Q20/HCTZ 25. In the present study, the response for Q20/HCTZ 12.5 was -14mmHg. The responses to Q monotherapy 20mgm was -16.5 in Prot -303 and -11.8 in the present one. The respective responses to HCTZ 12.5mgm were -12.2mm and -9.5mm. In Protocol -303 and in the present study intent-to- treat values for the response to combination treatment, above, significantly differed from the monotherapies.

In study 906-241, in the previous submission, direct examination of combinations involving QUIN 20mgm were not possible, but marginal analyses of HCTZ + Quin 10mgm gave a response of -11.5mm while QUIN 40mgm gave -12.0. Thus an approximation to a combination of QUIN 20mgm/HCTZ 12.5 would be -12mmHg for that study; -14mm for QUIN 10/HCTZ12.5 in Prot- 303; and -14mm in the present study for QUIN20/HCTZ12.5.

Combination therapy with QUIN20/HCTZ is proposed by the Sponsor as being an effective dose. It is the same dose proposed in the submission of Dec 13, 1990 as an alternative step 2 should a dose of QUIN 10/ HCTZ 12.5 have insufficient effect in a particular patient, a reasonable conclusion taking efficacy results alone.

2. Safety

The present study is a relatively short-term one and is designed to explore dosage effects of a particular combination. That information provided by this trial tends generally to support the doses used as relatively safe. The present study, like the previous one, 906- 303, do not confirm a problem of pyuria seen in study 906- 241.

It should be noted that symptomatic orthostatic hypotension did occur in this study and though not very frequent was severe in some instances and after a first dose. In addition, older subjects had larger responses when compared to younger ones.

3. Recommendations

Despite the impression of relative safety given by the data from this study and from the two previously- submitted studies, 904- 241 and 303, this Reviewer does not recommend combination therapy for initial use in the treatment of hypertension under circumstances in which treatment is not very urgent. It seems more rational to at least try a simpler monotherapy which is not an ace inhibitor since some subjects will respond and may be spared the risks of the more complex treatment. Nor are the arguments that ace inhibition minimizes potassium and uric acid abnormalities sufficient since not all subjects necessarily can be shown to need correction of alterations that may be minimal on other therapy. Some subgroup, such as older subjects, may have increased responses to combination treatment possibly because of a tendency toward contracted plasma volume. In such cases, treatment with a diuretic- containing combination might prove unnecessarily vigorous.

/S/

Philip L. Bern M.D.

Orig:
HFD-110
HFD-110/CSO
HFD-110/PLD
pld 2/11/91

K. BONGIOVANNI

MAR 6 1992

NDA 20,125

DIVISION OF CARDIO- RENAL DRUG PRODUCTS
MEDICAL OFFICER'S NDA REVIEW

NDA: 20- 125
DRUG: Accuretic (quinapril/HCTZ)
SPONSOR: Parke-Davis Pharmaceutical Research
INDICATION: Treament of hypertension
DATE SUBMITTED: Dec 13, 1990. Transferred to present Reviewer later.
DATE REVIEW: Dec 5, 1991

RESUME:
This NDA is submitted by the Sponsor for the indication, hypertension. The proposed label adds "in patients for whom combination therapy is appropriate".

Rationale: The Sponsor's rationale for combination of an ACE-inhibitor with a diuretic is based on the enhancement of blood pressure reduction by "diuretic- induced dependence" of BP regulation on the renin/angiotension system. The expectation is of an increase in the response rate to an ACE inhibitor from "50- 60%" to "70- 80%" as a result of the addition of hydrochlorothiazide to the ACE-inhibitor, quinapril.

Summary of Pharmacology with emphasis on combination of quinapril/HCTZ: In the spontaneously- hypertensive rat mono-therapy with either quinapril of HCTZ was ineffective in lowering blood pressure but the combination reduced it. HCTZ was shown to increase plasma renin activity in these rats. Combination therapy was also effective in the renal hypertensive dog whereas monotherapy with quinapril to 20mgm/kg was not. Increased heart rate accompanied the hypotension.

Urine volume in the normotensive rat was unchanged by combination therapy except at high doses, which diminished volumer, sodium, and potassium excretion possibly due to hypotension and/or increased renal sympathetic tone. Single doses of quinapril had no effect on the diuretic/natriuretic response to HCTZ in acutely saline-loaded, rats. In spontaneously hypertensive rats increased potassium, sodium, and urine volume excretion occurred at doses of 0.3mgm/kg

that was more pronounced when combination with diuretic was given.

Toxicology Summary:

Quinapril monotherapy showed increase plasma renin activity, size and granularity of the juxtaglomerular apparatus and decreased heart weight in
dogs and rats. Liver changes consisting of bile duct hyperplasia, periportal fatty change, and occasional hepatocyte necrosis were reported for doses of 60- 80 times that used in humans. Emesis and mucosal irritation were also noted.

Quinapril combined with diuretic in acute toxicity studies in dogs showed
diffuse renal tubular changes, interstitial edema, increased BUN and creatinine. Combination therapy in rats over 13- weeks (doses 50 quin/31 HCTZ to 500 quin/312 HCTZ mgm/kg/day) showed tubular and interstitial mononuclear cell infiltrates and increased BUN. In dogs given doses 25/16 to 150/94 mgm/kg/day elevated BUN; renal tubular dilatation at low and high doses; renal interstitial cell infiltration and hemorrhage was found.

The Sponsor concluded that in chronic studies the combination therapy produced more renal and GI irritation than did monotherapy.

Pharmacokinetics: In dogs, but not rats or man, increased hydrochlorothiazide blood levels were noted when quinapril was given.
In man the pharmacokinetics of quinapril and the metabolite quinaprilat were similar to findings after addition of hydrochlorothiazide. In addition, the Sponsor has conducted three bioequivalence studies using quinapril/HCTZ 10mgm/12.5mgm; 20mgm/12.5mgm and 20mgm/25mgm versus the individual ingredients.

Clinical Trials:

Preliminary Comments: APPENDIX A of this Review has Table 1 of the Sponsor's submission and describes the trials. The two, major, controlled trials are 906- 241, a factorial experiment with dose response, and 906-313 a parallel comparison among specific doses of combination versus monotherapy. The first trial had less severe hypertensives and provides serial measurements to obtain peak response. The determination of efficacy from the factorial experiment involves interpolation and confidence limits whereas the second trial involves direct tests of observed cell means. The Reader should note that some of the Sponsor's dosage

recommendations are based on the interpolation and some on direct comparisons from a different trial. In addition, the interpolation in the factorial experiment was done on results obtained from a per- protocol ("evaluable") analysis.

RESULTS:

I. Study 906- 241

This was a 31- center trial of which 26 centers were non- US. N= 16 parallel treatment groups were assigned as a 4 X 4 factorial experiment as follows:

HCTZ Dose (mg Per Day)	Quinapril Dose (mg Per Day): Placebo	2.5	10	40
Placebo	P/P	2.5/P	10/P	40/P
6.25	P/6.25	2.5/6.25	10/6.25	40/6.25
12.5	P/12.5	2.5/12.5	10/12.5	40/12.5
25	P/25	2.5/25	10/25	40/25

Minimum of 25 Patients Per Treatment Group

FIGURE 1. Study Design

Patient selection: Male and females aged 18yrs or older were eligible if sitting diastolic BP at randomization was >=100 and =<115 mm Hg at each of the last two visits of a 2- 4 week placebo baseline period. Exclusion included non-essential hypertension, eyegrounds worse than KW II, orthostatic hypotension, decompensated congestive heart failure, significant other disease or medication (valvular heart disease, renal or hepatic disease; gout, unstable angina, recent myocardial infarction or CVA, NSAID Rx).

Schedule of visits:

TABLE 3. Schedule of Visits, Observations, and Procedures

Observation/Procedure	Study Week: Screening	Placebo Baseline[a] -4	-3	-2	-1	Double-Blind 0	1	2	4	6	8
Medical History	X										
Physical Examination	X										X
Vital Signs	X	X	X	X	X	X[b]	X	X	X[b]	X	X
Clinical Laboratory	X					X		X[c]	X[c]	X[c]	X
12-Lead Electrocardiogram	X					X					X
Medication Dispensing		X	X	X	X	X	X	X	X	X	
Patient Compliance			X	X	X	X	X	X	X	X	X
Concurrent Medication		X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X

[a] Patients were to be off antihypertensive medication for a minimum of 28 days and on placebo for a minimum of 14 days before entering the double-blind period. Therefore some placebo baseline visits were optional.

[b] Hourly for 2 hours after the first dose and for 4 hours after the dose taken at the Week 4 visit.

[c] Serum electrolytes only

The study efficacy criteria were sitting DBP at trough (20- 28hrs postdose)
with sitting DBP at trough, sitting systolic BP and standing BP at trough as secondary measures. BP hourly x 2 was recorded after the first dose of double-blind medication and additional measurements were optional.

Statistical aspects: Contrasts were planned for quinapril/HCTZ marginal analyses versus monotherapy but not for monotherapy versus placebo. Power was 80% to detect a 3.5 mm Hg difference.

PATIENT DISPOSITION:

TABLE 10. Patient Disposition

Patients	Number (%) of Patients
Randomized to Treatment	460
Withdrawals[a]	
Lack of Efficacy	15 (3.3)
Adverse Events	14 (3.0)
Personal Reasons	4 (0.9)
Loss to Follow-up	4 (0.9)
Noncompliance	3 (0.7)
Surgery	1 (0.2)
Total	41 (8.9)
Time in Study	
2 Weeks	452 (98.3)
4 Weeks	437 (95.0)
6 Weeks	422 (91.7)
8 Weeks	398 (86.5)

[a] Investigator opinion

TABLE 11. Withdrawals Due to Lack of Efficacy [N (%)]

HCTZ (mg)	Quinapril (mg) 0	2.5	10	40
0	3 (11.1)	0 (0.0)	1 (3.2)	1 (3.6)
6.25	2 (6.7)	0 (0.0)	2 (6.5)	0 (0.0)
12.50	2 (6.7)	1 (3.8)	0 (0.0)	1 (3.6)
25.00	1 (3.6)	0 (0.0)	1 (3.3)	0 (0.0)

TABLE 12. Withdrawals Due to Adverse Events [N (%)]

HCTZ (mg)	Quinapril (mg) 0	2.5	10	40
0	1 (3.7)	0 (0.0)	0 (0.0)	1 (3.6)
6.25	0 (0.0)	2 (6.9)	0 (0.0)	1 (3.4)
12.50	0 (0.0)	1 (3.8)	1 (3.4)	3 (10.7)
25.00	0 (0.0)	1 (3.3)	1 (3.3)	2 (7.1)

Number of patients entering each phase of the analysis:

Entered PLAC baseline phase	N= 525
Randomized	N= 460
Intent- to- treat	N= 458*
Evaluable (per-protocol)	N= 374

* n=2 subjects with either no baseline or followup data excluded

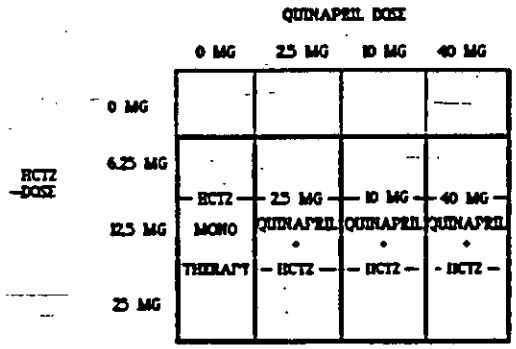
Adjusted mean changes to last visit in sitting diastolic BP from analysis of covariance:

QUI	HCT	0 Adj	Raw	2.5 Adj	Raw	10 Adj	Raw	40 Adj	Raw
0	Eval	-2.2		-6.6		-7.3		-10.3	
	Int-to Rx	-2.9	-3.0	-7.2	-7.3	-10.7	-10.7	-12.0	-12
6.25	Eval	-5.9		-8.9		-10.3		-11.7	

	Int-to Rx	-5.2	-5.2	-7.5	-7.4	-10.7	-10.7	-12.0	-12
12	Eval	-7.2		-9.4		-8.2		-14.9	
	Int-to Rx	-6.0	-5.9	-7.2	-7.2	-8.8	-8.8	-10.7	-10
25	Eval	-11.4		-11.6		-14.7		-14.3	
	Int-to Rx	-8.5	-8.5	-11.4	-11.4	-15.1	-15.1	-13.3	13

Note that there is dose response accross QUIN dose levels within HCTZ dose levels but less obviously accross HCTZ dose levels especially for the intent-to-treat responses.

Marginal Analyses: The following figure (FIG 2 P13 1.18) from the submission shows the part of the 4X4 table of responses showing quinapril dose response in the presence of HCTZ. The means of the n=3 active HCTZ doses are taken within each vertical rectangle.



The following table (Table 19 P37 1.18) shows that only the highest quinapril dose, 40mgm, significantly differs from HCTZ monotherapy for the Evaluable patients.

TABLE 19. Quinapril Dose Response in the Presence of HCTZ (Marginal Analysis of Evaluable DBP Data)

	Quinapril (mg)			
	0	2.5	10	40
N	68	70	76	68
Mean Change in DBP (mm Hg)	-8.2	-10.0	-11.0	-13.6*
Standard Error	1.0	1.0	1.0	1.0
Critical Value			2.032	2.040
Test Statistic			1.992	3.684

* Significantly different from HCTZ monotherapy (Williams' procedure)

The same type of analysis for intent- to- treat subjects shows that both the 10mgm and 40mgm doses differ significantly from HCTZ monotherapy.

Response Surface Analysis:

A quadratic function of quinapril and HCTZ dose was fit to the EVALUABLE patient data for the response, Y= change in sitting DBP. The cross product term, Dose Quin x Dose HCTZ was not significant (p= 0.3675) so that we may reasonably accept the use of the marginal analyses shown above, without having to specify results within a particular level.

The following plot shows the Sponsor's surface predicted by the quadratic model. Observed and predicted values showed good agreement in another plot.

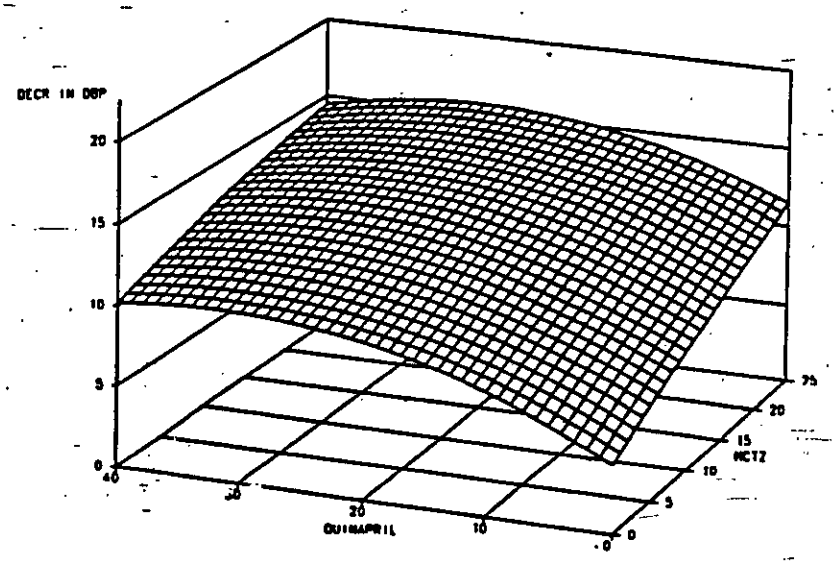


FIGURE 13. Response Surface for Mean Reduction in Sitting DBP from Baseline to the Last Evaluable Visit ≥Week 4 (Quadratic Equation)

The Sponsor computed the maximum expected response but found it outside the region encompassed by the dosages actually used in the trial. The maximum expected response using the quadratic equation was, according to the Sponsor's calculation, -15.7mm change in DBP with a standard error of 1.5 and 95% confidence limits of -18.6 to -12.7.

The following plot (Fig 15 from the submission) shows the region within which the estimated responses are proposed by the Sponsor as indistinguishable from the maximal response since the responses from those doses lie within the lower confidence region on the maximum effect.

Figure 15 below shows the range of doses of quinapril and HCTZ within the doses studied that are expected to produce a response greater than the lower limit of the 95% confidence interval (-12.7 mm Hg). Note that monotherapy axes are not included, supporting the greater effectiveness of concomitant therapy over the monotherapies.

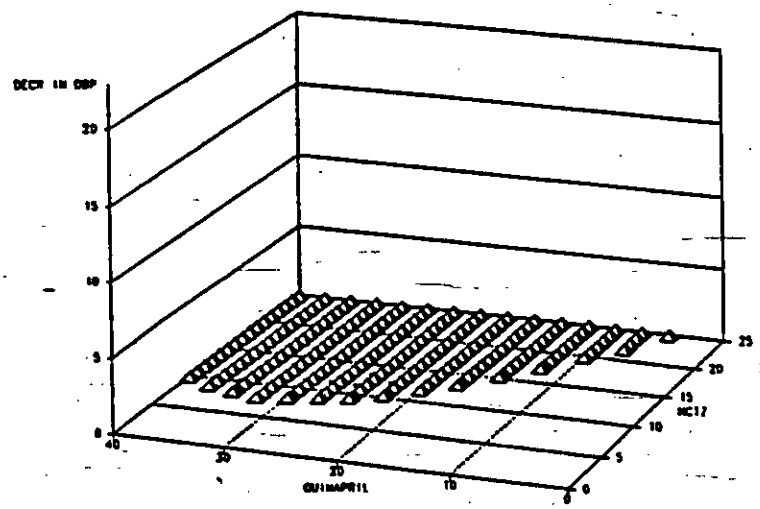


FIGURE 15. Confidence Region (Quadratic Equation)

RESPONSE RATES: These are provided only for the Evaluable patients. The following table (Table 28 p56 1.18) shows evidence

for dose response:

TABLE 28. Response Rate (Percentage of Patients Responding at the Last Evaluable Visit 2Week 4)

HCTZ (mg)	Quinapril (mg) 0	2.5	10	40
0	20%[a] (4/20)	39% (9/23)	37% (10/27)	50% (11/22)
6.25	33% (8/24)	52% (13/25)	46% (12/26)	56% (14/25)
12.50	36% (8/22)	47% (9/19)	54% (13/24)	75% (15/20)
25.00	55% (12/22)	54% (14/26)	69% (18/26)	74% (17/23)

[a] Response Rate (N Responding/N Evaluable)

The marginal response to quinapril, averaging over HCTZ doses, was 68% (>= 10mm fall in sitting DBP) for the highest, 40mgm, dose of quinapril, the only one showing a significant difference from HCTZ monotherapy.

The marginal response to HCTZ in the presence of quinapril was significant only for the highest HCTZ dose, 25mgm, versus quinapril monotherapy.

Trough/peak analysis of sitting DBP:

Blood pressure measurements were taken at week 4 for 4 hours after dosing. The percent of peak response (mean of BP at hours 2,3, and 4) remaining at trough is shown below (Table 35 p64 1.18). Except for the QUIN 2.5/HCTZ 6.25 dose, the percentages of peak remaining at trough were at least 59% and usually exceeded 67%. Note that the results pertain to Evaluable cases.

TABLE 35. Trough/Peak Changes in Sitting DBP and Percent of Peak Remaining at Trough
N = 293 Evaluable Patients

HCTZ (mg)	Quinapril (mg) 0	2.5	10	40
0	16[a] -3.9/-7.2 54%	18 -10.2/-12.6 81%	21 -8.6/-15.1 57%	16 -10.9/-16.4 66%
6.25	20 -6.9/-7.8 88%	18 -5.7/-12.3 46%	20 -9.9/-14.6 68%	21 -10.8/-17.5 62%
12.50	19 -5.4/-7.4 73%	16 -11.0/-13.9 79%	21 -9.0/-14.0 64%	16 -12.9/-16.8 77%
25.00	17 -10.8/-11.4 95%	21 -10.8/-15.5 70%	18 -10.8/-15.2 71%	15 -12.3/-17.5 70%

[a] Number of patients with peak and trough data
Mean trough change/mean peak change
Percent of peak at trough

SUMMARY OF EFFICACY DATA: The following tables (Table 69,70 pp115,116 1.18) show the results of mainly the marginal analyses.

TABLE 69. Concomitant HCTZ Plus Quinapril Therapy vs HCTZ Monotherapy

	HCTZ Monotherapy	Plus Quinapril (mg) 2.5	10	40
Mean Change in Sitting DBP (mm Hg)				
Evaluable	-8.2	-10.0	-11.0	-13.6*
Intent-to-Treat	-6.5	-8.7	-11.5*	-12.0*
Response Rates (%)	41	51	57	68*
Mean Change in Sitting SBP (mm Hg)				
Evaluable	-6.9	-13.3*	-15.8*	-19.2*
Intent-to-Treat	-5.9	-10.7*	-15.7*	-16.8*
Range of doses expected to produce a response similar to the predicted maximum response does not intersect HCTZ monotherapy				
Dose-response curve has a significant slope for quinapril dose (quadratic, p = 0.0154; linear, p = 0.0001)				

* Significantly different from HCTZ monotherapy

TABLE 70. Concomitant Quinapril Plus HCTZ Therapy vs Quinapril Monotherapy

	Quinapril Monotherapy	Plus HCTZ (mg) 6.25	12.5	25
Mean Change in Sitting DBP (mm Hg)				
Evaluable	-8.1	-10.3	-10.8	-13.5*
Intent-to-Treat	-8.2	-10.0	-8.9	-13.3*
Response Rates (%)	42	51	59	65*
Mean Change in Sitting SBP (mm Hg)				
Evaluable	-8.5	-13.0	-17.1*	-18.2*
Intent-to-Treat	-9.3	-12.4	-12.6	-18.1*
Range of doses expected to produce a response similar to the predicted maximum response does not intersect quinapril monotherapy				
Dose-response curve has a significant slope for HCTZ dose (quadratic, p = 0.0637; linear, p = 0.0001)				

Discussion:

The marginal analyses show that sitting DBP was reduced by Quinapril 10 and 40mgm, averaging over HCTZ doses, by an amount exceeding that due to HCTZ monotherapy. For sitting systolic BP the 2.5mgm QUIN dose also exceeded the HCTZ monotherapy response.

For HCTZ, averaging over Quinapril doses, the 25mgm dose was significantly better than Quinapril monotherapy in reducing sitting

DBP and SBP.

The question arises as to how these marginal findings are to be translated into information about specific dose combinations. Note that the contrasts of different doses of Quinapril or HCTZ with HCTZ or Quinapril monotherapy, respectively, are based on combination doses averaged accross all three levels of active therapy. For example, Quinapril responses to particular doses are given in terms of the combination with the average of three HCTZ doses and contrasted with the average of three HCTZ doses, the "monotherapy". There is no contrast of, say, Quinapril 10mgm plus HCTZ 12.5mgm with

either Quinapril 10mgm or HCTZ 12.5. The sample size estimates were based on the assumption that the marginal contrasts were at issue rather than individual cell comparisons. Since the marginal analyses do not provide evidence for specific cell contrasts, they do not directly provide evidence that a particular dosage combination improves upon a component.

A second type of analysis, the quadratic response surface, is used to justify doses such as QUIN 20/ HCTZ 12.5 and 20/25 that are interpolated between those actually used in the trial. The response surface anaysis is interpreted by the Sponsor as showing that these doses produce effects that are within the confidence limits on the maximum effect seen. It must be noted that the response surface was based on Evaluable patients not intention- to- treat ones.

Additional evidence consisted of tests on discrete responses and are subject to the criticism expressed on marginal analyses above.

The adjusted responses from covariance analysis are presented by the Sponsor but do not figure in arguments provided for dosages.

In summary, the Sponsor has provided evidence from intention-to-treat marginal analyses that Quinapril 10 or 40mgm plus an average dose of HCTZ over 6.25 to 25mgm reduced sitting DBP more than that average HCTZ effect. In addition, a dose of HCTZ 25mgm plus an average of 2.5 through 40mgm of Quinapril exceeded that averge Quinapril response.

The Sponsor's conclusion that the "QUIN 10/HCTZ 12.5 dose was more effective than monotherapy" is not justified by the marginal analyses used in this study since they did not make the contrast with components implied; but, rather, made entirely different contrasts involving averages of three dosage levels of each drug. The contrasts on the components were from separate analyses and not from a contrast with the combination.

Regarding doses of 20/12.5, and 20/25, which were interpolated on the response surface, the Sponsor is more conservative and states these " would be expected to be as efficacious....." as higher doses.

This study provides strong support for combination therapy itself though ,taken alone, insufficient evidence for efficacy of particular combinations of Quinapril and HCTZ.

STUDY PR 906- 303 :

This was an eight- week, 29- center, European study.

DESIGN: Patients 18years of age or older with moderate to severe hypertension (DBP >=105mm to =<120) at two visits after a 4- week placebo baseline phase were randomized to one of three treatments, 1)quinapril 10mgm; 2) quin 10mgm/HCTZ 12.5mgm; or 3) HCTZ 12.5 mgm. Medications was given once daily. After 4 weeks the dose was doubled unless BP was unusually low or high. Clinical observations were made weekly throughout the placebo baseline and double- blind periods.

The primary evaluation criteria was trough supine DBP (20- 28hrs post dose) measured 3 times.

PATIENTS: Exclusions included secondary hypertension, CHF, recent myocardial infarction, retinopathy worse than KW II, gout, abnormal renal or hepatic function, other antihypertensive drugs, NSAIDS.

Baseline characteristics of the patients showed good agreement accross treatment groups in supine DBP, age, and sex.

Withdrawals during treatment were similar for QUIN, QUIN/HCTZ,and HCTZ, (8,7,7, respectively, and the distribution of assigned reasons was similar. The number of cases excluded from the intent- to- treat group due to lack of minimal BP measurements was similar, 1 or 2 in each treatment group.

EFFICACY: Note that, unlike the previous study, this one sought to make contrasts with specific doses and combinations. One might consider this study a natural extension of the response surface trial since it concentrates on a few rather than many responses or an overall function fit to the data.

The following table (Table 47 vol 1.26 page 85) shows the adjusted mean changes from baseline, the "responses", adjusted for baseline

BP. The changes in the intent-to- treat group for supine SBP/DBP are significantly different from both monotherapies for the "low" dose (QUIN/HCTZ vs QUIN p 0.008; vs HCTZ p 0.020) and "high" dose (p 0.023; p 0.025) periods. Note that the responses are substantially larger at "last visit" (end of the high dose period).

TABLE 47. Summary of Adjusted Mean Changes From Baseline (mm Hg) in Supine Blood Pressure

	Quinapril Monotherapy SBP/DBP (N)	Quinapril + HCTZ SBP/DBP (N)	HCTZ Monotherapy SBP/DBP (N)
Low Dose (Week 3 to 5)			
Evaluable Data	-13.1/-12.1 (101)	-17.7/-14.6 (108)	-11.6/-12.5 (109)
High Dose (3 to 5 weeks)			
Evaluable Data	-19.7/-17.0 (91)	-27.1/-19.5 (94)	-20.4/-17.2 (98)
Intent-to-Treat			
Low Dose ≤ Week 5	-13.2/-11.8 (118)	-17.2/-14.4 (121)	-11.5/-12.2 (123)
Last Visit ≤ Week 8[a]	-18.7/-16.5 (118)	-24.7/-18.7 (121)	-19.2/-16.5 (123)

[a] Independent of dose

RESPONSE BY AGE: The submission provides a tabulation of the response by age for "evaluable" (per- protocol) cases only. Only supine BP are listed. The responses are similar in the group aged < 65 and =>65 for treatments other than HCTZ, for which the mean response was larger in the older subjects; -24mm vs -17.1 mm.

CONCLUSION EFFICACY PROT 906-241,906-303: This last study shows that QUIN10mgm/HCTZ 12.5 reduces supine diastolic blood pressure significantly thus confirming the results of the marginal, intent-to-treat analysis of Protocol 906- 241 to the extent that that they tested the same individual doses when given with an average, background dose of the other drug. (See interpretation of marginal analyses under PROT 906-241). There are no intent-to-treat trough/peak ratios available although, for "eligible cases" the average ratio was 64%. Eligible cases were less responsive to the above dosage than intent-to-treat ones so the in the trough peak/ratios may have been more favorable to the latter.

SUPPORTIVE EFFICACY STUDIES:

Positive- controlled trial of once daily quinapril vs propranolol twice-daily.

This was a 16-week, double-blind, trial carried out in 15 centers

in Canada and Europe. Patients with sitting diastolic BP (SIDBP) 95- 115mm after a 2- 4 week placebo phase were randomized to quinapril 20mgm once- daily or

propranolol 40mgm twice- daily for 4 weeks. Cases failing to have an SIDBP below 90mm (or a change of >=10mmHg if baseline BP <100mmHg) had their dose doubled for another 4 weeks. Treatment continued for a total of 12 weeks and was then followed by withdrawal if BP reduction failed to meet the above criteria. If BP was satisfactory, treatment continued another 4 weeks and longer in a very few cases as an open label extension.

Results:

Baseline data showed a small but statistically significant increase in diastolic BP in the quinapril group. The following table (Table 18 vol 1.33 p33) shows the baseline BP and the adjusted mean differences by treatment group for weeks 1-8 and 9-16, the mono and combined therapy phases, respectively. The responses are larger for the propranolol group before and after addition of HCTZ. The global response rate, the proportion of all cases responding with a fall of BP >=10mmHg, was also higher in the propranolol group.

TABLE 18. Mean[a] Difference From Baseline in Intent-to-Treat Sitting Trough DBP in mm Hg (Standard Error) and Global Response Rate

Variable	Quinapril N = 86	Propranolol N = 76	P-value
Baseline DBP	102.5 (0.5)	100.8 (0.5)	0.03[b]
Adjusted Mean Difference in DBP			
Last Visit Weeks 1-8	-8.3 (0.9)	-9.7 (1.0)	0.30
Last Visit Weeks 9-16	-10.4 (0.9)	-12.3 (1.0)	0.16
Global Response	60%	66%	0.36

[a] Least squares mean
[b] Statistically significant

Comment on the analyis:

Since there was a slight difference in baseline BP means it is reasonable, in addition to getting increased precision, to adjust the estimated responses by the baseline values. In the intent-to-treat group, there was no heterogeneity of slopes between Rx groups of treated BP on baseline BP so covariance was reasonable. No significant difference in adjusted means were found though the estimates favored propranolol. Adding a term for-interaction with center was not useful.

A substantial number of withdrawals occurred. For QUIN cases 69.8% remained until week 16; for PROP 75.9%. More subjects withdrew for lack of efficacy in the QUIN group (12.8%) than in the PROP one (7.6%). The PROP cases tended to withdraw earlier than the QUIN ones suggesting that addition of HCTZ had been less effective for the latter.

One notes that the QUIN/HCTZ response after the low and high dose phases was -8.3 and -10,4, respectively. Compare this with the results in study 906-303, which were -14 and -18.7. This is compatible in the present study with a poor early response to QUIN, perhaps associated with lack of diuretic activation of the renin/angiotensin system, and a late poor response due to limiting diuretic addition to failures. One suspects that when diuretic is given both early and late, BP averages are much lower since cases who would be mono- therapy responders still receive combination therapy.

Conclusion: This trial has the difficulties of both titration and positive control plus some possible defects associated with limitation of use of diuretics in non- responders to ACE inhibitor monotherapy. In addition, if some speculation is allowed, the delay in adding HCTZ might have been expected to be unfavorable to early QUIN effects since the RAS (renin/angiotension system) would not have been activated. The net effect of this could have been the relatively poor absolute changes in BP in the QUIN group as compared to responses in the first two trials reviewed.
The Reviewer concludes that difficulties in design mitigate the smaller blood pressure responses to QUIN that occurred in this trial relative to those that occurred in first two studies or in the propranolol group in the present one. The results have essentially neutral weight in an evaluation except, perhaps, raising a question about the utility of a stepped- care approach with and ACE inhibitor.

<u>A POSITIVELY-CONTROLLED TRIAL OF QUINAPRIL AND CAPTOPRIL:</u>

This was an eight- center, foreign, trial in which hypertensive patients

underwent a 1 to 4-week placebo phase followed by randomization to QUIN 5mgm BID or captopril (CAP) 12.5mgm tid. If BP did not fall below 90mm (or fall >10mm given a baseline BP <100mm), with an optional titration at 2- week intervals to a total dose of QUIN 20mgm or CAP 50mgm. At end of week 6, non- responders were given 25mgm HCTZ once daily in the AM.

Criteria for efficacy on blood pressure were the same as for guiding titrations as is not surprising.

Results:

Baseline characteristics for BP, age, sex, and race distributions were quite similar between treatment groups both for means and ranges. Duration of hypertension was somewhat longer in the CAP group (75.3 vs 57.2 months).

The following table (TABLE 16 Vol 1.43 p28) shows that the intent-to-treat adjusted SIDBP changes were similar in the QUIN and CAP groups. Unlike the previous study, the magnitude of the change in SIDBP was moderate in the monotherapy and substantial in the combination therapy phases.

Conclusion: The contrasts with captopril is not very helpful. The magnitude of the QUIN responses can be examined relative to those in the previous three trials and tends toward being supportive for the QUIN response in them.

<u>A 12-WEEK POSITIVELY-CONTROLLED STUDY IN MODERATE TO SEVERE HYPERTENSIVES OF QUINAPRIL VS CAPTOPRIL USING BACKGROUND DIURETIC THERAPY.</u>

This five- center, foreign trial studied the use of QUIN 10- 40mgm once- daily versus CAP 25 to 100mgm, both on background HCTZ 25mgm once daily, in subjects with SIDBP >= 105 and <131mmHg after a 2 to 4- week baseline, HCTZ period. Eligible subjects were then randomized to either dose group. After two and four weeks of these initial doses, doses could be increased to quin 20mgm each AM and CAP 25mgm BID and then QUIN 40mgm qd and CAP 50mgm BID, respectively, provided SIDBP had fallen less than 10mm Hg.

Results:
Baseline characteristics showed that the mean systolic and diastolic BP were
not more than 1mmHg different bewteen treatment groups. The range of BP tended to be wider and the mean weight and age a bit lower in the CAP group.

About half (49%) of the trial subjects took the highest-QUIN dose,

40mgm, and 53% of the CAP group took 50mgm BID.

The pattern of withdrawals by time in study was similar between treatments.

The following table (Table 28 Vol 1:37 p41) shows that there were no significant differences between treatment adjusted means although those for sitting systolic BP were almost so (p 0.09) in favor of QUIN. One also notes that the magnitude of the changes were substantial and thus provide some support for efficacy of QUIN combination therapy although the size of the effects may be due to the more severely hypertensive subjects entered into this study. An analysis stratified on baseline BP did in fact show larger reductions for higher baselines.

Conclusions: As in all of the positive controlled studies reviewed so far, contrasts with the control agent have provided little information. The magnitudes of the responses are useful to the extent they are similar accross trials.

TRIAL OF CAPTOPRIL VS QUINAPRIL AS MONOTHERAPY WITH OPTIONAL DIURETIC ADDED LATER(PROTOCOL 906-171):

After a 1- 14-day placebo baseline, subjects with severe hypertension (SIDBP >=115 and <=130) were randomized to either captopril 25mgm BID or quinapril 5mgm BID with subsequent titration to 100mgm BID or 20mgm BID, respectively, at weekly intervals. Response was defined as a fall of 10mmHg in BP.

Results:
Baseline mean SIDBP was only 1mm different between groups but the range was larger (109-130) in the QUIN cases than in the CAP ones (115-130). The CAP group was 2 years younger on average; a wider range of ages, and half as many black subjects (12% vs 28%) and significantly more men (76% vs 57% p 0.05) than did the QUIN cases.

Withdrawals by time in study were approximately the same in both treatment groups.

The following table shows the distribution of dose levels and of cases on added HCTZ during the study (Table 11 p16 vol 1.46). At the end of the study more subjects were on low doses of QUIN than CAP (13% vs 2%) although a similar proportion were on high doses of the drugs plus HCTZ, 74 and 76%, respectively.

TABLE 11. Dose Levels at End of Monotherapy and End of Study
[Number (%) of Patients]

	Treatment Group		
	Quinapril† N = 47	Captopril‡ N = 50	Total N = 97
End of Monotherapy (Week 4			
Low	7 (15)	2 (4)	9 (9)
Medium	4 (9)	9 (18)	13 (13)
High	36 (77)	39 (78)	75 (77)
End of Study			
Low	6 (13)	1 (2)	7 (7)
Medium	1 (2)	4 (8)	5 (5)
High	5 (11)	7 (14)	12 (12)
High + HCTZ§	35 (74)	38 (76)	73 (75)

† low = 5 mg b.i.d; medium = 10 mg b.i.d; high = 20 mg b.i.d
‡ low = 25 mg b.i.d; medium = 50 mg b.i.d; high = 100 mg b.i.d
§ Hydrochlorothiazide 25 mg q.d.

A higher proportion, 87%, of QUIN cases completed the study than CAP ones (80%), the difference being ascribable to several more cases in the CAP group withdrawing for lack of efficacy or adverse effects.

The next table (Table 22,p25,vol1.46) shows that intent- to- treat adjusted mean responses were slightly larger in the CAP group after monotherapy whereas the reverse was true for the optional HCTZ (end-of- study) phase. None of the between-group contrasts reached statistical significance.

TABLE 22. Intent-to-Treat: Mean Blood Pressure (mm Hg) Changes From Baseline

	Treatment Group		
	Quinapril	Captopril	p-value
End of Monotherapy (Week 4	N = 47	N = 50	
Baseline DBP	118.4	119.2	
Baseline SBP	170.6	170.7	
Adjusted Mean Change DBP	-9.7	-10.5	0.6510
Adjusted Mean Change SBP	-9.9	-10.5	0.8457
End of Study	N = 47	N = 50	
Baseline DBP	118.4	119.2	
Baseline SBP	170.6	170.7	
Adjusted Mean Change DBP	-17.7	-16.4	0.5539
Adjusted Mean Change SBP	-24.1	-21.1	0.3670

The next table shows ("Evaluable" or per- protocol cases only, Table 20 page 24, vol 1.46) that responses were on average larger in those QUIN cases that received HCTZ as compared to CAP subjects given diuretic. Significance testing was thought in-appropriate by the Sponsor.

TABLE 20. Evaluable Data: Mean Blood Pressure Changes From Baseline and Response Rates at Last Visit With Drug and HCTZ

	Treatment Group	
	Quinapril N = 32	Captopril N = 36
Baseline DBP	118.8	118.7
Baseline SBP	172.6	170.8
Adjusted Mean Change DBP	-21.9	-17.1
Adjusted Mean Change SBP	-30.8	-25.2
Response Rate†	91	83

† Decrease in DBP of ≥10 mm Hg from baseline

TABLE 11. Dose Levels at End of Monotherapy and End of Study
[Number (%) of Patients]

	Treatment Group		
	Quinapril† N = 47	Captopril‡ N = 50	Total N = 97
End of Monotherapy (Week 6			
Low	7 (15)	2 (4)	9 (9)
Medium	4 (9)	9 (18)	13 (13)
High	36 (77)	39 (78)	75 (77)
End of Study			
Low	6 (13)	1 (2)	7 (7)
Medium	1 (2)	4 (8)	5 (5)
High	5 (11)	7 (14)	12 (12)
High + HCTZ§	35 (74)	38 (76)	73 (75)

† low = 5 mg b.i.d; medium = 10 mg b.i.d; high = 20 mg b.i.d
‡ low = 25 mg b.i.d; medium = 50 mg b.i.d; high = 100 mg b.i.d
§ Hydrochlorothiazide 25 mg q.d.

Conclusions: This study shows that mono-therapy reduced to some degree in both QUIN and CAP, about 10mm, and that substantial additional effects probably occurred on adding HCTZ, which was required in about 75% of these severe hypertensives. As before, the QUIN responses can be examined along with those in all the studies to compare the size of the responses.

The above study is the last of the controlled efficacy trial submitted.

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Comment: The magnitudes of the reductions from baseline are all quite substantial given experience with antihypertensive trials in general.

Duration of activity: In the first two trials it is possible to examine duration of activity since trough BP responses were obtained. In the first trial "peak" values were also available assuming several hours of readings was a sufficient period to detect them. Duration is best discussed in conjunction with dose response.

Dose: The first two trials provide most of the information on dose effects. Trial (906- 303) showed that QUIN 10 / HCTZ 12.5 was more effective than monotherapy (QUIN/HCTZ -14.4; QUIN -11.8, HCTZ -12.2). Doubling the doses led to the following results, respectively, -18.7, -16.5, -16.5.

The factorial experiment, 906- 241, is more complex to interpret due to the pooling of active dose cells to allow marginal analyses (see review of the trial). This means that the background therapy for contrasts involving either monotherapy agent are the average

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doses of the other respective agent. That is, for the contrast QUIN / HCTZ vs HCTZ , the HCTZ responses are those for the average of all HCTZ active doses, 6.25, 12.5, and 25mgm. Likewise, for contrasts with QUIN are based on the average of 2.5, 10, and 40 mgm of QUIN.

Taking account of the above convention the responses to both QUIN 10mgm /HCTZ average (-11.5) and QUIN 40 mgm/HCTZ average (-12.0) were better than than the monotherapies HCTZ (-6.5), QUIN (-8.2).

Thus QUIN 10/ HCTZ is an effective dose in both trial -241 and -303 and the dose of HCTZ was either 12.5mgm (Protocol-303) or the average of three HCTZ doses (Protocol- 241). The dose of QUIN was either 10mgm (HCTZ 12.5) or 20mgm (HCTZ 25mgm) in Protocol -303. In Protocol -241 doses of either QUIN 10 or 40 were significantly different from HCTZ (average).

Safety in DB, Controlled Trials:

Protocol 906-241:
The following plot (submission, FIG 30, vol 18) shows that at the highest quinapril level (40mgm) there was positive dose response for ADEs as dose of HCTZ increased.

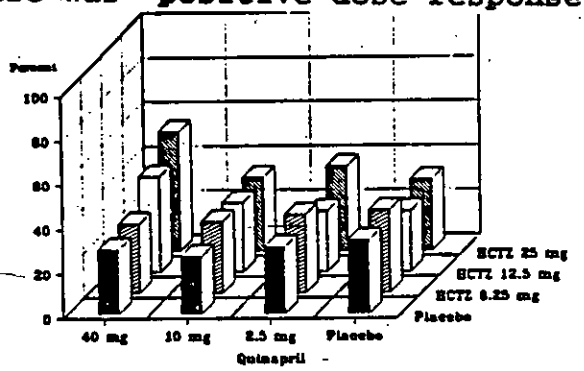


FIGURE 3C. Percentage of Patients With Adverse Events

Submission TABLE 48 (see APPENDIX A this review) shows ADEs classified as "ALL" and "ASSOCIATED", the latter being those ascribed to the drug by the Investigators. Note that : 1) there are small increases in ADEs going from quinapril monotherapy, HCTZ monotherapy, through the combination; 2) the frequency on placebo is higher than on either monotherapy; 3) there is no clear suggestion of an increase in overall ADEs for older subjects; 4)no deaths were reported; 5) more withdrawals for ADEs occurred on the combination than on monotherapy.
Table 49 (pages 1-5; APPENDIX A this review) shows all ADEs by treatment group regardless of Investigators' evaluation of causality by treatment. In particular, (Reviewer's selection) note that:

ADE	PLACEBO	HCTZ	QUIN	QUIN/HCTZ
HYPOTENSION	0(0.0)	0(0.0)	0(0.0)	2(0.8)
DIZZINESS	0(0.0)	2(2.3)	2(2.3)	13(5.0)
SYNCOPE	0(0.0)	1(1.1)	0(0.0)	1(0.4)
COUGH	0(0.0)	2(2.3)	0(0.0)	6(2.3)
RASH (erythematous)		0(0.0)	0(0.0)	0(0.0)
				3(1.2)

In the combination treatment group single instances of decreased hematocrit, and wbc were listed and n=4 (1.5%) cases of urinary abnormality were described. Note that the sample size for the combination group was N= 259 versus N= 86 for HCTZ and N= 88 for QUIN monotherapies.

All the cases of hypotension, of syncope and all but n=3 cases of dizziness were in the <65yr old age group.

The Sponsor considered that n=9 cases had clinically significant adverse effects. Syncope was reported at day 50 on HCTZ 12.5 and at day 48 on Q10/H6.25 (in a second patient). One case, taking Q40/12.5, had atrial tachycardia on day 6 although short runs were noted 3 months after withdrawal. One case had a transient ischemic attack and severe hypertension on Q40/H12.5. One case had facial paralysis on Q10/H25 with recovery after withdrawal. One case had angina on Q40/H12.5. Two subjects had either injury or surgery but were listed as ADEs since they were withdrawn. One subject, on Q40/H12.5 had GI bleeding at day 46. Another had reflux esophagitis on Q2.5/H12.5.

The following table lists those withdrawals considered as due to ADEs in the submission:

TABLE 52. Withdrawals Due to Adverse Events

Treatment		Center	Patient	Age	Study Day	Adverse Event	Attributable to Study Drug by Investigator
Quinapril	HCTZ			Sex	Began		
0	0	31	3	58 F	3	Vasodilation	Probably
2.5	6.25	11	7	61 M	2	Headache, Malaise	Possibly
2.5	6.25	12	4	54 F	10	Palpitation, Insomnia	Possibly
2.5	12.5	28	14	67 M	2	Nausea/Vomiting, Tremor, Abdominal Pain	Possibly
2.5	25	14	6	48 F	45	Fracture	Definitely Not
10	12.5	31	11	40 F	19	Dizziness	Unlikely
10	25	12	31	41 F	1	Facial Paralysis	Unlikely
40	0	8	3	56 M	4	Nausea/Vomiting	Possibly
40	6.25	22	24	51 M	2	Chest Pain	Possibly
40	12.5	6	5	61 F	23	Transischemic Attack	Unlikely
40	12.5	12	29	42 M	2	Angina Pectoris	Probably
40	12.5	27	8	59 M	10	Hypotension	Possibly
40	25	8	1	59 F	11	Fatigue, Vertigo	Probably
40	[illegible]	23	4	49 M	6	Somnolence, Dizziness, Sweating, Tachycardia	Probably

First dose Effect: BP was checked for 2hrs after the first dose of medication. The following table shows that most of the cases occurred on the highest two doses of QUIN/HCTZ. Hypotension was defined as a fall of >20mm on standing. Only one subject a BP <100.

TABLE 55. Number (%) of Patients Experiencing First-Dose Orthostatic Hypotension (N = 23 to 31/Treatment Group)

HCTZ (mg)	Quinapril (mg) 0	2.5	10	40
0	2 (8)	1 (4)	2 (6)	1 (4)
6.25	1 (3)	0 (0)	2 (6)	1 (4)
12.50	0 (0)	1 (4)	3 (10)	2 (8)
25.00	0 (0)	0 (0)	1 (4)	2 (7)

Orthostatic hypotension: The following table shows only the Q40/H25 group had a more instances than did the placebo group:

TABLE 56. Number (%) of Patients with Orthostatic Hypotension at Peak (N = 17 to 26/Treatment Group)

HCTZ (mg)	Quinapril (mg) 0	2.5	10	40
0	2 (11)	0 (0)	2 (8)	1 (4)
6.25	2 (9)	1 (5)	1 (5)	1 (4)
12.50	1 (4)	0 (0)	1 (4)	0 (0)
25.00	2 (10)	1 (4)	2 (11)	4 (24)

The next table shows that the number of cases with a fall in standing SBP >20mm on any trough reading in the study was fairly evenly distributed by treatment category.

TABLE 57. Number of Patients with Orthostatic Hypotension at Trough (N = 26 to 31/Treatment Group)

HCTZ (mg)	Quinapril (mg) 0	2.5	10	40
0	3	3	3	4
6.25	4	6	2	4
12.50	4	3	4	3
25.0	3	2	5	4

N=8 subjects had SBP values <100mm. Of these n=5 were on QUIN 40 mgm with HCTZ 12.5 or 25mgm.

Clinical Laboratory Values;

Serum potassium: The next table and figure show that the HCTZ-associatd fall in serum potassium was attenuated more at an added dose of 40mgm QUIN than at 10mgm.

TABLE 53. Mean Change in Serum Potassium (mmol/L) from Baseline to the Last Visit (N = 422)

HCTZ (mg)	Quinapril (mg) 0	2.5	10	40
0	-0.07	0.06	0.02	0.10
6.25	-0.15	0.02	-0.03	0.01
12.50	-0.19	0.05	-0.10	-0.15
25.00	-0.15	-0.25	-0.12	-0.09

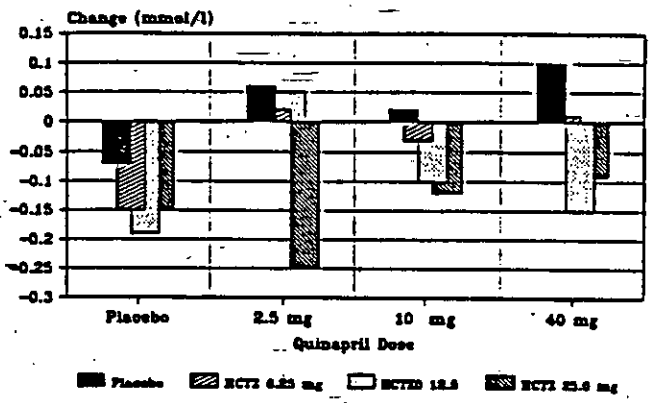


FIGURE 31. Mean Change in Serum Potassium (mmol/L)

Safety:

I. Overview

The safety data in the submission for QUIN/HCTZ is based upon:

A. N= 73 healthy volunteers in- N=4 pharmacokinetic or bioequivalence studies.

B. N= 1384 hypertensive subjects (n= 2 major, double- blind studies; n= 9 supportive double- blind studies; and n= 9 open-label studies. N= 825 cases received QUIN/HCTZ in these

"controlled" studies.

C. N= 303 cases received the combination in the two major trials, 906- 241 and 906- 303.

1. Study 906- 241

A. overall percentage of patients with adverse effects by dose

Table 47 vol 18 (not attached) shows that the overall percentage of ADEs on quinapril 2.5 mgm and 10 mgm approximate those on 0mgm for HCTZ doses of 0,6.25,12.5,and 25 mgm (33%, 37%, 27%, 32%, respectively). For quinapril 40 mgm there is dose response for the above increasing HCTZ doses (29%, 31%, 43%, 54%, respectively).

B. Adverse effects by treatment given

Table 48 vol 18 (next page) distinguishes "first occurrences" from "tpotal reports" since the former counts each events only once; the latter, multiple occurrences per subject.

1. The number of patients with ADEs: For "ALL ADEs" the percentage on the combination slightly exceeds that on placebo (36 vs 36%). "Associated" ADEs, those thought Rx- related by Investigators, are similar accross treatments.

2. Percentage by age group: For both "all" and "associated" ADEs there are more ADEs on combination Rx than on monotherapy. The trend is more obvious for age >65 years.

3. Percentage-with "clinically important" ADEs (as determined by Sponsor): None are listed for placebo or quinapril monotherapy, but for HCTZ and the combination, the respective values were 2% and 3%.

4. Percentage withdrawn for adverse effects: For "all ADEs" more cases, 5%, were withdrawn on the combination than on monotherapy but the value, 4%, was the same as on placebo.

table 48 v 18 p81

TABLE 48. Summary of Adverse Events (AEs)

	Placebo (N = 27)	Quinapril Monotherapy (N = 86)	HCTZ Monotherapy (N = 88)	Quinapril + HCTZ (N = 259)
Number of Patients with Adverse Events (%)				
All AEs	9 (33)	24 (28)	28 (32)	93 (36)
Associated[a] AEs	5 (19)	11 (13)	13 (15)	46 (18)
Number of First Occurrences and Total Reports				
All AEs				
First Occurrences	14	44	51	171
Total Reports	15	47	51	176
Associated AEs				
First Occurrences	8	15	17	70
Total Reports	8	15	17	70
Number of Patients with Adverse Events by Age				
All AEs				
<65 years (N = 395)	8 (32)	23 (32)	25 (32)	78 (35)
≥65 years (N = 65)	1 (50)	1 (7)	3 (30)	15 (38)
Associated AEs				
<65 years	5 (20)	11 (15)	11 (14)	37 (17)
≥65 years	0 (0)	0 (0)	2 (20)	9 (23)
Number of Total Reports by Severity				
All AEs				
Mild	8	31	31	93
Moderate	7	16	15	56
Severe	0	0	5	13
Not Specified	0	0	0	14
Associated AEs				
Mild	5	12	12	33
Moderate	3	3	3	21
Severe	0	0	2	9
Not Specified	0	0	0	5
Number of Patients with Clinically Important Adverse Events (%)	0 (0)	0 (0)	2 (2)	8 (3)
Number of Deaths	0	0	0	0
Number of Patients Withdrawn for Adverse Events (%)				
All AEs	1 (4)	1 (1)	0 (0)	12 (5)
Associated AEs	1 (4)	1 (1)	0 (0)	8 (3)

[a] Considered by the investigator possibly, probably, or definitely related to study drug.

C. Adverse events by system and treatment: Table 49 (attached) shows that:

1. Digestive system: abdominal pain was noted in slightly more (1.9%) of combination patients than in monotherapy cases (HCTZ: 1.1%; QUIN 1.2%);placebo cases had more (7.4%) but sample N small.

2. Cardiovascular system: hypotension less than 1% (2/259); dizziness 5% of combination cases versus 0 to 2.3% for placebo and monotherapy. There was no increase in syncope for the combination.

3. Respiratory system: Cough was reported in 2.3% of combination and of HCTZ cases.

4. Skin: erythematous rash was reorted in 1.2% of combination cases.

5.On the last page urinary abnormalities are noted in 1.5%, decreased white cell counts in a single instance.

6. The most frequently noted ADEs are shown in table 51 below.

TABLE 51. Most Frequently Reported Adverse Events (Percent of Patients)

Adverse Event	Placebo (N = 27)	Quinapril Monotherapy (N = 86)	HCTZ Monotherapy (N = 88)	Quinapril + HCTZ (N = 259)	Total (N = 460)
Headache	14.8	4.7	13.6	4.6	7.0
Dizziness	0.0	2.3	2.3	5.0	3.7
Fatigue	0.0	2.3	1.1	3.1	2.4
Myalgia	0.0	3.5	2.3	2.3	2.4
Abdominal Pain	7.4	1.2	1.1	1.9	2.0
Vertigo	3.7	2.3	1.1	1.9	2.0
Rhinitis	0.0	1.2	1.1	2.7	2.0
Coughing	0.0	0.0	2.3	2.3	1.7
Nausea and/or Vomiting	3.7	1.2	2.3	1.5	1.7
Viral Infection	0.0	1.2	1.1	1.9	1.5
Asthenia	0.0	1.2	1.1	1.5	1.3
Pharyngitis	0.0	3.5	1.1	0.8	1.3
Sinusitis	3.7	2.3	2.3	0.4	1.3

D. Age- relationships for certain ADEs:

Only N= 2 of the cases of "dizziness" occurred in cases over 65yrs of age (3%). Dosage for these cases was QUIN 40/HCTZ 25, the largest levels available.

Clinical laboratory tests: Table 65 page 146 showed that N= 10 subjects had a fall in hematocrit. Of these this Reviewer found that N= 2 had a low baseline value so 8/231 or 3.5% had a true fall versus 4/82 or 5% for HCTZ monotherapy.

Table 66, below, shows that N= 3 QUIN/HCTZ cases (1.4%) had "possibly clinically important" falls in platelet counts versus

1/82 or 1.2% of placebo cases.

TABLE 66. Patients with a Possibly Clinically Important Decrease in Platelets Below Normal Range at Final Value

Treatment		Center	Patient	Platelets (x $10^3/mm^3$)	
Quinapril	HCTZ			Baseline	Final Value
0	0	4	1	233	172
0	25	15	9	153	122
2.5	6.25	32	11	102	70
10	6.25	12	14	265	130
40	6.25	15	3	211	108

No "possibly clinically important" increases in BUN or creatinine were noted by the Sponsor. The median difference for QUIN/HCTZ was 0 for creatinine; and 0.21 for BUN versus 0 and 0.3 for HCTZ monotherapy.

Most (4/6) of the hypokalemic subjects receiving QUIN were also on high dose (25mgm) HCTZ. N= 2 were also on QUIN 40mgm, suggesting that doses that large of QUIN may not necessarily reverse hypokalemia.

Comment on data sources: The following table (Table 63 Vol 18 next page) due to the Sponsor lists the results of "shift tables" by showing the percentage of cases having a change in laboratory tests in an adverse direction for each treatment group.

Comment on missing data: There are substantial differences in the number of data that are missing for specific laboratory tests. For example, for QUIN + HCTZ, the number of cases randomized was N= 259 though the number cases with available measurements is always less and sometimes very much less. For example, creatinine 232; wbc 231; potassium 248; urine protein 218; platelets 218; urine rbc/hpf 156; BUN 73. Therefore in taking inferences from the laboratory data the reader should note the substantial differences among tests for available information.

Safety in Protocol 906- 303:

A. Summary
1. ADEs by dose

Table 29 (attached) shows that for "all" ADEs (regardless of Investigator oponion) the percentage was least (6.5%) on combination and larger, though equal, on the two monotherapies (HCTZ 9.7%; QUIN 9.2%)
2. The same trend was true for first occurrences.
3. For cases older than 65yrs of age there were more ADEs on HCTZ monotherapy (4%) than on QUIN (2%) or combination (0%). The number of ADEs was not increased in older subjects.
4. QUIN had more "associated" (Investigator opinion) severe ADEs; HCTZ the least. There were no study deaths.
6. N= 4 subjects were withdrawn for ADEs.

B. ADEs by treatment and system

Table 30, attached, shows under "nervous system" that N= 1 case of syncope occurred and that was in the QUIN monotherapy group.

Digestive symptoms occurred in 2.5% of each treatment group but no instances of abdominal pain are noted in either QUIN dosage group.

C. Age effects: Older subjects reported smaller values for one or more ADEs than did young subjects.

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E. Withdrawals due to ADEs

One subject was withdrawn for palpitations on 10mgm QUIN. Another withdrew for dizziness and syncope on the same dose. N=2 others withdrew for ADEs; both from the HCTZ group.

F. First- dose effects: BP was checked after first dose and first doubled- dose. N= 16 patients had an orthostatic fall in systolic BP of >20mm after the first dose; N=7 after the doubled dose.

G. Trough hypotension: An orthostatic fall >20mm occurred at low dose (QUIN: 6.7%; QUIN/HCTZ : 8.9%; HCTZ 5.6%. At high dose the respective figures were 5%, 6.7%, and 7.0%.

Clinical Laboratory data: Table 34, below, shows attenuation by QUIN of the fall in serum K on HCTZ.

	Quinapril Monotherapy	Quinapril + HCTZ	HCTZ Monotherapy
Low Dose	(N = 114)	(N = 121)	(N = 122)
Mean Baseline	4.27	4.27	4.31
Raw Mean Change from Baseline	0.09	-0.03	-0.12
High Dose	(N = 99)	(N = 103)	(N = 114)
Mean Baseline	4.28	4.29	4.31
Raw Mean Change from Baseline	0.02	-0.08	-0.19

Table 41 shows the number of "possibly clinically important" deviations. Roughly similar percentages between QUIN or QUIN/HCTZ and HCTZ are noted for hematocrit, platelets, BUN, creatinine, and the liver function enzymes.

TABLE 41. Patients with Possibly Clinically Important Deviations in Laboratory Values [Number (%) of Patients]

Parameter	Quinapril Monotherapy (N=96-114)	Quinapril + HCTZ (N=101-121)	HCTZ Monotherapy (N=102-122)
Hemoglobin	0 (0)	1 (1)	0 (0)
Hematocrit	1 (1)	2 (2)	1 (1)
Platelets	1 (1)	3 (3)	2 (2)
White Blood Count	5 (5)	3 (3)	1 (1)
Eosinophils	1 (1)	4 (4)	4 (4)
Fasting Glucose	9 (8)	9 (8)	10 (9)
Blood Urea Nitrogen (BUN)	2 (2)	4 (4)	3 (3)
Creatinine	0 (0)	1 (1)	0 (0)
Phosphokinase (CPK)	0 (0)	0 (0)	0 (0)
Alkaline Phosphatase	1 (1)	0 (0)	1 (1)
Bilirubin (Total)	0 (0)	1 (1)	3 (3)
LDH	0 (0)	0 (0)	0 (0)
SGOT	0 (0)	0 (0)	0 (0)
SGPT	0 (0)	0 (0)	0 (0)
Cholesterol (Total)	6 (6)	6 (5)	6 (5)
Uric Acid	2 (2)	1 (1)	0 (0)
Sodium	10 (9)	11 (9)	13 (11)
Potassium	16 (14)	16 (13)	20 (16)
Calcium	1 (1)	0 (0)	1 (1)
Chloride[a]	3 (3)	4 (4)	7 (7)
Protein (Total)	1 (1)	3 (3)	0 (0)
Albumin	1 (1)	0 (0)	0 (0)

[a] N=89-94

Table 44, below, shows that N= 2 QUIN or QUIN/HCTZ- treated cases had falls in hematocrit and N= 2 cases had reductions in platelets or wbc counts by definition

Treatment (mg) Quinapril	HCTZ	Center-Patient	Normal Range	Screening	Baseline	Final Value
Hemoglobin (g/L)						
20	25	24-4	140-180	155	153	131
Hematocrit (%)						
20	--	3-16	45.7-47.8	48.5	53.2	43.1
20	25	10-5	40-50	45.3	44.8	39.5
--	25	3-2	38.2-43	42.3	42.8	34.3
Platelets (x 10^9/L)						
20	--	13- 5	150-300	118	166	132
20	25	22-14	150-350	184	176	109
--	25	22-12	150-350	155	152	113
White Blood Count (x 10^9/L)						
20	--	6-3	4-10	5.1	5.6	3.5
20	--	10-14	4.5-11	6.4	6.3	3.0
--	25	10-2	4.5-11	5.7	6.5	4.4

Patient 23, center 16, a 75-yr- old woman on high dose combination Rx, had an increase in serum creatinine from 88 and 62 micromol/l to a final value of 124. BUN and urinalysis were unremarkable.

Liver function evaluation showed a small elevation (23micromol/l to 29) in a patient on QUIN/HCTZ 10/25. One case on QUIN 10mgm had an increase of alkaline phosphatase from 78- 90 U/L. One case on QUIN had a reduction of serum albumen from 43 g/L to 2.9 g/L.

Urine protein values shifted to "high" in QUIN: 7% and QUIN/HCTZ: 14%; HCTZ :9% of cases. Shifts of urine occult blood of 5%, 5%, and 4% occurred for QUIN, QUIN/HCTZ, and HCTZ. For urine wbc/hpf the respective shifts for the above three groups were 28%,21%, and 28%. Urine sediment rbc were not provided. The above numerical values were taken by the Reviewer from the Sponsor's Table 43 Vol 26, a summary of the "shift tables". Table 43 follows on the next page.

Conclusions for Safety in the two, major, controlled trials (Protocols 906- 241 and -303): Areas of special concern with respect to the combination treatment, especially renal impairment with rising serum creatinine and symptomatic orthostatic hypotension were not a prominant feature of these studies.).n.b. see Reviewer's subsequent analysis of pyuria.

<u>Saftey in Quinapril vs Propranolol Trial (with optional HCTZ):</u>

I. Summary of ADEs

A. N= 54 of 86 (63%) QUIN cases and 40/79 (51%) of Propranolol cases had an ADE regardless of Investigator- assigned causality.

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I. Summary of ADEs

A. N= 54 of 86 (63%) QUIN cases and 40/79 (51%) of Propranolol cases had an ADE regardless of Investigator- assigned causality.

B. N= 3 QUIN cases and N= 2 propranolol cases had "clinically important" ADEs (Sponsor- assigned).

C. No deaths occurred.

D. N= 12 QUIN cases and N+ 10 PROP cases were withdrawn for ADEs.

II. ADEs by treatment and system

Table 25 p43 v33 (not attached) provides a listing of the percent of cases with first occurrences and number of reports of an ADE.

Digestive symptoms (dyspepsia, nausea and/or vomiting, diarrhea, constipation) occurred in 2.3- 4.7% of the QUIN group and about 1.3% of the PROP group. Abdominal pain occurred in 7.0% of the QUIN group versus 2.5% of the PROP cases.

"Clinically- important" ADEs in the QUIN cases receiving HCTZ included instances of ventricular ectopic beats, cramps, syncope, and hypokalemia (latter two in same case), insomnia with depression and orthostatic light- headedness.

Withdrawals due to ADEs are shown in TABLE 28, on the following two pages.

Hypotension and orthostatic hypotension:

Blood pressure was measured 2hrs after both first dose and after first dose titration step. No patients had BP <100mm systolic. N=3 QUIN cases and N=2 PROP cases had orthostatic decreases of >20mm systolic BP. All standing BP in these cases were >100mm. One case had a 20mm decrease in standing BP after addition of HCTZ to PROP. None of the orthostatic falls in BP were associated with symptoms. n.b. N= 6 cases of "dizziness" occurred in QUIN cases.

Clinical Laboratory tests:

The Sponsor provided a listing of patients with " possibly clinically important deviations".

This showed 3/86 (3%) of QUIN cases with alterations in hemoglobin and 0/75 (0%) in the PROP group. One of the QUIN cases had a value of 159gm/l at baseline and 140 at last value. Another had an

TABLE 28. Withdrawals Due to Adverse Events
(Page 1 of 2)

Treatment	Center	Patient	Age	Sex	Dose mg/day	Study Day Began	Study Day Ended	Adverse Event	Attributability[a]
Quinapril	172	6	34	M	20	8	26	Tiredness, forgetfulness, depression	Study drug
	172	8	57	M	40	29	Cont	Increased serum glucose	Concurrent illness
	173	7	63	F	40	40	43	Weakness, dizziness, epigastric pain	Possibly study drug
	173	10	54	F	20	26	33	Epigastric pain	Possibly study drug
	173	11	50	F	20	10	Cont	Stomach pain	Possibly study drug
	174	3	57	M	40	112	127	Perspiration, weakness	Possibly study drug
	174	9	53	M	20	16	36	Tickle in throat, food doesn't taste right, tired, dry cough	Possibly study drug
	177	13	45	M	20	14	28	Headache	Possibly study drug
						26	28	Nausea, diarrhea	Possibly study drug
	181	6	58	F	20	9	29	Tiredness	Study drug
						16	27	Cold hands	Study drug
	185	6	36	F	20	27	43	Depression, anger, dystonia, insomnia	Possibly study drug
	185	10	47	F	40 + 25	62	70	Vasovagal syncope, dehydration, stress	Possibly study drug
						66	70	Hypokalemia	Study drug
	187	7	58	M	20	39	43	Calf pain, pain in arm, neck pain, palpitation, anxiety	Unknown

a Investigator's judgement

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TABLE 28. Withdrawals Due to Adverse Events
(Page 2 of 2)

Treatment	Center	Patient	Age	Sex	Dose mg/day	Study Day Began	Study Day Ended	Adverse Event	Attributability[a]
Propranolol	171	1	55	M	80	1	7	Extrasystoles ventricular	Possibly study drug
	172	4	57	M	80	29	39	Bradycardia	Study drug
	173	2	72	M	80	15	22	Insomnia, nightmares	Possibly study drug
	173	5	75	M	80	4	12	Insomnia, nightmares	Possibly study drug
	174	2	46	M	80	26	31	Wheezing	Possibly study drug
	181	5	61	F	80	29	43	Tiredness, wheezing	Possibly study drug
	184	11	71	F	80	55	66	Atrial fibrillation, sinoatrial dissociation (intermittent)	Concurrent illness
	186	1	37	M	80	29	Cont	Impotence	Study drug
	186	5	40	F	160	57	71	Dizziness with position change	Possibly study drug
					160 + 25	71	84	Insomnia, depression	Possibly study drug
	187	12	54	F	160	39	44	Esophageal burning	Possibly study drug

[a] Investigator's judgement

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increase in hemoglobin. The third case had a screening value of 133 and a level of 131 at last value. The median fall over all cases was -2.5g/l for QUIN and -1.0g/l for PROP.

Low wbc counts at the end of the study were found in 2% of QUIN cases and 0% of PROP cases as shown in the Sponsor's submission. N= 2 cases had values of 3.8 10E9/l and 3.9 10E9/l. Each case had fluctuations including values nearly as low and substantially higher. The median change in the QUIN group was an increase of 0.1 x 10E9/l and 0.2 x 10E9/l in the PROP cases.

BUN was elevated in a QUIN case to 9.7MMOL/l at last visit (day 119) but the serum creatinine was not comparably altered at 89 MMOL/l. No earlier values were recorded. HCTZ had been started at day 89. The median increase of BUN was 0.3MMOL/l (QUIN) and 0.1MMOL/l (PROP). Serum creatinine fell in the QUIN group and rose very slightly in the PROP cases.

Laboratory details on N=3 cases withdrawing for abdominal pain:

One case had a baseline hemoglobin of 134 g/l and 138 at day 43. A second case had values of 139 at baseline and 142 at day 29. Case 11 had values of 141 and 137 following a screening value of 131.

Under nervous system, vertigo occurred only in the PROP group (N= 1 case). Syncope occurred in N=1 QUIN case.

Respiratory system: Cough occurred in N= 3 (3.5%) of QUIN cases and in none of the PROP ones.

Skin: Rash occurred in N=1 case (QUIN).

Safety in Trial of Quinapril vs Captopril (added HCTZ):

I. Summary of ADEs

Table 29 of the submission (vol 37 p33, not attached) shows that:

TABLE 63. Percentage of Patients Changing to "Low" or "High" Values at the End of The Study

Parameter	(Adv/ Neu)	Placebo Adv/Neu	Quinapril Monotherapy Adv/Neu	HCTZ Monotherapy Adv/Neu	Quinapril + HCTZ Adv/Neu
Hemoglobin	(L/H)	0/5	3/0	5/3	3/5
Hematocrit	(L/H)	4/5	6/0	3/1	5/5
Platelets	(L/H)	5/0	0/0	1/5	1/2
Erythrocytes	(L/H)	0/8	4/3	3/4	7/3
WBC	(L/H)	4/4	0/4	1/1	3/5
Stabs	(L/H)	0/10	3/10	3/12	1/6
Polymorphs	(L/H)	5/5	3/13	8/9	7/6
Eosinophils	(H/L)	5/5	3/3	7/9	6/8
Basophils	(L/H)	0/11	1/9	0/6	0/6
Monocytes	(L/H)	0/13	12/6	12/4	16/6
Lymphocytes	(L/H)	0/5	3/3	6/9	3/10
Nonfasting Glucose	(H/L)	0/0	6/1	2/0	8/5
Urea (BUN)	(H/L)	0/0	4/5	0/0	3/1
Blood Urea	(H/L)	7/0	15/4	12/0	9/0
Creatinine	(H/L)	5/0	5/0	3/1	1/1
Alkaline Phosphatase	(H/L)	0/0	4/0	1/0	1/1
Bilirubin	(H/L)	0/0	8/0	7/0	3/0
LDH	(H/L)	14/0	6/2	6/3	3/2
SGOT	(H/L)	10/0	6/0	10/0	4/0
SGPT	(H/L)	6/4	3/1	11/0	5/0
Uric Acid	(H/L)	5/0	6/1	9/0	10/0
Sodium	(L/H)	0/0	0/1	2/1	1/2
Potassium	(L/H)	0/0	0/1	2/0	4/0
Calcium	(L/H)	0/0	3/0	8/0	3/0
Chloride	(L/H)	0/9	0/9	2/4	1/2
Carbon Dioxide	(L/H)	7/0	10/14	0/6	1/12
Total Protein	(L/H)	0/4	1/7	1/1	1/3
Albumin	(L/H)	0/0	3/0	0/1	2/4
Urine pH	(H/L)	0/0	0/0	0/3	3/1
Urine Specific Wt.	(H/L)	10/0	0/11	3/0	1/4
Urine Protein	(H/L)	0/0	9/0	8/0	9/0
Urine Glucose	(H/L)	0/0	0/0	3/0	2/0
Ketones	(H/L)	0/0	0/0	3/0	1/0
Urine Blood	(H/L)	5/0	0/0	1/0	5/0
WBC/hpf	(H/L)	30/0	18/0	15/0	26/0
RBC/hpf	(H/L)	0/0	2/0	2/0	9/0
Granular Casts	(H/L)	0/0	0/0	2/0	1/0
Hyaline Casts	(H/L)	0/0	2/0	5/0	1/0
Urine Bilirubin	(H/L)	0/0	0/0	2/0	1/0

Adv = potentially adverse change
Neu = change of minimal clinical significance or possibly beneficial change
L = Normal or high at baseline and low at the end of the study
H = Normal or low at baseline and high at the end of the study

TABLE 29. Summary of Adverse Events (AEs)

	Quinapril Monotherapy (N = 120)	Quinapril + HCTZ (N = 124)	HCTZ Monotherapy (N = 124)
Number of Patients Reporting Adverse Events (%)			
All AEs	11 (9.2)	8 (6.5)	12 (9.7)
Associated[a] AEs	8 (6.7)	5 (4.0)	2 (1.6)
Number of First Occurrences and Total Reports			
All AEs			
First Occurrences	18	8	19
Total Reports	19	9	19
Associated[a] AEs			
First Occurrences	13	5	4
Total Reports	14	6	4
Number of Patients Reporting Adverse Events by Age (%)			
All AEs			
< 65 years	9 (10.8)	8 (9.0)	8 (10.1)
≥ 65 years	2 (5.4)	0 (0.0)	4 (8.9)
Associated[a] AEs			
< 65 years	8 (9.6)	5 (5.6)	2 (2.5)
≥ 65 years	0 (0.0)	0 (0.0)	0 (0.0)
Number of Total Reports by Severity			
All AEs			
Mild	9	5	7
Moderate	10	4	11
Severe	0	0	1
Associated[a] AEs			
Mild	5	3	2
Moderate	9	3	2
Number of Patients with Clinically Important AEs (%)	1 (0.8)	0 (0.0)	2 (1.6)
Number of Deaths	0	0	0
Number of Patients Withdrawn for Adverse Events			
All AEs	2	0	1
Associated[a] AEs	1	0	0

[a] Considered by the investigator possibly, probably, or definitely related to study drug.