A. 26% of N=101 QUIN cases and 21% of N= 105 CAPTO cases had ADEs.

B. The total number of reports (more than one per case could occur) was larger in the QUIN group (N=58) than in the CAPTO one (44%).

C. No deaths nor "clinically important" ADEs were reported in either Rx group.

D. The percentage of cases reporting ADEs was larger in subjects >= 65yrs of age in both treatments but the percentage in the QUIN group (32%) was smaller than in the CAPTO cases (44%).

E. About the same number of cases were withdrawn for ADEs (N=5, N=6) from the QUIN and CAPTO groups.

II. ADEs by treatment and system (as shown in the Sponsor's Table 30, unattached):

A. Hypotension was reported in N=2 (2%) of QUIN and N=1 (1%) of CAPTO cases.

B. Abdominal pain occurred in N= 3 (3%) of QUIN and N=1 (1%) of CAPTO cases.

C. Dizziness was reported in N=3 (3%) of QUIN and N=6 (6%) of CAPTO cases.
D. Cough was reported in 3 and 4% of the above groups, respectively.

III. Withdrawals due to ADEs

A. N= 5 such withdrawals occurred in the QUIN group (n=1 vomiting and hematemesis; N=2 headache with or without cough; N=2 cough). N= 6 cases withdrew in the CAPTO group.

B. Hypotension

N= 18 QUIN cases and N= 17 CAPTO cases had falls in systolic BP of >20mm on standing under test conditions. No symptoms occurred at these times. More subjects had dizziness on CAPTO than on QUIN at other times.

IV. Clinical Laboratory tests

A. Examination by the Reviewer of the Sponsor's listings of ranked results of laboratory data showed that N= 6 subjects in the QUIN group had falls in hemoglobin of >= 2.0 g/l. WBC and platelet

counts were available in all but one case in the QUIN group and were normal. One of N= 3 cases with increases in creatinine had a normal value at last visit; N= 2 others had only small increases.

B. Table 36 (submission, unattached) shows that the median fall in hemoglobin was -2 g/l in each Rx group.

C. The median change in platelets was an increase of 1.5 and 2.0 x 10E9/l in the QUIN and CAPTO groups.

D. The median change in wbc was -0.03 x 10E9/l (QUIN) and +2.0 x 10E9/l (CAPTO).

E. Median changes for BUN and creatinine were identical in each treatment group, 0.2 and 0.0 for the respective laboratory tests.

F.Table 37 of the submission, unattached, showed the number and percentage changing to low or high values. For QUIN, then Capto, the respective changes in the clinically- meaningful direction, were: hemoglobin: 5%, 3%; platelets: 1%, 1%; wbc count: 2%, 3%; BUN: 16%, 15%; creatinine: 6%, 6%. SGPT:3%, 12%.

Safety: Uncontrolled studies:

Protocol 906- 241X (1 year extension of dose- response study):

I. Summary of ADEs

A. ADEs occurred in 102/236 (43%) of subjects.

B. No deaths were reported. N= 11 ADEs were judged "clinically important".

C. N= 25 of 236 (11%) withdrew due to ADEs.

II. ADEs by Rx and system (taken from Table 12 of submission v49).

A. Under Cardiovascular system, hypotension was listed for 0.8% of the subjects.

B. Digestive system: Complaints included abdominal pain in 1.3% of cases; perforated bowel in N= 1 case (0.4%).

C. Nervous system: Dizziness N= 22 cases (9.3%); vertigo N=4 cases (1.7%).

D. Respiratory complains included cough in n= 24 cases ((10.2%).

E. Skin: rash (1.7%) or maculopapular rash (0.4%).

III. "Clinically- important ADEs" (submission)

N= 3 of these were malignancies (colon, breast, stomach); one hip fracture; one myocardial infarction; N= 2 appendectomies; N= 1 severe pruritis; N=1 Guillan- Barre syndrome.

IV. Withdrawals ascribed to ADEs

Tables 16 (submission v49 pages 35,36, attached) shows these cases. The frequency of cough in theses cases was notable (10/25).

V. Orthostatic hypotension

N= 22 patients (10%) had orthostatic decreases of >20mm of systolic BP. The percentage was nearly the same in cases taking QUIN/HCTZ 10/12.5, 20/25, and 40/50. Almost all instances were asymptomatic.

VI. Clinical laboratory tests

A. Possibly clinically- important deviations (submission)

Aside from electrolyte alterations, the most frequent instances were for hematocrit (9%), blood urea (9%), eosinophils (7%) and, both platelets and wbc, 6%. Sample sizes for each test were about N= 220 except for blood urea (136). These alterations could be in either direction, up or down.

B. Median change from baseline (from submission Table B15, p189, v49).

FINAL VALUE MINUS BASELINE

TEST UNITS	MIN	MED	MAX	
Hematocit %	-8.0	-0.7	42.6	

Platelets x10E9	-218.0	0.0	210.0	
WBCx10E9	-53.2	0.2	4.8	
BUN MM/L	-66.3	0.4	11.1	
Creat UM/l	-61.0	0.0	40.0	

C. Specific parameters

For the following N= 6 tests the Sponsor's listings of all serial data for cases with "clinically important" deviations were examined:
Platelets: N= 3 cases had final values not far below the normal limits for the laboratory but with low normal baseline values.
WBC counts:N=1 case had a value of 4.2 x 10E9 with a fluctuating set of prior values including one near that level and another twice that level.
Eosinophils: N=6 cases had elevated levels with respect to the normals for that center.
BUN: N= 7 cases were elevated a final value. Only N=1 case of elevated creatinine occurred (to 2.3mgm%).
Alkaline phosphatase:The highest level was 183 (baseline 129; lab upper limit 140 units). One lesser increase also occurred.
Bilirubin: N= 3 cases had substantial increases; one of these had an increase

within the normal zone for SGOT but no elevation or trend for alkaline phosphatase. Another case had mildly elevated levels of SGOT and SGPT at baseline and later but no change in alkaline phosphatase. A final case had an isolated elevation.

Safety information from Integrated Summary of Safety (vol 17):

I. Total exposure to QUIN/HCTZ in clinical trials is more than 11,680 patient- months. Individual case exposure ranged from 1 day to 36 months.

II. Identification of Studies on which the Integrated Summary of Safety (ISS) is based:

A. N= 73 healthy volunteers

B. N= 1384 hypertensive cases in clinical studies (N= 2 major, double -blind trials; N= 9 supportive, double- blind trials in which HCTZ was added optionally to patients whoc responded inadequately to QUIN monotherapy or vice versus; N= 9 short and long- term open- label studies.

1. Major controlled clinical studies (Protocols 906- 241; 906-303) compared combination therapy with each monotherapy. The total number of subjects receiving QUIN/HCTZ was N= 383.

2. In addition to the two major controlled studies, N= 9 supportive controlled studies provided a total of N= 825 patients receiving QUIN/HCTZ.

3. Safety data from N= 3 open- label studies plus N= 6 long-term open- label extensions of double- blind trials gave a cumulative total (including items 1 and 2 above) of N= 1384 hypertensive subjects who received the combination at some time.

C. ADEs in Clinical Pharmacology studies

Of N= 73 volunteers, 51% had ADEs (headache: 26%; dizziness: 18%; dyspepsia: 6%- were the most frequent). One subject had a syncopal episode (see under subsequent discussion of serious ADEs).

D. ADEs in the major controlled studies (Prot 906- 241; 906- 303): The percentage of cases with one or more ADEs was QUIN/HCTZ: 26%; QUIN: 18%; HCTZ: 19%.

Under Digestive System the percentage of subjects with abdominal pain was QUIN/HCTZ: 1.3%; QUIN 0.5%; HCTZ 1.4%.

Under Nervous System the percentage of subjects with dizziness was higher in QUIN/HCTZ (3.7%) than for QUIN (1.5%) or HCTZ (0.9%).

In addition, there were N= 2 instances of hypotension, both on combination therapy; N= 3 episodes of syncope- one in each Rx category.

E. ADEs in all controlled studies
These, when added to results from the N= 2 major controlled studies, provided safety data in N= 825 hypertensive subjects on QUIN/HCTZ. Table 4 (attached) shows, in particular, that Nausea and/ or vomiting (QUIN/HCTZ: 2.2%), abdominal pain (QUIN/HCTZ: 1.8%), dyspepsia(QUIN/HCTZ 1.2%) or diarrhea (QUIN/HCTZ 1.2% occurred less often in the QUIN/HCTZ group than on QUIN mono-therapy.

Dizziness occurred in 5.2% of QUIN/HCTZ cases; 4.7% of PLAC cases and 4.8% of QUIN cases. n.b. The above- listed ADEs (those shown in Table 4) were listed as occurring on QUIN/HCTZ if at any time in a study the subjects received that combination. Thus an ADE could have been reported as occurring on the combination even if monotherapy was being given. A second set of tables was provided which restricted the reported ADEs to those occurring on the specific combination or reference monotherapy. However, these data were pooled over Investigator, demographics, baseline BP etc. These tables (Table 5 vol 17 p98-99) show:
Items in parentheses are values for ADE that may have occurred on QUIN without HCTZ but was assigned to the combination because of previous use.

Symptom\Rx	QUIN/HCTZ On known Rx	QUIN/HCTZ Ever	QUIN On known Rx	QUIN Ever
N & V	2.1	2	2.0	2.6
Abd Pain	1.8	1.8	1.6	1.9
Dyspepsia	1.2	1.2	2.2	1.7
Diarrhea	1.2	1.2	2.0	1.9
Dizzy	5.2	5.2	3.0	4.8

The estimates of the frequency of these specific ADEs are quite close whether or not one or the other type of estimate is used. The relationship between the percentage of cases with the ADE on QUIN/HCTZ and QUIN monotherapy is slightly different for the two methods. For example nausea and/or vomiting is higher on QUIN (2.6%) than on the combination (2.1%) if any previous use of the combination is equated to use at time of the ADE but is very slightly higher on QUIN/HCTZ (2.1% vs 2.0%) if cases on the specific treatment at the time of the ADE are used .The same is true for abdominal pain.

F. ADEs in all clinical studies

The following estimates are based on N= 1384 hypertensive subjects treated with QUIN/HCTZ at some time in their course. N= 517 patients had at least 1 yr of exposure to the combination; N= 203 had at least 2 years.

Person- months of exposure to QUIN/HCTZ: 11,680.

TABLE 4. Controlled Studies: ACCURETIC Proposed Package Insert - Adverse Events Occurring in ≥1% of Patients Treated With Quinapril/HCTZ [Percent of Patients]

Adverse Event	Quinapril Monotherapy from ACCUPRIL Draft Package Insert N = 2260	ACCURETIC NDA Quinapril/HCTZ All N = 825	ACCURETIC NDA Quinapril/HCTZ ≥65 Years N = 135	ACCURETIC NDA Placebo All N = 85
Headache	6.8	6.8	3.0	21.2
Dizziness	4.8	5.2	3.0	4.7
Coughing	3.0	3.3	0.7	2.4
Fatigue	3.1	3.0	0.7	2.4
Myalgia	1.8	2.7	0.0	5.9
Viral Infection	1.5	2.3	0.7	3.5
Rhinitis	2.6	2.2	1.5	3.5
Nausea and/or Vomiting	2.6	2.1	2.2	5.9
Abdominal Pain	1.9	1.8	1.5	4.7
Back Pain	1.2	1.5	1.5	1.2
Upper Respiratory Infection	1.5	1.5	0.0	3.5
Insomnia	1.2	1.3	0.7	1.2
Somnolence	1.0	1.3	1.5	0.0
Bronchitis	0.9	1.3	1.5	1.2
Asthenia	0.9	1.2	0.7	1.2
Dyspepsia	1.7	1.2	0.0	1.2
Diarrhea	1.9	1.2	0.7	1.2
Pharyngitis	1.2	1.2	0.7	2.4
Vasodilatation	0.5	1.1	0.7	1.2
Vertigo	0.5	1.1	1.5	2.4
Chest Pain	1.8	1.0	0.0	2.4

I. ADE by age

Overall, patients <65yrs of age had fewer (28.6%) side effects than did older subjects (16.5%). Subjects >=65yrs of age had a rate of 1.8% hypotension; those <65yrs had 1.0%. Dizziness occurred more frequently (10.5%) in younger than in older subjects (5.5%). Syncope occurred in 0.8% of the younger and 1.8% of the older cases.

II. ADE by dose

Taking HCTZ doses of 0, 6.25, 12.50, 25.00 mgm , only the QUIN 40mgm dose allowed a clear- cut dose response (29,31,43,54%) for total ADEs.

III. Serious events and deaths

Using all volunteer and clinical studies, N= 1457 cases provided information on serious events and deaths.

Definitions: The Sponsor defined ADEs as "serious" if they were fatal, immediately life- threatening, disabling, casused prolonged hospitalization, were an overdose, or a cancer. In addition, certain ADEs were added to the list if they had particular clinical importance (syncope, gout, pneumonia, hematuria, face and tongue edema, diabetes, and transient ischemic attacks.

A. Table 10 p115-117 v17 showed that n=1 cases (0.1%) of facial edema; n=1 (0.1%) of tongue edema; n=15 (1%) of GI complaints, including 3 cases of hemorrhage and 1 case of hematemesis; n= 15 (1%) of gout; n=11 (0.8%) of syncope; n=5 (0.3%) myocardial infarction occurred on combination treatment.

B. Summary of more frequent serious ADEs

1. Gout

Gout was reported in N= 15 cases of which one- third had a prior history or elevated baseline levels.

2. Syncope

Syncope occurred in N= 11 patients and in N=13 episodes. All cases were on QUIN/HCTZ therapy. Of interest is that only N= 2 events occurred earlier than the 45th day of Rx. The Sponsor examined all cases of fracture and found that none had been associated with syncope.

3. Myocardial infarction (see under deaths).

C. Deaths

N= 6 (0.4%) of 1457 cases or volunteers died on QUIN/HCTZ. N= 4 were due to myocardial infarction; N=1 each had CVA or cancer.

N= 4 cases died on QUIN monotherapy; n=1 each due to joint neoplasm, respiratory infection, suicide, and sepsis following a stroke and respiratory infection.

All of the deaths on QUIN/HCTZ occurred after more than 150 days of treatment. N= 4 of the 6 deaths were >= 60yrs of age.

Of the N= 4 myocardial infarction deaths, one occurred suddenly after mild exercise without preceding chest pain; another also occurred suddenly.

N=1 cancer death occurred due to a squamous cell lesion.

N=1 case died due to cerebral vascular accident associated with hypertension.

D. Serious events in ongoing studies

As of the date of this submisssion N= 12 studies with an expected enrollment of 2500- 3000 subjects are in progress. Adverse events in N= 12 subjects were reported. It is not known at this time whether the subjects were taking HCTZ in addition to QUIN. The cases include N= 4 instances of myocardial infarction, one fatal, or angina pectoris; N= 1 instance each of peripheral ischemia, hemoptysis, hematuria, leukocytosis, pulmonary edema, cancer, pneumonia, and erythema.

E. Withdrawals "due to ADEs".

The Sponsor provides a plot of the cumulative hazard function for withdrawal due to ADEs. This may be described as follows: The function gives the risk of withdrawal at some time, t, given no withdrawal up to time t. The plot is fairly steep up to about N= 16 months and then flattens indicating a greater risk of withdrawal relatively early in the study(s).

A total of 88 (6.1%) of 1457 volunteers or cases withdrew due to ADEs while on QUIN/HCTZ. Of these N= 18 were considered "serious".

Under "Cardiovascular System" hypotension was listed in N= 3 (0.2%) instances of withdrawal. Under "Digestive system" N= 7 (0.5%) of nausea and/or vomiting occurred and N= 2 instances of abdominal pain plus N=1 case of hematemesis. Dizziness was a cause of withdrawal in N= 5 (0.3%). No withdrawals due to syncope occurred.

Cases withdrawing due to hypotension:

Patient 12 (Study 906-82x, Center 85), age 60 withdrew from Captopril due to dizziness and lightheadedness leading to syncope. After the first dose of QUIN/HCTZ 10/25 the BP fell from 155/103 to 112/84 and the patient was withdrawn.

Patent 8 (Study 906- 241, Center 27), age 59, had orthostatic

dizziness on QUIN/HCTZ 40/25. His sitting BP was 123/80. Treatment was discontinued and "the ADE resolved".

Patient 10 (906-241x, Center 24), age 50, had hypotension on standing after 10 days of QUIN/HCTZ 10/12.5. BP values were not specified but treatment was discontinued and the problem abated.

F. First- dose effect, hypotension, and orthostatic hypotension: These were in two studies (906- 241 and 906- 303). "Hypotension" was defined as a systolic BP <100mm in any position or time. "Orthostatic hypotension" was a fall in SBP of >20mm on standing. "First- dose effect" was either of above within 4hours of first double- blind dose.

1. First- dose effect

In Study 906- 241 N= 1 patient had hypotension after a single dose of 10mgm QUIN. N= 19 cases had first dose orthostatic hypotension. There was no clear association with dose.

In Study 906- 303 no patient had hypotension. N= 16 cases had orthostatic hypotension after the first dose of Rx including N= 7 cases (6%) on low dose QUIN/HCTZ.

2. Hypotension and orthostatic hypotension (based on application of the definitions, above, to all peak and trough data in the DB phases of the two protocols):

For Prot 906- 241 only QUIN/HCTZ 40/25 had a greater incidence of orthostatic hypotension (24%) than did the placebo group (11%). In Prot 906- 303 the incidence of trough orthostatic hypotension on QUIN/HCTZ was greater than on each monotherapy in the "low dose" and greater than HCTZ monotherapy in the "high dose" group (Low dose: 8.9%; QUIN: 6.7%; HCTZ: 5.6%; High dose: 6.6%; QUIN: 5%; HCTZ: 7%).

IV. Clinical Laboratory data

Clinical laboratory data in the Integrated Summary of Safety were based on a) pooled results from the two major controlled trials, PROT 906-241 and 303; b) all controlled and uncontrolled trials; c) trials including a comparative agent, captopril/HCTZ.

A."Possibly clinically important changes" in the two major trials and in all studies.

TABLE 19 (Attached, next page) shows increases for QUIN/HCTZ over each monotherapy in the two major trials for deviations in hemoglobin, hematocrit, eosinophils, chloride, and calcium. Usually, the excess deviation was "small", about 1%. Contrasts are more meaningful with the monotherapies since the sample size is very small for placebo.

TABLE 19. All Clinical Studies: Percentage of Patients (Total N Available For Each Laboratory Parameter) With Possibly Clinically Important Deviations of Laboratory Values

Test	Studies 906-241 and 906-303								All Studies	
	Quin/HCTZ		Quinapril Monotherapy		HCTZ Monotherapy		Placebo		Quin/HCTZ	
	%	N	%	N	%	N	%	N	%	N
Hemoglobin	2	349	1	186	1	197	0	24	6	1043
Hematocrit	4	346	1	183	3	192	0	24	9	760
Platelets	3	338	1	183	3	195	9	23	7	951
WBC	3	348	4	187	2	198	4	24	9	1042
Eosinophils	4	328	2	171	3	180	4	24	10	1010
CPK	0	102	0	96	0	101	ND[a]	ND	0	102
Glucose	8	116	8	110	9	116	ND	ND	16	454
Creatinine	1	351	1	186	1	200	0	24	3	1046
Urea (BUN)	2	183	2	125	2	131	0	7	4	613
Blood Urea	4	146	2	49	9	58	0	15	9	383
Total Protein	1	348	1	186	0	197	4	24	2	760
Albumin	1	309	1	167	0	184	0	22	2	719
Bilirubin	1	338	3	181	2	190	0	23	3	929
Alkaline Phosphatase	0	346	1	184	1	195	0	24	0	1042
LDH	0	310	1	175	0	184	0	23	0	724
SGOT	0	348	0	186	0	194	0	24	0	1041
SGPT	0	334	0	181	0	192	4	23	0	959
Uric Acid	0	346	1	185	1	198	0	24	3	976
Sodium	8	370	7	198	8	208	0	26	9	1063
Potassium	8	370	11	198	13	208	8	26	11	1062
Chloride	7	331	4	168	6	176	8	26	10	920
Carbon Dioxide	15	143	28	50	15	47	7	15	13	578
Calcium	1	334	0	182	0	192	0	21	0	761
Cholesterol	5	114	6	109	5	114	ND	ND	5	332
Triglycerides	ND	ND	ND	ND	ND	ND	ND	ND	56	218

[a] ND = Not done

Table 20, next page, lists the median changes from baseline.

Neither hemoglobin nor hematocrit show a decrease on QUIN/HCTZ using the median. Glucose shows a slight increase on the combination. The findings for eosinophils, chloride, and calcium noted on "possibly clinically significant" analysis are not

confirmed with median changes. BUN and blood urea, though increasing in QUIN/HCTZ, do not exceed the changes seen on monotherapies. Liver function tests and uric acid show median changes that are less than comparative agents and serum potassium falls less than on HCTZ alone.

In TABLE 21 (not attached), the Sponsor shows the number of cases shifting to either high or low (L/H) with respect to the normal range for a specific test. The table lists the shifts as either ADVERSE or NEUTRAL (Adv/Neu).

For hematocrit there were an equal number of adverse shifts (n=5 falls) in QUIN/HCTZ and on each monotherapy. For eosinophils n=8 increases occurred on combination therapy and on HCTZ alone. N=3 decreases in wbc count occurred in the above two treatments.

Fewer increases in glucose (16) occurred on combination treatment than on either monotherapy, QUIN: 17; HCTZ: 18. Fewer increases in creatinine, BUN, blood urea occurred on QUIN/HCTZ than on the monotherapies. For bilirubin, alk phos, LDH, SGOT, and SGPT fewer increases were seen on combination therapy than on one or other monotherapy. Only half as many decreases in serum potassium (4) occurred on combination therapy than on HCTZ alone (9). Urine protein increased in N= 9 QUIN/HCTZ cases versus N=6 each for the monotherapies. In N= 10 instances urinary rbc/HPF increased in the QUIN/HCTZ group versus N= 2 each for the monotherpies (see urine sediment in review of safety for individual studies).

None of the cases with proteinuria >=1+ had an elevated serum creatinine at the last value obtained in the trial. The dose of HCTZ in the QUIN + HCTZ group varied from 6.25- 25mgm (12.5 N=3; 25 N=2; 6.25 N=2).

V. Summary for Safety

In the two, major, controlled trials show that for "all ADEs" there is a positive dose response accross levels of HCTZ only at the highest dose of QUIN, 40mgm (Prot 906- 241). In Prot 906- 303, in which the dose was QUIN/HCTZ 10/12.5 and later 20/25, the percentages for "all ADE" were smaller on the combination than on either monotherapy.

For specific ADEs by treatment in 906- 241 the percentages for "hypotension" were QUIN/HCTZ 0.8% vs 0% in each monotherapy; syncope 0.4% vs 1.1% in HCTZ and
0.0% in QUIN. "Dizziness", which might have been related to low blood pressure, occurred in 5% of the combination cases vs 2.3% in

each single drug therapy. The results in 906- 303 show that the low- dose combination QUIN/HCTZ 10/12.5 and HCTZ alone were associated with no cases of syncope vs 0.8% in QUIN monotherapy. "Dizziness" was also infrequent on the combination, 0.8%. These results are consistant with a smmller numberhypotension- associated "types" of symptoms on the "low" dose of QUIN/HCTZ 10/12.5 or "high" dose 20/25 used in Prot 906- 303.

In Prot 906- 241 abdominal pain occurred in 5/259 (1.9%) of QUIN/HCTZ cases
vs N= 1 case each (1.2 and 1.1%) in N= 86 QUIN and N= 88 HCTZ cases. Peptic ulcer and GI hemmorhage were reported in single instances of combination but not in mono= therapy. In Prot 906- 333 the percentages with abdominal pain were QUIN/HCTZ 0%; QUIN 0%; HCTZ 1.6% for denominators of about N= 120 in each treatment.

Cough occurred on combination therapy in N= 1 case (0.8%) in Prot 906- 303 and N= 6 cases (2.3%) in Prot 906- 241.

Withdrawals "due to ADEs" occurred in N= 14/86 in Prot 906-241 of which N= 6 were on QUIN 40 mgm and HCTZ; N= 1 was on QUIN 40mgm and HCTZ 0mgm; N= 2 were on QUIN 10mgm and HCTZ; N= 4 were on QUIN 2.5mgm and HCTZ. In Prot 906-333 withdrawals due the above cause occurred in N= 3/ 368 of which no cases were on the combination.

In 906- 241 only N=2 cases of "dizziness" occurred in the N= 65 cases over 65yrs of age; both were on the highest dose levels of QUIN/HCTZ 40/25. There were more subjects with ADEs on combination therapy in the older age group. In 906- 303 there was no trend for older subjects to have more ADEs.

Clinical laboratory testing showed that in Prot 906- 241 8/231 or 3.5% of QUIN/HCTZ cases had a fall in hematocrit on treatment using the Sponsor's criteria (fall of 20g/L and 5% points). The Sponsor listed 2 additional cases with low baseline values rather than falls over the treatment period. In Prot 906- 303 only N= 1 QUIN/HCTZ case is listed with a fall in hematocrit. n.b. falls in hematocrit are probably more extensive than implied by the Sponsor's criteria, which restricts attention to the larger changes. A disorder involving hematopoetin has been implicated in some literature references.

In 906-241 most of the combination cases developing low serum potassium were on the highest dose of QUIN, 40mgm. For 25mgm HCTZ serum potassium fell on average for all doses of QUIN up to the highest, 40mgm, suggesting that such a dose of QUIN was unable to

block completely the fall in serum potassium at a dose of HCTZ of 25mgm. For HCTZ 12.5mgm QUIN 10 and 40mgm also failed to block the fall in potassium completely. However, mean falls in potassium were smaller on QUIN and HCTZ than on HCTZ alone for dose of QUIN of 10 and 40mgm and HCTZ of 6.25 and 12.5mgm. In Prot 906- 333 attenuation of the fall in serum potassium on HCTZ (12.5 or 25mgm) was shown by the effects of QUIN 10 or 20 in separate tabulations by the Sponsor.

In study 906- 241 notable increases in BUN or creatinine did not occur and the median change in creatinine was 0.0 for the combination and 0.21 for BUN vs 0 and 0.3 for HCTZ monotherapy. In study 906- 333 the median change for creatinine was 0.0 for the combination and 1.0 for HCTZ. Renal function as measured by these parameters was not adversely affected by the addition of HCTZ to QUIN taking account of the overall group results and excluding possibility of changes within normal zones.

Reviewer's analyses of the urine sediment and proteinuria data in Protocols -241, -241X, and 303:

Since the animal toxicity data suggested interstitial renal changes, the Reviewer decided to examine and analyze the Sponsor's "shift tables" for urine sediment components and urinary protein changes. This was done "apriori" rather than after inspection of all the laboratory data. The primary method used by the Reviewer was to pool the monotherapy shift tables and then to compare them with the combination- drug, shift tables. If the 0.95 confidence limits on the difference between the proportion of changers from LOW to HIGH and HIGH to LOW overlapped and if a test showed no interaction of Rx (pooled, comb) and time (Pre-Rx, end) using SAS CATMOD weighted least squares on marginal proportions, then no difference in pooled vs comb Rx was claimed for the urine test. The latter test was also used to determine poolability of monotherapies. No differences among were shown.

The standard error of the 2 by 2 shift table, LOW to HIGH, and HIGH to LOW, with row 1= A,B and row 2= C,D, was taken as (sq root(B+C))/A+B+C+D for calculation of the confidence limits.
A test of significance of the shift in the pooled and in the combination tables, taken individually, was done using chi sq with df=1. MacNemar's test. These chi square tests and estimates of proportions changing characterize the "within patient" response for the laboratory test using a single table whereas the overlapping confidence limits and the weighted least squares analyses examine the "between patient" aspect on two different tables.
McNemar tests on Sponsor's "shift tables" for renal items:

The Sponsor's tables have three categorical levels for baseline (BL) and final value (FINAL) as on the table at the lower left.

BASE-LINE	FINAL			BASE-LINE	FINAL		
	LOW	NORM	HIGH		L+N	H	
LOW	A	B	C	L+N	A	B	
NORM	D	E	F	H	C	D	
HIGH	G	H	I				

The 3- level table on the left has been collapsed on the right to a 2X2 format for the analytical convenience of a 2X2 table and because there is less clinical significance of distinguishing "LOW" from "NORMAL". Similar tables are constructed for each Rx group.

Using the collapsed table, Let:

P(1) = (B+D)/A+B+C+D : Proportion of "FINAL" cases with "HIGH" values.

P(2) = (C+D)/A+B+C+D : Proportion of "BL (baseline)" cases with HIGH values.

The values, below, of A,B,C,D are taken from the Sponsor's "shift tables".

P(1)- P(2)= excess or deficit in proportion of "HIGH" cases in "FINAL" group. Algebra lead to the equivalent expression B-C/total N, or proportion of changers from LOW to HIGH - HIGH to LOW. A chi square test or confidence limits may be obtained on this difference. Note that this tests the individual table rather than a contrast with another.

Results of contrast of P(1) vs P(2):

PROT 906-241 PROTEINURIA

A,B,C,D:QUIN 59,6,4,4	A,B,C,D:HCTZ 65,6,6,2	A,B,C,D:Q+H 181,18,8,11	Q+H (POOLED)
P(1) 0.13	0.10	.13	
P(2) 0.11	0.10	.09	
SIG: P 0.53	P >.10	.05< P <.10	P>.10

PROT 906-241 HEMATURIA (rbc/HPF)

A,B,C,D:QUIN 42,1,4,4	A,B,C,D:HCTZ 52,1,4,3	A,B,C,D:Q+H 118,12,9,17	Q+H(POOLED)
P(1) 0.10	0.07	0.19	
P(2) 0.16	0.12	0.17	
SIG P 0.18	0.18	0.51	>.50

PROT 906- 241 PYURIA

A,B,C,D:QUIN 32,7,6,6	A,B,C,D:HCTZ 35,6,11,8	A,B,C,D:Q+H 82,29,11,34	Q+H(POOLED)
P(1) 0.26	0.23	0.40	
P(2) 0.24	0.31	0.28	
SIG P 0.78	0.52	0.004 SIG	>.50

PROT 906- 303 PROTEINURIA

A,B,C,D:QUIN 92,7,3,3	A,B,C,D:HCTZ 95,9,5,4	A,B,C,D:Q+H 87,14,6,3	Q+H(pooled)
P(1) 0.10	0.12	0.16	
P(2) 0.06	0.08	0.12	
SIG P 0.21	0.17	0.07+-	>.10

PROT 906- 303 URINE OCCULT BLOOD (rbc/hpf not avail.)

A,B,C,D:QUIN 94,5,2,2	A,B,C,D:HCTZ 99,4,5,5	A,B,C,D:Q+H 95,5,5,4	Q+H(POOLED)
P(1) 0.07	0.08	0.08	
P(2) 0.04	0.09	0.08	
SIG P >.10	>.10	>.10	>.50

PROT 906- 303 PYURIA

A,B,C,D:QUIN 50,19,10,20	A,B,C,D:HCTZ 49,19,19,20	A,B,C,D:Q+H 54,14,13,26	Q+H(pooled
P(1) 0.39	0.36	0.37	
P(2) 0.33	0.36	0.36	
SIG P >.10	>.10	>.10	>.10

Note that the Sponsor's shift table for "pyuria" in Q+ H gave a strongly significant test by the Reviewer in Protocol 906- 241 but not 906- 303.

Also note that for proteinuria the Reviewer's test gave borderline significant p value in -241 and -303.

Further, note that hematuria does not give a significant shift table by the test used in -241. Prot -303 does not provide rbc/hpf, only occult blood, and that gave a non-significant shift table..

Conclusion (Sponsor's shift tables): The analyses of the shift tables of the "within- subject" response show that pyuria was increased in Protocol- 241. Proteinuria and hematuria gave borderline and non-significant tests, respectively.

Comparisons of combination drug versus pooled monotherapies:

I.Hematuria (rbc/hpf for Pr- 241; urine occult blood for Pr-303)

PROTOCOL	Rx	B-C/N	DIFF OF B-C/N	0.95 CL ON DIFF
906-241	QH(POOL)	-.0541		-.1145 TO .0063
			-.0749	
	QH(COMB)	+.0192		-.0418 TO .0798
906- 303	QH(POOL)	.0096		-.0293 TO .0479
			.0093	
	QH(COMB)	.0000		-.0614 TO .0614

PROTOCOL (test)	Rx	B-C/N	DIFF of B-C/N	0.95 CL on diff
906-241 (wbc)	QH(POOL)	-.0360		-.1372 to .0652***
			-.1514	@@@@@
	QH(COMB)	.1154		.1043 to .1265***
906-303 (wbc)	QH(POOL)	-.0437		-.0366 to .1240
			-.0344	
	QH(COMB)	-.0094		-.0905 to .1240
906-241 (protein)	QH(POOL)	.0132		-.0507 to .0771
			-.0327	
	QH(COMB)	.0457		-.0023 to .0941
906-303 (protein)	QH(POOL)	.0413		-.0097 to .0831
			-.0316	
	QH(COMB)	.0729		-.0116 to .1570

***: 0.95 CONF LIMITS DO NOT OVERLAP
@@@@: Test of Rx x TIME sig p=0.0012

n.b. A significant test of Rx x TIME interaction means a difference between pooled and combination Rx with respect to symmetry of the N= 4 cell frequencies of the two "shift tables".

Note the large, negative difference for Q+H(pooled) - (QH combined) of -0.1514 for pyuria in Prot - 241 is consistent with a larger increase in the combination Rx than in the pooled monotherapies. Recall that the shift table for combination treatment alone was also significant. Thus both a "within" and "between" type of analysis were significant for pyuria in one but not both studies. For proteinuria the test of the shift table for combination therapy alone showed previously that the "within" type of analysis was borderline for an increase over baseline in both Prot 241 and -303. The comparison of tables showed neither reached significance on the"between" type of analysis. Hematuria was significant only on

the "between"- type of analysis just above and in the only Protocol with rbc tests.

So far, pyuria ("within and "between" analyses and hematuria ("between"), both in Protocol- 241 appeared to be of greatest interest and an examination for persistance of findings was carried out in - 241 and the long-term continuation, -241X.

Persistance of pyuria was studied by examining individual laboratory record sheets of cases in Protocol - 241 who had data for combined treatment with HCTZ and QUIN in the long- term extension, Protocol -241X. The Reviewer found N= 30 cases in Prot - 241 whose pyuria values at final visit exceed that at baseline. The Sponsor's shift table for pyuria contained N= 29 cases. The Reviewer placed no requirement on whether levels of pyuria exceeded normal limits for the laboratory, though the Sponsor did.

Protocol:- 241
N cases (final value > baseline): 30
N cases (of 16) pyuria (final > bl) Prot 241,241X: 8
N cases (of 16) pyuria (final not > bl) Prot-241X: 5
N cases with pyuria Prot 241; no data in 241x 17

Since N= 17 cases had no follow-up data in Prot -241X, the characteristics of such cases were examined to see if it was likely that their absence might bias the results.

WBC/ HPF	1-5	6-10	11-20	21-50	>50	tot
\N	11	0	2	3	1	17
\N FEMALE	4	0	2	3	1	10

The cases in Prot- 241 with data missing in 241X were usually female for wbc/hpf counts greater than 1-5 cells and might be related to contamination of the urine samples though not necessarily.

\PROT	NEG	TRACE	2+	TOT
\N	13	3	1	17

\RBC	NEG	1-5	>50	TOT
\N	12	4	1	17

Most cases with missing pyuria data in the continuation study were negative for proteinuria and hematuria.

negative for proteinuria and hematuria.

\CHGE CREAT	BETTER	SAME	WORSE
\N	3	9	2

Usually these cases had stable creatinines. In the N= 2 worsening cases the changes were small.

Conclusion for missing PYURIA data: Although cases with missing data Prot -241x were frequent, their urinary sediment, proteinuria, and serum creatinine values in Prot 241 did not suggest that the cases had severe abnormalities that would be likely to bias, by virtue of the absence of these cases, the assessment in the overall data. Protocol 241X represented a much longer exposure to treatment, however.

Characteristics of cases with pyuria "persisting" through Prot 241X:

\WBC/HPF	0	1-5	>1-5
N	0	5	0

\RBC/HPF	0	1-5	>1-5
n	3	2	0

\PROT -	NEG	POS
\N	5	0

The N=5 observed cases with pyuria greater at final value than at baseline in -Prot 241x and in Prot 241 did not have proteinuria. The pyuria was of low-level and so was hematuria in N=2 cases having it in association.

Serial serum creatinine * in Prot -241 and -241x:
1.pyuria+

Prot-241				Prot-241X			
CASE	BL	FINAL	BL	T1	T2	T3	T4
14-5	70	60	10*	10	10	10	10
17-3	74	77	78	78	82	83	82
17-19	85	96	84	84	94	95	94
17-23	65	68	69	69	78	76	75
34-15	90	110	90	90	120	110	110
16-2	87	88	82	86	81	84	86
17-6	79	77	87	82			
18-3	87	89	99	80	85	92	91

* micromol/l

2. Pyuria cleared

	BL	FV	BL			FV	
11-11	60	59	59	60	61	59	-
16-15	77	88	77	80	84	83	81
18-23	100	100	100	87	104		
25- 1	95	103	90	101	104	99	
35-10	100	110	100	110	100	110	110

n.b. First two columns:Prot -241; Last four(five) columns: Prot 241X

Conclusions for urine sediment and proteinuria:
Examination of the table on page 49 will allow the reader to see how many cases shifted adversely versus favorably for pyuria using the Sponsor's findings. For combination therapy N=29 shifted from LOW to HIGH and N=11 shifted favorably giving a significant excess for the within- patient change. Since the confidence limits do not overlap the change for the pooled monotherapies, see page 52, there seems to be an excess of cases in the combination treatment.

When the persistance of pyuria through the continuation protocol 241X is examined using the Reviewer's tally, only N=13 cases had followup data. Of these N=6 had cleared and N= 7 had not. The N=7 cases who persisted with pyuria

all had pyuria of less than 5 cells/HPF; 2 had a similar degree of hematuria; none had proteinuria. Eosinophilia was found in one case out of the N= 30 original pyuric cases in Prot -241. Serum creatinine tended to rise in both the "clearers" and "non-clearers".

It is not clear why the pyuria was notable in only one of the two main trials. The trial not showing pyuria was an entirely overseas one; the other trial had some US centers. The trial without pyuria allowed tests of urine occult blood rather than direct examination for microhematuria but it is far from clear this means less attention was paid to the other elements.

Overall Conclusions for the submission:

I. Efficacy at trough

The factorial experiment, Protocol 906- 241, clearly demonstrated overall efficacy of QUIN/HCTZ by virtue of dose response. The interpretation of results for any specific dose combination is complex due to the pooling of active- dose cell data to allow marginal analysis. This means that the background therapy for contrasts involving either monotherapy agent are the average of the responses to the other agent. That is for the contrast QUIN / HCTZ vs HCTZ the HCTZ responses are those for the average of 6.25, 12.5, and 25mgm. For QUIN /HCTZ responses to QUIN doses 2.5, 10, and 40mgm were averaged.

Taking account of this, the responses to both QUIN 10mgm / average of HCTZ and QUIN 40mgm/ average HCTZ were better than the monotherapies.

The efficacy of doses such as QUIN 20/HCTZ 12.5 and 20/25 is based on interpolation between those used in the trial. As such, the results from the trial are quite strongly supportive of efficacy overall of the combination at trough but require the addition of data from the direct comparions of a more limited set of doses in study -303.

Study - 303 showed that QUIN 10mgm/ HCTZ 12.5 reduced diastolic blood pressure significantly. HCTZ monotherapy 12.5mgm/daily also reduced blood pressure though to a lesser degree.

ii. Efficacy at peak
Trial -241 evaluated blood pressure on treatment at week 4 hourly for 4 readings. At doses of HCTZ 12.5/Quin >2.5 peak responses were substantial and the Trough/peak ratio well- maintained.

III. Safety
Because of the findings in animal toxicology studies of diffuse renal tubular changes, interstitial edema, renal interstitial tissue cell infiltration and hemorrhage , the urinary sediment and proteinuria was examined on an a priori basis. The Sponsor's shift tables in Prot 906- 241 showed a statistically significant excess of pyuria above the laboratories' upper limits of normal between baseline and end-of-study according to the Reviewer's tests. This increase was also significantly greater than that in the pooled monotherapy group. Eosinophilia, a finding in interstitial nephritis, was not characteristic of the original pyuric cases.

Only about half of the cases with pyuria had long-term followup and about 40% of those were clear of pyuria at the end of that trial. The N= 8 cases with persisting pyuria had low- grade sediment findings(1-5 cells/hpf) ; one case had proteinuria (1+); and in N= 4 cases had low- grade hematuria. Eosinophilia was not charcteristic. Increased wbc in the sediment did not occur in the other major trial, Prot 906- 303, a trial that differed from -241 in having no US Centers and in allowing urine occult blood tests to replace microscopic examination for hematuria.
The excess urinary white cell counts in Prot -241 are difficult to explain.

IV Methodological developments: Attention is called to the characterization of the statistical significance "within" and "between" responses of "shift tables" developed by the Reviewer. Attention is also called to the Reviewer's multiple dependent-variable contour plots which enable mean response to be examined for a continuous set of combination- drug doses in regions that are favorable or not.

V. Approvability of doses: 1)Quinapril/HCTZ, though approvable, may not be the best initial therapy for some hypertensives. Some may respond to diuretic alone (Prot-241 36%; Prot -303, 58%) and time spent on diuretic is not wasted since the stage is set for the ACE inhibitor. The Sponsor's doses, 12.5H/QUIN/10 and then, 12.5H/QUIN20 are both reasonable (see APP Bp 64-65) but H25/Q20 is likely to have more side effects than the step to 12.5H/QUIN20 (also see APP B p64-65 for a demonstration using contour plots of a more favorable substitute for the last step- 6.25 to 12.5H/Q25

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Orig:
HFD-110
HFD-110/CSO
HFD-110/PLD
pld/1/6/92

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APPENDIX A

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	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)	8 (3)

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

6.3.1.2. All Adverse Events[29]

All adverse events which started during the double-blind phase of the study are given in Table 49 with the number of first occurrences (number and percent of patients reporting) and number of total reports of each adverse event in each group.

[29] Supportive Documentation: Appendix B.18 - Adverse Events by Body System and Treatment Group

TABLE 49. All Adverse Events by Body System and Treatment Group
(Page 1 of 5)

BODY SYSTEM/ Adverse Event	Placebo (N = 27)		Quinapril Monotherapy (N = 86)		HCTZ Monotherapy (N = 88)		Quinapril + HCTZ (N = 259)	
	Number (%) of Patients	Total Reports	Number (%) of Patients	Total Reports	Number (%) of Patients	Total Reports	Number (%) of Patients	Total Reports
BODY AS A WHOLE	6 (22.2)[a]	8	9 (10.5)[a]	13	19 (21.6)[a]	21	30 (11.6)[a]	41
Asthenia	0 (0.0)	0	1 (1.2)	1	1 (1.1)	1	4 (1.5)	4
Chill	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Fatigue	0 (0.0)	0	2 (2.3)	2	1 (1.1)	1	8 (3.1)	8
Fever	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Chest Pain, Anterior	1 (3.7)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Headache	4 (14.8)	5	4 (4.7)	6	12 (13.6)	12	12 (4.6)	16
Malaise	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	2 (0.8)	2
Back Pain	0 (0.0)	0	1 (1.2)	1	2 (2.3)	2	1 (0.4)	1
Pain	1 (3.7)	1	1 (1.2)	1	1 (1.1)	1	0 (0.0)	0
Chest Pain	1 (3.7)	1	0 (0.0)	0	2 (2.3)	2	1 (0.4)	1
Chest Pain Substernal	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Peripheral Edema	0 (0.0)	0	1 (1.2)	1	1 (1.1)	1	1 (0.4)	1
Viral Infection	0 (0.0)	0	1 (1.2)	1	1 (1.1)	1	5 (1.9)	5
CARDIOVASCULAR SYSTEM	1 (3.7)	1	0 (0.0)	0	1 (1.1)	1	13 (5.0)	13
Hypotension	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	2 (0.8)	2
Angina Pectoris	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.4	1
Transischemic Attack	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Vasodilatation	1 (3.7)	1	0 (0.0)	0	0 (0.0)	0	2 (0.8)	2
Palpitation	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	3 (1.2)	3
Tachycardia	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	2 (0.8)	2
Extrasystoles Ventricular	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Arrhythmia	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Atrial Tachycardia	0 (0.0)	0	0 (0.0)	0	1 (1.1)	1	0 (0.0)	0

[a] Total number of patients reporting adverse events related to the body system is less than the combined number of first occurrences of reports within the body system as one or more patients had more than one adverse event.

APPENDIX B

This appendix contains analyses by the Reviewer consisting of response surfaces for blood pressure, serum potassium, and total adverse reactions, singly and together.

The Reviewer evaluated the Sponsor's data on 1) adjusted mean change from baseline to last visit at or beyond week 4 in supine diastolic blood pressure (Table 18, Vol 18, page 35 of submission); change in serum potassium (Table 53 page 24 this review); and proportion of all ADEs (graph of these is on page 21 this review.

Each of the above mean response variables was fit to a quadratic multiple regression model consisting of dose of HCTZ and of QUIN. To allow superimposition of contour plots of the resulting surfaces, the dose levels of each treatment were coded over the range -1 to +1. Such coding is commonly done and does not alter inferences. The regression coefficients and their significance levels are shown below. As noted by the Sponsor the quadratic terms for BP would be optional, as would be true for K change too, since they did not reach significance though some prominant authorities suggest leaving them in the model. The Reviewer used a linear regression for change in K and BP; a quadratic for ADE.

REGRESSION ANALYSIS

Y	a	b1	b2	b3	b4	b5
BP chge	-10.94	-3.06**	-2.51*			
K chge	-0.03	-0.08**	0.07*			
ADE prop.@@	33.99	3.93**	2.41*	0.62	2.9	3.881**

significance of (betas) coefficients: ** <= .007; * < .05.
Abbreviations: Y= response variable. For BP and K this is a difference from baseline but for ADE it is the arcsin of the absolue value on treatment. For BP it is an adjusted mean difference.
@@: For ADE the regression was carried out using the angular(arcsin) tranformation on the proportion of ADE to improve the distribution.The transformed values differ from the original percentages by less than 4 percentage points and may be taken as roughly similar.

a: Intercept of the regression
b1: regression coefficient on HCTZ dose code.
b2: regression coefficient on QUIN dose code.
b3: coefficient on HCTZ squared
b4: coefficient on QUIN squared
b5: coefficient on HCTZ x QUIN

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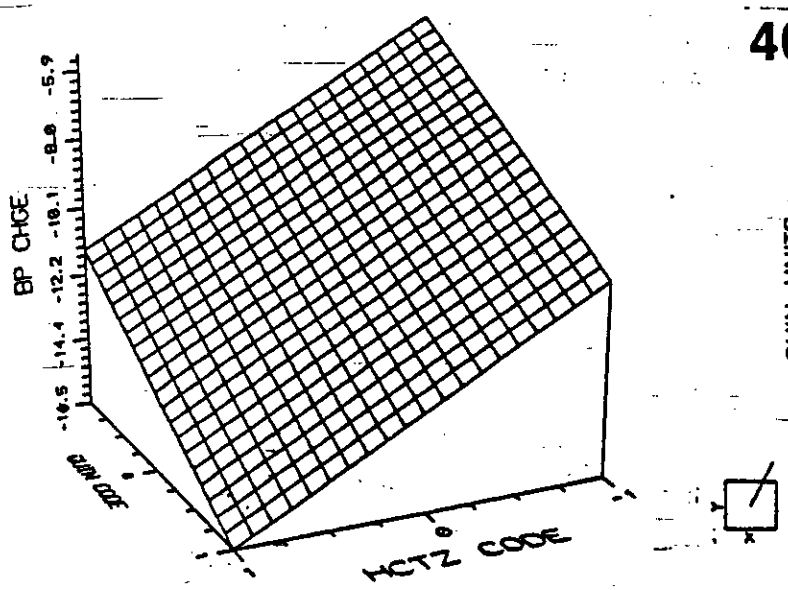
On the two pages following the next are shown the response surfaces and contour plots generated by the regression functions.

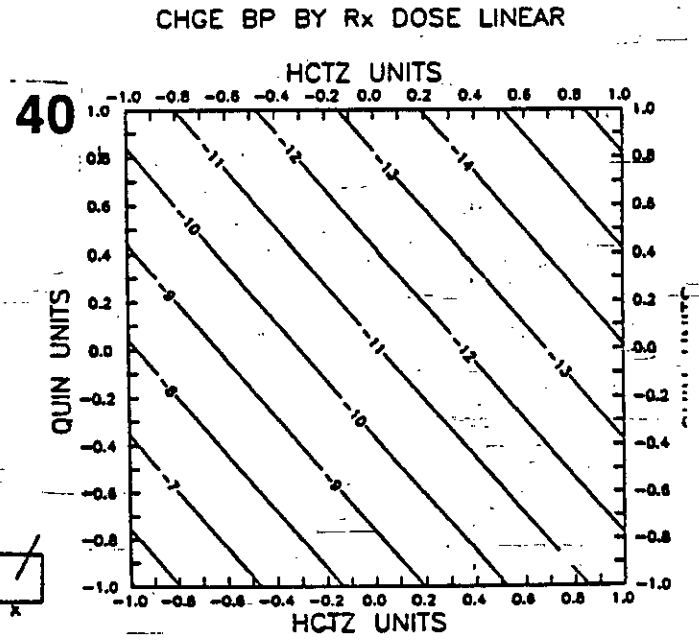
Note that the surface for adjusted mean BP change dips low (has a large fall in BP) for extreme doses of the two drugs (codes +1; equivalent to 40mgm QUIN and 25mgm HCTZ) as one might expect.

For change in serum potassium note that the largest fall (the lowest value on the vertical axis) occurs on the highest dose of HCTZ, as expected, but the fall is less if the QUIN dose is large. Also note that if no HCTZ is given, potassium changes become positive. Again, the surfaces do not conflict with experience.

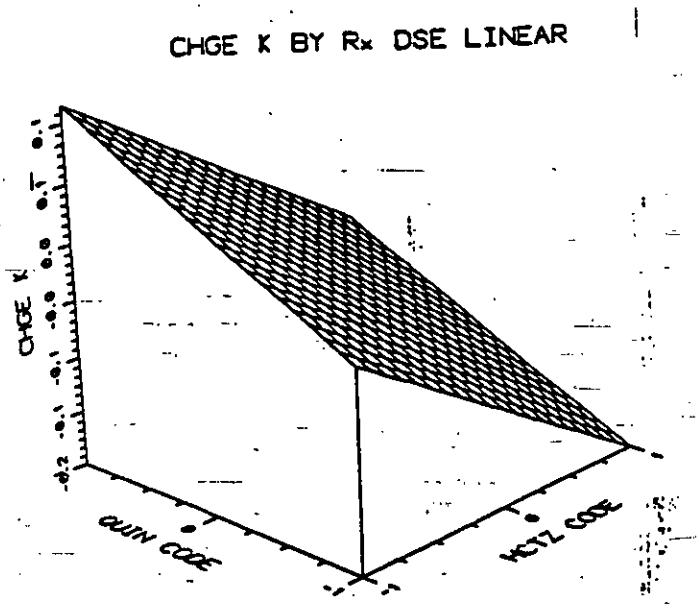
The surface for ADE showed that total ADE were most frequent on the combination of the highest doses of both drugs. At any QUIN dose side effects depended upon the level of HCTZ. n.b. there are slight to moderate differences between the transformed proportions plotted and the true proportions (the highest plotted, transformed proportion is 0.48, actual 0.55; lowest 0.30, actual 0.25).

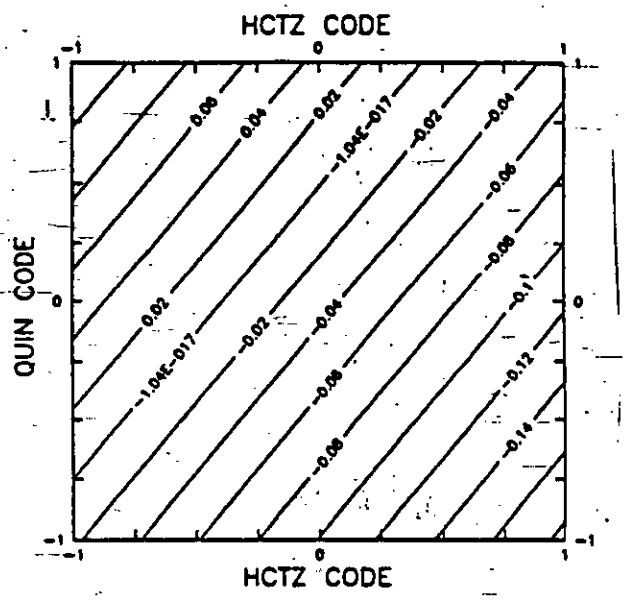
The contour plots show more detail and are provided for each surface. By examining the intersection of lines extended from each dose axis one may find the estimated average response. Or, by selecting a range of responses one may find what dose combinations yield it.

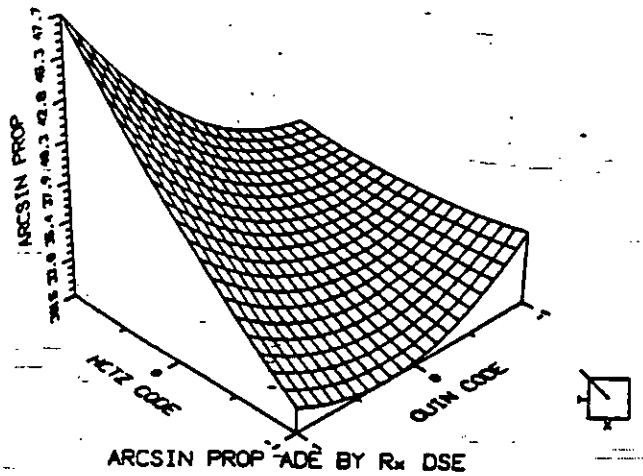


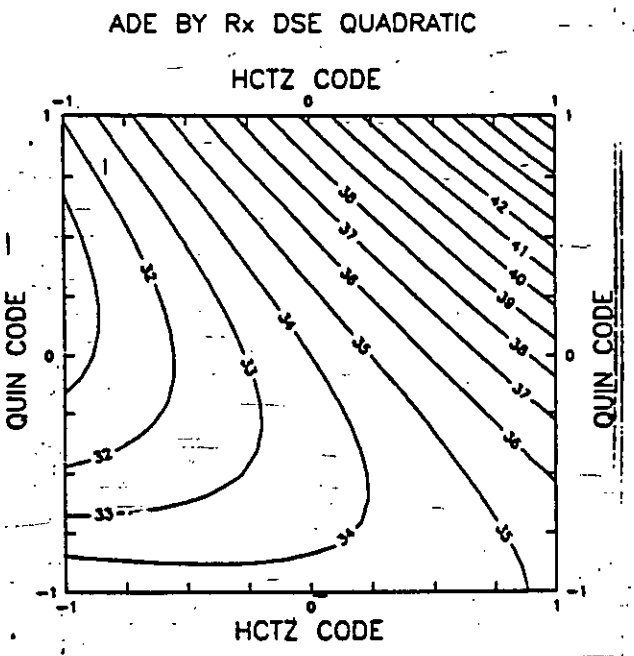


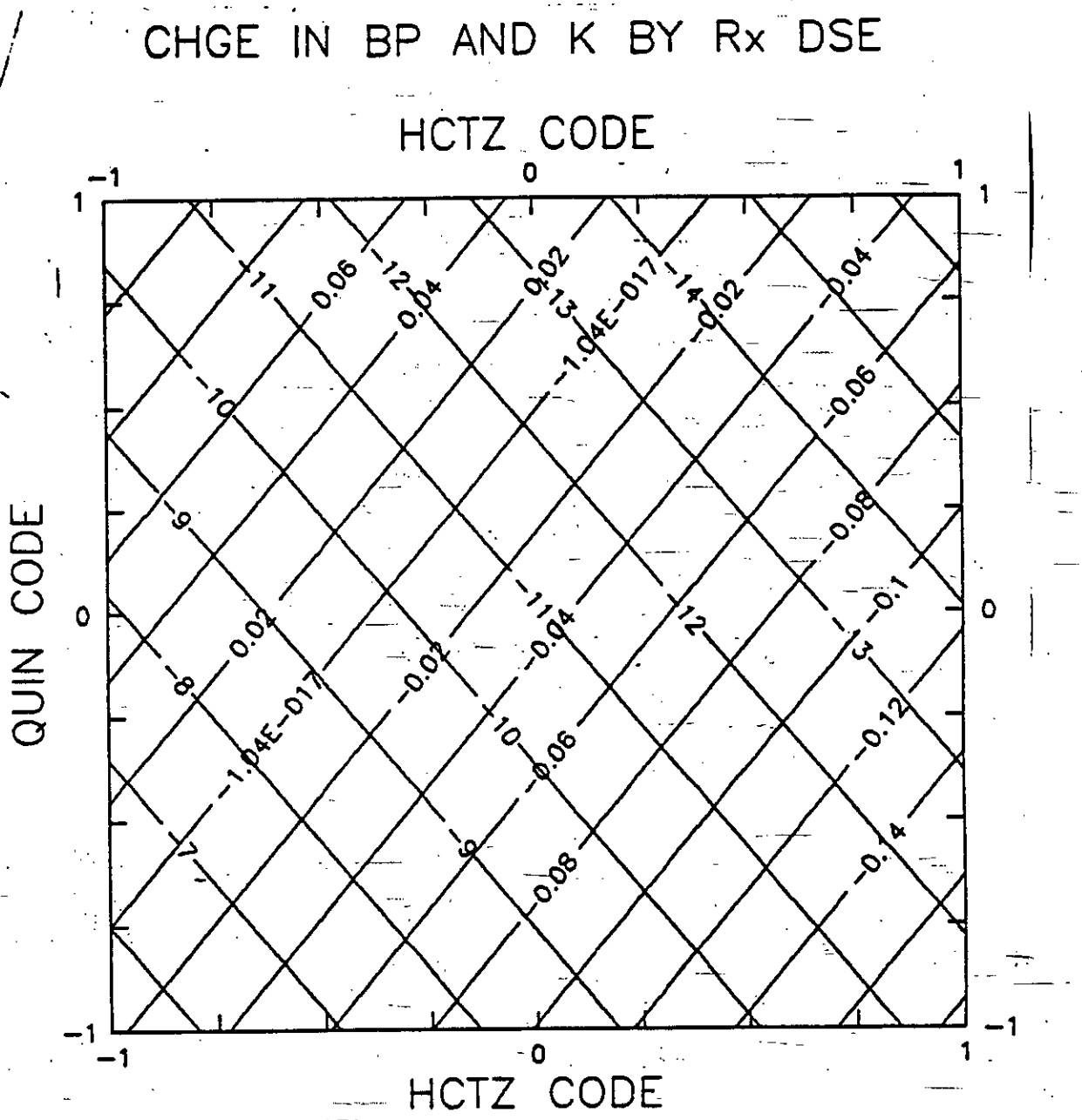
0 mgm 25


CHGE K BY Rx DSE LINEAR
CHGE K
QUIN CODE
HCTZ CODE

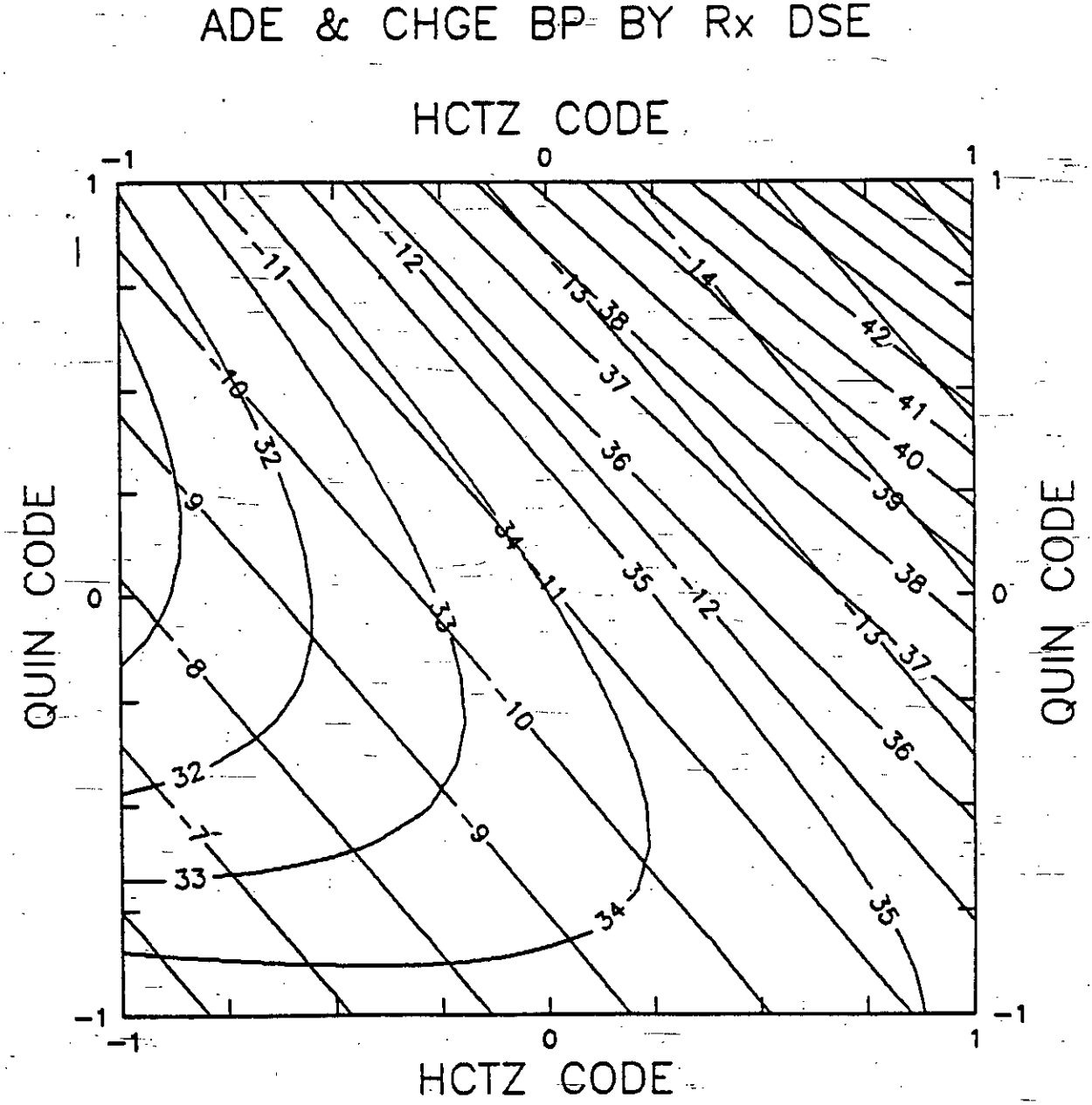

HCTZ CODE
QUIN CODE
HCTZ CODE


ARCSIN PROP
HCTZ CODE
QUIN CODE
ARCSIN PROP ADE BY Rx DSE


ADE BY Rx DSE QUADRATIC
HCTZ CODE
QUIN CODE
QUIN CODE
HCTZ CODE



The heavy contours enclose a zone in which serum K, on average, does not change or increases and at least a 10mmHg fall in diastolic BP occurs. The zone is defined by 17.2mgm on the HCTZ axis and 36mgm on the QUIN axis. A more liberal zone for K decrease is shown by the lower heavy line, -0.08mEq.



This plot shows BP change and the absolute value of total adverse events (ADE) as the arcsin of the proportion of events. Of particular interest is the shallowness of the increase in ADE as dose of QUIN increases if HCTZ dose is below 12.5mgm. Above that dose, increases in QUIN are associated with a steeper increase in ADE manifested as a straightening of the S- shaped ADE contour into a set of straight lines best seen at the upper right corner of the

The following plot has all three contours superimposed, one each for blood pressure change; potassium change; and absolute proportion of total ADE as arcsin (Pr). Referring back to the individual contours may help distinguish them on the crowded plot though the emphasis is on intersections on the treatment axes.

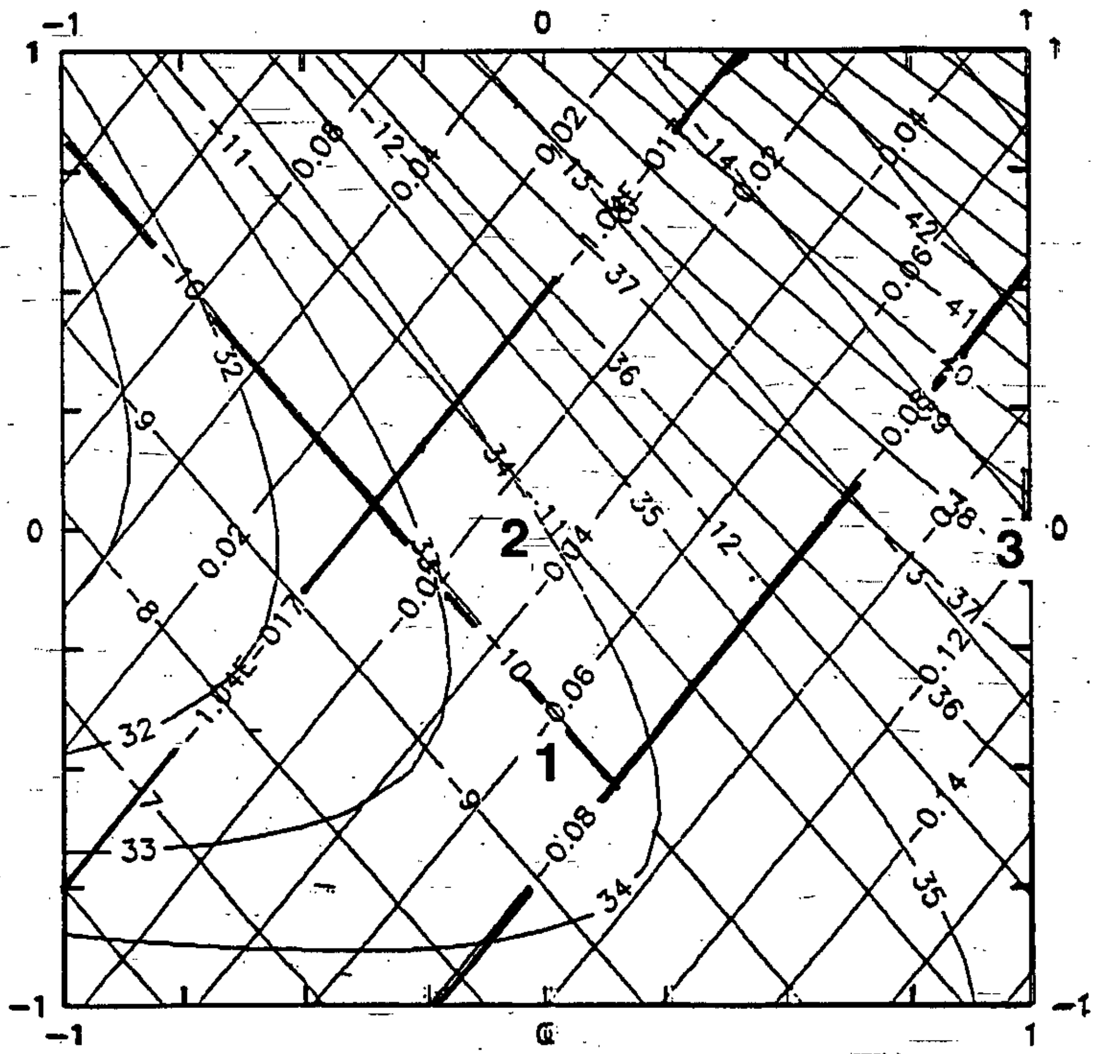
Taking the Sponsor's proposed starting doses of 12.5 HCTZ/QUIN 10, one would expect to find average fall from baseline of a little less than -10mmHg diastolic BP; a fall of -0.07mEq K; and a rate of total ADE of 30%- 31% (based on re-tranforming the 33% - 34% contour to actual values). The three proposed combinations proposed as initial and step-up dosages are shown on the plot by the numbers, 1,2, and 3. The proposed label suggests that if the inital dose fails the next step (#2 on the plot) would be to H12.5/Q20 (#2 on the plot) or to H25/Q20 (#3 on the plot). The increase to H12.5 /Q20 would be, on average, associated with a -11mm fall in BP; a serum K change near 0.03 mEq; and an ADE rate of 31%, very close to that from the proposed initial dose. These dosages seem reasonable given the mean contours on the plot though the second step would be expected to have very similar effects to the initial dose combination.

Note that the maximum BP reduction shown on the the Reviewer's plots based on the Sponsor's mean data, as seen in the contour in the top right (-16 to -17mmHg), is the same as that found in the Sponsor's surface analysis, -16.7mmHg. Also note no upper limit is shown for response of BP.

The alternative for increased dosage proposed by the Sponsor if the initial dose is inadequate is H25/Q20. This combination includes contours representing a further decrease, to -14mmHg of BP; a decrease of -0.12mEq K and an increased estimated percentage of all ADE to 38%. Reducing HCTZ and increasing QUIN to 12.5H/25Q or 6.25H/25Q would ,graphically, reduce side effects and K loss at the expense of some BP reduction. Maintaining HCTZ at 25mgm and increasing QUIN would seem, on average, likely to increase side effects rapidly since the ADE contours are closer together at high HCTZ doses for increasing QUIN. Therefore there are some alternatives, using these plots, to the proposed second- step dosage changes proposed.

Caution: In using these contour plots keep in mind that they were generated from mean responses shown in the Sponsor's tabulations. heir best use would be in understanding patterns in the overall relationship of variables rather than to recommend a specific dosage combination. For example, it seems useful to see the estimated difference in the response to QUIN over increasing doses of HCTZ for all ADE.

ADE & CHANGE IN BP & K BY Rx DOSE



MAR 17 1992

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

NDA: 20- 125

DRUG: Accuretic(R) quinapril/ hydrochlorothiazide tablets

SPONSOR: Parke- Davis

TYPE OF DOCUMENT: NDA original amendment

DATE SUBMITTED: November 25, 1991

DATE REVIEWED: March 13, 1992

REVIEWER: Philip L. Dern M.D.

RESUME:

This document is the "Second Safety Update" for the above drug and is a cumulative summary of adverse events in both completed and ongoing studies from January 4, 1991 to October 10, 1991. This update summarizes data from 1571 patients and 85 normal volunteers.

All events occurring in subjects who were or had been at any time on combination therapy were described as occurring on that therapy provided it had been taken during a double- blind or open-label phase of a study. The one exception was that serious ADE were considered associated with combination therapy only if they occurred while the subject was on it.

Patient exposure in controlled studies: A total of 2281 person- months of exposure occurrred of which roughly three-quarters (77%) or 1749 person- months included true exposure to the combination.

Demographics in controlled studies: Age, sex, and race distributions, not surprisingly, were similar to those of the NDA sample and included 59% males, 7% blacks, and a mean age of 54 yrs.

Total adverse effects by Rx: For QUIN/HCTZ, QUIN, HCTZ, and PLAC, the respective percentages of cases with an ADE were 34%, 33%, 17%, 57%.

Adverse effects considered for package insert listing: Those ADE occurring equal to or more often than 1% of subjects in controlled studies, regardless of their attributability to therapy, are shown in The Sponsor's TABLE 3, which follows. Events occurring in 0.5 to <1% of cases in controlled or uncontrolled trials are also shown. Clinically significant, though less frequent, clinically significant ADEs are also shown.

The pattern of ADEs remained different in the placebo group from the QUIN/HCTZ one by virtue of the large percentage in the former of headache; the infrequency of cough and somnolence. The bottom part of TABLE 3 lists certain events by body system using the frequency criteria given above.

Patient exposure in all controlled and uncontrolled studies: This was 14,170 patient months of which 12,226 was on actual combination therapy.

TABLE 3. Proposed Package Insert - Adverse Reactions Section

Adverse Events Definitely, Probably, or Possibly Related to Therapy or of Unknown Relationship Occurring in ≥1% of Quinapril/HCTZ-Treated Patients in Controlled Clinical Studies
[Percent of Patients]

Adverse Event	NDA[a]		Second Safety Update	
	Quinapril/HCTZ N = 820	Placebo N = 85	Quinapril/HCTZ N = 943	Placebo N = 100
Headache	4.6	18.8	4.3	19.0
Dizziness	4.4	4.7	4.0	4.0
Fatigue	2.7	2.4	2.4	3.0
Coughing	1.8	0.0	1.6	0.0
Nausea and/or Vomiting	1.3	4.7	1.2	4.0
Somnolence	1.2	0.0	1.1	0.0
Myalgia	1.1	2.4	1.1	2.0
Abdominal Pain	1.1	3.5	1.1	3.0

Adverse Events Definitely, Probably, or Possibly Related to Therapy or of Unknown Relationship Occurring in 0.5% to <1% of Quinapril/HCTZ-Treated Patients in Controlled and Uncontrolled Studies (N = 1571) and Less Frequent, Clinically Significant Events in Clinical Trials or Postmarketing Experience[b] with Quinapril or Quinapril/HCTZ

BODY SYSTEM	NDA	Second Safety Update
BODY AS A WHOLE	Asthenia, Malaise	Asthenia, Malaise
CARDIOVASCULAR	Vasodilatation, Palpitation, Tachycardia, *Heart Failure, Hyperkalemia, Myocardial Infarction, Cerebrovascular Accident, Hypertensive Crisis, Angina Pectoris, Orthostatic Hypotension, Cardiac Rhythm Disturbance*	Vasodilatation, Palpitation, Tachycardia, *Heart Failure, Hyperkalemia, Myocardial Infarction, Cerebrovascular Accident, Hypertensive Crisis, Angina Pectoris, Orthostatic Hypotension, Cardiac Rhythm Disturbance*
GASTROINTESTINAL	Constipation, *Gastrointestinal Hemorrhage, Pancreatitis, Abnormal Liver Function Tests*	Mouth or Throat Dry, *Gastrointestinal Hemorrhage, Pancreatitis, Abnormal Liver Function Tests*
NERVOUS/PSYCHIATRIC	Nervousness, Anxiety, Somnolence	Nervousness, Vertigo, Somnolence
RESPIRATORY	Pharyngitis, Sinusitis, Bronchitis, Dyspnea	Pharyngitis, Sinusitis, Bronchitis, Dyspnea
INTEGUMENTARY	Pruritus, Sweating Increased, *Exfoliative Dermatitis, Photosensitivity Reaction*	Pruritus, Sweating Increased, *Exfoliative Dermatitis, Photosensitivity Reaction*
UROGENITAL SYSTEM	*Acute Renal Failure*	*Acute Renal Failure*
OTHER	*Agranulocytosis, Thrombocytopenia*	*Agranulocytosis, Thrombocytopenia*

[a] NDA proposed package insert presented adverse events regardless of attributability.
[b] Rarer events are in italics

Demographics in all studies: This was similar to the distribution found in the controlled studies.

Adverse events occurring in >1% of subjects: Table 5, below and on the next page, provides such figures by body system and adverse effect. Note that the total number of cases in the second safety update is very little different from that in the NDA so one would expect relative magnitudes to be similar and they are.

TABLE 5. Adverse Events Occurring in ≥1% of Quinapril/HCTZ Patients in All Clinical Studies [Number (%) of Patients]
(Page 1 of 2)

BODY SYSTEM/ Adverse Event	NDA		Second Safety Update	
	All N = 1379	Associated N = 1379	All N = 1571	Associated N = 1571
BODY AS A WHOLE	367 (26.6)	87 (6.3)	406 (25.8)	99 (6.3)
Asthenia	32 (2.3)	9 (0.7)	34 (2.2)	9 (0.6)
Fatigue	84 (6.1)	28 (2.0)	89 (5.7)	30 (1.9)
Headache	172 (12.5)	43 (3.1)	195 (12.4)	51 (3.2)
Back Pain	58 (4.2)	1 (0.1)	64 (4.1)	2 (0.1)
Pain	17 (1.2)	0 (0.0)	17 (1.1)	0 (0.0)
Chest Pain	42 (3.0)	5 (0.4)	46 (2.9)	6 (0.4)
Peripheral Edema	27 (2.0)	4 (0.3)	30 (1.9)	5 (0.3)
Viral Infection	60 (4.4)	1 (0.1)	67 (4.3)	1 (0.1)
CARDIOVASCULAR SYSTEM	89 (6.5)	30 (2.2)	98 (6.2)	34 (2.2)
Hypotension	16 (1.2)	11 (0.8)	19 (1.2)	13 (0.8)
Vasodilatation	18 (1.3)	7 (0.5)	19 (1.2)	7 (0.4)
DIGESTIVE SYSTEM	216 (15.7)	44 (3.2)	231 (14.7)	48 (3.1)
Dental Abnormalities	18 (1.3)	0 (0.0)	19 (1.2)	0 (0.0)
Mouth or Throat Dry	22 (1.6)	11 (0.8)	23 (1.5)	11 (0.7)
Dyspepsia	34 (2.5)	6 (0.4)	35 (2.2)	7 (0.4)
Nausea and/or Vomiting	69 (5.0)	16 (1.2)	73 (4.6)	17 (1.1)
Diarrhea	47 (3.4)	4 (0.3)	52 (3.3)	5 (0.3)
Abdominal Pain	42 (3.0)	9 (0.7)	45 (2.9)	10 (0.6)
MUSCULOSKELETAL SYSTEM	191 (13.9)	10 (0.7)	203 (12.9)	12 (0.8)
Arthralgia	27 (2.0)	1 (0.1)	28 (1.8)	1 (0.1)
Gout	18 (1.3)	2 (0.1)	18 (1.1)	2 (0.1)
Myalgia	112 (8.1)	8 (0.6)	119 (7.6)	9 (0.6)
NERVOUS SYSTEM	246 (17.8)	120 (7.4)	266 (16.9)	111 (7.1)
Dizziness	135 (9.8)	68 (4.9)	149 (9.5)	75 (4.8)
Insomnia	33 (2.4)	5 (0.4)	35 (2.2)	5 (0.3)
Somnolence	21 (1.5)	7 (0.5)	24 (1.5)	8 (0.5)
Vertigo	17 (1.2)	11 (0.8)	17 (1.1)	11 (0.7)
Paresthesia	38 (2.8)	10 (0.7)	39 (2.5)	10 (0.6)
PSYCHOBIOLOGIC FUNCTION	56 (4.1)	5 (0.4)	66 (4.2)	5 (0.3)
Anxiety	19 (1.4)	1 (0.1)	26 (1.7)	1 (0.1)
Depression	13 (0.9)	0 (0.0)	15 (1.0)	0 (0.0)
Nervousness	19 (1.4)	1 (0.1)	19 (1.2)	1 (0.1)

TABLE 5. Adverse Events Occurring in ≥1% of Quinapril/HCTZ Patients in All Clinical Studies [Number (%) of Patients]
(Page 2 of 2)

BODY SYSTEM/ Adverse Event	NDA		Second Safety Update	
	All N = 1379	Associated N = 1379	All N = 1571	Associated N = 1571
RESPIRATORY SYSTEM	335 (24.3)	69 (5.0)	372 (23.7)	73 (4.6)
Pharyngitis	48 (3.5)	1 (0.1)	51 (3.2)	1 (0.1)
Rhinitis	115 (8.3)	11 (0.8)	124 (7.9)	12 (0.8)
Sinusitis	67 (4.9)	3 (0.2)	77 (4.9)	3 (0.2)
Bronchitis	42 (3.0)	5 (0.4)	44 (2.8)	5 (0.3)
Coughing	129 (9.4)	57 (4.1)	143 (9.1)	59 (3.8)
Upper Respiratory Infection	69 (5.0)	0 (0.0)	86 (5.5)	0 (0.0)
Dyspnea	22 (1.6)	3 (0.2)	23 (1.5)	3 (0.2)
SKIN AND APPENDAGES	118 (8.6)	27 (2.0)	129 (8.2)	28 (1.8)
Pruritus	14 (1.0)	4 (0.3)	15 (1.0)	4 (0.3)
Rash	31 (2.2)	6 (0.4)	33 (2.1)	7 (0.4)
Sweating Increased	15 (1.1)	6 (0.4)	17 (1.1)	6 (0.4)
UROGENITAL SYSTEM	116 (8.4)	17 (1.2)	128 (8.1)	17 (1.1)
Urinary Tract Infection	26 (1.9)	0 (0.0)	30 (1.9)	0 (0.0)
Impotence	32 (2.3)	10 (0.7)	32 (2.0)	10 (0.6)

Adverse events by age:

The following two pages (Table A7) show ADEs occurring in greater than 1% of subjects according to age <65 and 65+ years. The distributions are not very different by age or by age and NDA vs Second Safety Review. In particular, one notes that hypotension (all) was only slightly increased in the older subjects (1.8%) vs younger ones (1%) in the NDA group and quite similar figures occurred in the update cases (1.1 and 1.7%, respectively). "Dizziness", which could be light-headedness rather than true vertigo, was more frequent (10.6%) in the younger subjects than in the older (5.5%) for the NDA group. Figures nearly identical to those just given were reported for the "all" group of the Second Safety Review (10.3 and 5.1%, respectively). Chest pain and peripheral edema were also more frequent in the younger patients in both the NDA and safety review groups.

Serious adverse effects:

One additional death occurred subsequent to the NDA, a patient with malignant bone tumor and metastases.

The Sponsor's definition of serious adverse events included any event that was immediately life-threatening, permanently- disabling, caused prolonged hospitalization, was due to overdose, anomaly, or malignancy. In addition, certain other events of particular medical interest were identified: syncope, gout,pneumonia,hematuria,cataracts, face and tongue edema, diabetes, and TIAs. The definition and additional medical items seem quite reasonable.

APPENDIX A.7
(PAGE 1 OF 2)

SUMMARY OF ALL AND ASSOCIATED ADVERSE EVENTS IN >1% OF QUINAPRIL/HCTZ PATIENTS <65 AND 65+ YEARS OF AGE IN CONTROLLED AND UNCONTROLLED STUDIES

	NDA								SECOND SAFETY UPDATE							
	ALL				ASSOCIATED				ALL				ASSOCIATED			
	<65 YR (N=1162)		65+ YR (N=217)		<65 YR (N=1162)		65+ YR (N=217)		<65 YR (N=1335)		65+ YR (N=236)		<65 YR (N=1335)		65+ YR (N=236)	
BODY SYSTEM ADVERSE EVENT	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
BODY AS A WHOLE	331	28.5	36	16.6	81	7.0	6	2.8	366	27.4	40	16.9	92	6.9	7	3.0
ASTHENIA	29	2.5	3	1.4	8	0.7	1	0.5	31	2.3	3	1.3	8	0.6	1	0.4
FATIGUE	78	6.7	6	2.8	26	2.2	2	0.9	83	6.2	6	2.5	28	2.1	2	0.8
HEADACHE	161	13.9	11	5.1	39	3.4	4	1.8	181	13.6	14	5.9	46	3.4	5	2.1
BACK PAIN	46	4.0	12	5.5	1	0.1	0	0.0	52	3.9	12	5.1	2	0.1	0	0.0
PAIN	16	1.4	1	0.5	0	0.0	0	0.0	16	1.2	1	0.4	0	0.0	0	0.0
CHEST PAIN	37	3.2	5	2.3	5	0.4	0	0.0	41	3.1	5	2.1	6	0.4	0	0.0
EDEMA - GENERALIZED	12	1.0	0	0.0	3	0.3	0	0.0	14	1.0	0	0.0	5	0.4	0	0.0
PERIPHERAL EDEMA	26	2.2	1	0.5	4	0.3	0	0.0	28	2.1	2	0.8	5	0.4	0	0.0
VIRAL INFECTION	54	4.6	6	2.8	1	0.1	0	0.0	61	4.6	6	2.5	1	0.1	0	0.0
CARDIOVASCULAR SYSTEM	74	6.4	15	6.9	27	2.3	3	1.4	81	6.1	17	7.2	30	2.2	4	1.7
HYPOTENSION	12	1.0	4	1.8	11	0.9	0	0.0	15	1.1	4	1.7	13	1.0	0	0.0
VASODILATATION	17	1.5	1	0.5	6	0.5	1	0.5	18	1.3	1	0.4	6	0.4	1	0.4
DIGESTIVE SYSTEM	182	15.7	34	15.7	34	2.9	10	4.6	194	14.5	37	15.7	37	2.8	11	4.7
DENTAL ABNORMALITIES	17	1.5	1	0.5	0	0.0	0	0.0	18	1.3	1	0.4	0	0.0	0	0.0
MOUTH OR THROAT DRY	19	1.6	3	1.4	9	0.8	2	0.9	20	1.5	3	1.3	9	0.7	2	0.8
DYSPEPSIA	29	2.5	5	2.3	6	0.5	0	0.0	30	2.2	5	2.1	7	0.5	0	0.0
NAUSEA &/OR VOMITING	62	5.3	7	3.2	13	1.1	3	1.4	66	4.9	7	3.0	14	1.0	3	1.3
DIARRHEA	43	3.7	4	1.8	4	0.3	0	0.0	47	3.5	5	2.1	5	0.4	0	0.0
FLATULENCE	12	1.0	0	0.0	1	0.1	0	0.0	13	1.0	0	0.0	1	0.1	0	0.0
ABDOMINAL PAIN	35	3.0	7	3.2	7	0.6	2	0.9	37	2.8	8	3.4	7	0.5	3	1.3
MUSCULOSKELETAL SYSTEM	170	14.6	21	9.7	8	0.7	2	0.9	180	13.5	23	9.7	9	0.7	3	1.3
ARTHRALGIA	24	2.1	3	1.4	1	0.1	0	0.0	25	1.9	3	1.3	1	0.1	0	0.0
GOUT	15	1.3	3	1.4	1	0.1	1	0.5	15	1.1	3	1.3	1	0.1	1	0.4
MYALGIA	103	8.9	9	4.1	7	0.6	1	0.5	109	8.2	10	4.2	7	0.5	2	0.8
NERVOUS SYSTEM	211	18.2	35	16.1	90	7.7	12	5.5	230	17.2	36	15.3	98	7.3	13	5.5
DIZZINESS	123	10.6	12	5.5	63	5.4	5	2.3	137	10.3	12	5.1	70	5.2	5	2.1
INSOMNIA	29	2.5	4	1.8	5	0.4	0	0.0	31	2.3	4	1.7	5	0.4	0	0.0
SOMNOLENCE	17	1.5	4	1.8	5	0.4	2	0.9	20	1.5	4	1.7	6	0.4	2	0.8
VERTIGO	15	1.3	2	0.9	9	0.8	2	0.9	15	1.1	2	0.8	9	0.7	2	0.8
PARESTHESIA	33	2.8	5	2.3	10	0.9	0	0.0	34	2.5	5	2.1	10	0.7	0	0.0
PSYCHOBIOLOGIC FUNCTION	51	4.4	5	2.3	4	0.3	1	0.5	60	4.5	6	2.5	4	0.3	1	0.4
ANXIETY	19	1.6	0	0.0	1	0.1	0	0.0	25	1.9	1	0.4	1	0.1	0	0.0
DEPRESSION	12	1.0	1	0.5	0	0.0	0	0.0	14	1.0	1	0.4	0	0.0	0	0.0

APPENDIX A.7
(PAGE 2 OF 2)

SUMMARY OF ALL AND ASSOCIATED ADVERSE EVENTS IN >1% OF QUINAPRIL/HCTZ PATIENTS <65 AND 65+ YEARS OF AGE
IN CONTROLLED AND UNCONTROLLED STUDIES

BODY SYSTEM ADVERSE EVENT	NDA ALL <65 YR (N=1162) N	%	NDA ALL 65+ YR (N=217) N	%	NDA ASSOCIATED <65 YR (N=1162) N	%	NDA ASSOCIATED 65+ YR (N=217) N	%	SECOND SAFETY UPDATE ALL <65 YR (N=1335) N	%	SECOND SAFETY UPDATE ALL 65+ YR (N=236) N	%	SECOND SAFETY UPDATE ASSOCIATED <65 YR (N=1335) N	%	SECOND SAFETY UPDATE ASSOCIATED 65+ YR (N=236) N	%
PSYCHOBIOLOGIC FUNCTION																
NERVOUSNESS	15	1.3	4	1.8	1	0.1	0	0.0	15	1.1	4	1.7	1	0.1	0	0.0
RESPIRATORY SYSTEM	295	25.4	40	18.4	57	4.9	12	5.5	329	24.6	43	18.2	60	4.5	13	5.5
PHARYNGITIS	43	3.7	5	2.3	1	0.1	0	0.0	46	3.4	5	2.1	1	0.1	0	0.0
RHINITIS	99	8.5	16	7.4	7	0.6	4	1.8	108	8.1	16	6.8	8	0.6	4	1.7
SINUSITIS	62	5.3	5	2.3	3	0.3	0	0.0	72	5.4	5	2.1	3	0.2	0	0.0
BRONCHITIS	36	3.1	6	2.8	4	0.3	1	0.5	38	2.8	6	2.5	4	0.3	1	0.4
COUGHING	113	9.7	16	7.4	49	4.2	8	3.7	125	9.4	18	7.6	50	3.7	9	3.8
UPPER RESPIRATORY INFECT	64	5.5	5	2.3	0	0.0	0	0.0	79	5.9	7	3.0	0	0.0	0	0.0
DYSPNEA	19	1.6	3	1.4	3	0.3	0	0.0	19	1.4	4	1.7	3	0.2	0	0.0
SKIN AND APPENDAGES	102	8.8	16	7.4	24	2.1	3	1.4	112	8.4	17	7.2	25	1.9	3	1.3
RASH	25	2.2	6	2.8	5	0.4	1	0.5	27	2.0	6	2.5	6	0.4	1	0.4
SWEATING, INCREASED	14	1.2	1	0.5	6	0.5	0	0.0	16	1.2	1	0.4	6	0.4	0	0.0
UROGENITAL SYSTEM	100	8.6	16	7.4	15	1.3	2	0.9	110	8.2	18	7.6	15	1.1	2	0.8
URINARY TRACT INFECT	22	1.9	4	1.8	0	0.0	0	0.0	25	1.9	5	2.1	0	0.0	0	0.0
IMPOTENCE	28	2.4	4	1.8	10	0.9	0	0.0	28	2.1	4	1.7	10	0.7	0	0.0

The following table (6), due to the Sponsor, shows that 5.6% of cases from all studies had serious ADEs although those cited as "associated" were 1.7%.

TABLE 6. Overview of Serious Adverse Events in Controlled Clinical Studies and All Studies

	Controlled				All Studies
	Quinapril/ HCTZ	Quinapril	HCTZ	Placebo	Quinapril /HCTZ
Patients Studied	943	804	365	100	1656
Patients With Serious Adverse Event(s) (%)	19 (2.0)	16 (2.0)	4 (1.1)	0 (0.0)	93 (5.6)
Patients With Associated Serious Adverse Event(s) (%)	4 (0.4)	8 (1.0)	1 (0.3)	0 (0.0)	28 (1.7)

The next four pages (Table 7) list serious ADEs from controlled studies and all clinical studies for both the NDA and safety review groups.

Taking the major headings, "BODY SYSTEM" (under which the type of ADE is listed, one sees that for "all studies" musculoskeletal problems have the highest rate, 1.4%. In the NDA goup and in the update one, 1.3%. The largest ADE under this heading is "gout", which occurred in about 1% of all combination Rx cases.

The second most frequent body system ADEs for "all studies" were those in the "Nervous system" category (1.0- 1.1%). The most frequent event was syncope (11 cases or 0.8% for the NDA group and 12 cases or 0.7% for the updated group. Syncope occurred in 0.2% of Q/H cases; 0.6% of Q cases, and 0% of placebo cases in the controlled trial update group.

The next most frequent events were under the heading "digestive system" which listed 1% ADEs among "all studies". The following GI events occurred in 0.2% of all studies: GI hemorrhage (n=3 cases of which N=1 occurred in the QUIN/HCTZ group of the controlled trials), appendectomy, and cholecystitis.

Cardiovascular system items were the 4th most frequent body system ADEs for "all studies" in the

NDA group. Myocardial infarction occurred in n=5 cases or 0.3% of Q/H cases in "all studies" for both the NDA and the update group. None occurred in controlled studies. No cases of heart failure were recorded.

T7 1

TABLE 7. Serious Adverse Events Reported in Controlled Studies and All Clinical and Clinical Pharmacology Studies

[Number (%) of Patients]
(Page 1 of 4)

BODY SYSTEM[a]/ Adverse Event	NDA					Second Safety Update				
	Controlled				All Studies	Controlled				All Studies
	Q/H N = 820	Quin N = 698	HCTZ N = 256	Placebo N = 85	Q/H N = 1452	Q/H N = 943	Quin N = 804	HCTZ N = 365	Placebo N = 100	Q/H N = 1656
BODY AS A WHOLE	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	10 (0.7)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	11 (0.7)
Face Edema	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Chest Pain	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	2 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Carcinoma, Suspected	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Neoplasm, General	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Surgery	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Cancer	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
CARDIOVASCULAR SYSTEM	2(0.2)	5(0.7)	0(0.0)	0 (0.0)	11 (0.8)	2 (0.2)	6 (0.7)	1 (0.3)	0 (0.0)	11 (0.7)
Heart Failure	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Myocardial Infarct	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	5 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.3)
Cardiovascular Disorder	0(0.0)	2(0.3)	0(0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular Accident	0(0.0)	2(0.3)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Transischemic Attack	1(0.1)	1(0.1)	0(0.0)	0 (0.0)	2 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)
Thrombophlebitis	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hemorrhage	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Heart Arrest	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
DIGESTIVE SYSTEM	2(0.2)	1(0.1)	0(0.0)	0 (0.0)	15 (1.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	15 0.9
Tongue Edema	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
GI Hemorrhage	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	3 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Hematemesis	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Ileus	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

[a] Total number of adverse events reported for a body system may be less than the combined number of reports within the body system as one or more patients may have had more than one adverse event.

TABLE 7. Serious Adverse Events Reported in Controlled Studies and All Clinical and Clinical Pharmacology Studies

[Number (%) of Patients]
(Page 2 of 4)

BODY SYSTEM[a]/ Adverse Event	NDA					Second Safety Update				
	Controlled				All Studies	Controlled				All Studies
	Q/H N = 820	Quin N = 698	HCTZ N = 256	Placebo N = 85	Q/H N = 1452	Q/H N = 943	Quin N = 804	HCTZ N = 365	Placebo N = 100	Q/H N = 1656
DIGESTIVE SYSTEM (cont)										
Cancer Colon	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Perforated Bowel	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Appendectomy	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Appendicitis	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Colon Neoplasm	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pancreatitis	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cholecystitis	0(0.0)	1(0.1)	0(0.0)	0 (0.0)	2 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)
Cholecystectomy	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
ENDOCRINE SYSTEM	0(0.0)	1(0.1)	0(0.0)	0 (0.0)	3 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	4 (0.2)
Diabetes	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)
Adrenal Tumor	0(0.0)	1(0.1)	0(0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
HEMIC AND LYMPHATIC SYSTEM	0(0.0)	2(0.3)	0(0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	0(0.0)	1(0.1)	0(0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pancytopenia	0(0.0)	1(0.1)	0(0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
MUSCULOSKELETAL SYSTEM	4(0.5)	0(0.0)	0(0.0)	0 (0.0)	21 (1.4)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	21 1.3
Fracture	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	2 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Hip Replacement Surgery	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gout	2(0.2)	0(0.0)	0(0.0)	0 (0.0)	15 (1.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	15 (0.9)
Joint Disorder	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Joint/Tendon Surgery	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

[a] Total number of adverse events reported for a body system may be less than the combined number of reports within the body system as one or more patients may have had more than one adverse event.

TABLE 7. Serious Adverse Events Reported in Controlled Studies and All Clinical and Clinical Pharmacology Studies

[Number (%) of Patients]
(Page 3 of 4)

BODY SYSTEM[a] / Adverse Event	NDA					Second Safety Update				
	Controlled				All Studies	Controlled				All Studies
	Q/H N = 820	Quin N = 698	HCTZ N = 256	Placebo N = 85	Q/H N = 1452	Q/H N = 943	Quin N = 804	HCTZ N = 365	Placebo N = 100	Q/H N = 1656
MUSCULOSKELETAL SYSTEM (cont)										
Myositis	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Tetany	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
NERVOUS SYSTEM	4(0.5)	6(0.9)	1(0.4)	0 (0.0)	16 (1.1)	4 (0.4)	6 (0.7)	2 (0.5)	0 (0.0)	17 (1.0)
Convulsions	0(0.0)	1(0.1)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Syncope	2(0.2)	5(0.7)	1(0.4)	0 (0.0)	11 (0.8)	2 (0.2)	5 (0.6)	2 (0.5)	0 (0.0)	12 (0.7)
Hemiplegia	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Facial Paralysis	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Bell's Palsy	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Polyneuritis	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
RESPIRATORY SYSTEM	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	4 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)
Hemoptysis	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pneumonia	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Cancer, Lung	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
SKIN AND APPENDAGES	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Basal Cell Carcinoma	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Squamous Cell Carcinoma	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

[a] Total number of adverse events reported for a body system may be less than the combined number of reports within the body system as one or more patients may have had more than one adverse event.

TABLE 7. Serious Adverse Events Reported in Controlled Studies and All Clinical and Clinical Pharmacology Studies

[Number (%) of Patients]
(Page 3 of 4)

BODY SYSTEM[a]/ Adverse Event	NDA					Second Safety Update				
	Controlled				All Studies	Controlled				All Studies
	Q/H N = 820	Quin N = 698	HCTZ N = 256	Placebo N = 85	Q/H N = 1452	Q/H N = 943	Quin N = 804	HCTZ N = 365	Placebo N = 100	Q/H N = 1656
MUSCULOSKELETAL SYSTEM (cont)										
Myositis	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Tetany	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
NERVOUS SYSTEM	4(0.5)	6(0.9)	1(0.4)	0 (0.0)	16 (1.1)	4 (0.4)	6 (0.7)	2 (0.5)	0 (0.0)	17 (1.0)
Convulsions	0(0.0)	1(0.1)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Syncope	2(0.2)	5(0.7)	1(0.4)	0 (0.0)	11 (0.8)	2 (0.2)	5 (0.6)	2 (0.5)	0 (0.0)	12 (0.7)
Hemiplegia	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Facial Paralysis	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Bell's Palsy	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Polyneuritis	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
RESPIRATORY SYSTEM	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	4 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)
Hemoptysis	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pneumonia	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Cancer, Lung	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
SKIN AND APPENDAGES	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Basal Cell Carcinoma	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Squamous Cell Carcinoma	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

[a] Total number of adverse events reported for a body system may be less than the combined number of reports within the body system as one or more patients may have had more than one adverse event.

TABLE 7. Serious Adverse Events Reported in Controlled Studies and All Clinical and Clinical Pharmacology Studies

[Number (%) of Patients]
(Page 4 of 4)

BODY SYSTEM[a]/ Adverse Event	NDA					Second Safety Update				
	Controlled				All Studies	Controlled				All Studies
	Q/H N = 820	Quin N = 698	HCTZ N = 256	Placebo N = 85	Q/H N = 1452	Q/H N = 943	Quin N = 804	HCTZ N = 365	Placebo N = 100	Q/H N = 1656
UROGENITAL SYSTEM	1(0.1)	0(0.0)	1(0.4)	0 (0.0)	8 (0.6)	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	9 (0.5)
Hematuria	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	5 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.3)
Renal Stone	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Dysuria	0(0.0)	0(0.0)	1(0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Bladder Tumor	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Breast Cancer	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Prostatectomy	0(0.0)	0(0.0)	1(0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
SPECIAL SENSES	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	7 (0.5)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.4)
Cataract	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Glaucoma	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	3 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Detached Retina	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Eye Surgery	0(0.0)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
LABORATORY DEVIATIONS	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hematuria	1(0.1)	0(0.0)	0(0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

[a] Total number of adverse events reported for a body system may be less than the combined number of reports within the body system as one or more patients may have had more than one adverse event.

Case histories of serious ADE: The following descriptions, due to the Sponsor, are N=4 new, "serious ADE" that occurred since the NDA:

The following are descriptions of the four new serious adverse events that occurred since the NDA:

Diabetes Mellitus[a] Patient 10 (Study 906-333X, Center 3), a 36-year-old man with hypertension and obesity, was treated with quinapril/HCTZ (40/25) daily for 77 days when he was diagnosed as diabetic. Glyburide was prescribed and the patient continued in the study. The investigator stated that this event was definitely not related to quinapril/HCTZ therapy.

Bladder Tumor[a] Patient 2 (Study 906-333X, Center 3), a 57-year-old man with hypertension was treated with quinapril/HCTZ (40/25) daily for 97 days. On Week 29 of the study the patient was diagnosed as having recurrent bladder tumors. The patient had a history of transitional cell bladder cancer and had undergone a transurethral prostatic resection on Day 13 of the double-blind phase while receiving placebo.

Syncope: Patient 9 (906-82X, Center 96), a 47-year-old woman with hypertension, had been treated with quinapril/HCTZ (40/25) when she experienced syncope (blacking out) on Day 602. The investigator indicated that the syncope might have been the result of orthostatic hypotension caused by volume depletion (the patient had been working in her garden during the heat of the day). The quinapril dose was decreased and HCTZ was discontinued. The investigator indicated that this event was related to quinapril/HCTZ therapy.

Death, Bone Neoplasm: See Section 4.1., Serious Adverse Events With an Outcome of Death

TABLE 8. Overview of Patients with Adverse Events Resulting in Withdrawal [N(%)]

	All Controlled				All Studies
	Quinapril/ HCTZ	Quinapril Monotherapy	HCTZ Monotherapy	Placebo	Quinapril/ HCTZ
Patients Studied	943	804	365	100	1656
Patients Withdrawing Due To An Adverse Event (%)	20 (2.1)	51 (6.3)	3 (0.8)	3 (3.0)	90 (5.4)

The next four pages consist of App A13 of the submission and show the ADEs for which subjects were considered to have withdrawn from the NDA; from "all studies" in the NDA and from similar categories in the safety update data.

Examination of the "BODY SYSTEM" headings shows that for both the NDA and the safety update group the most frequent categories having withdrawals are, in descending order, "body as a whole", "respiratory system", "nervous system", and "cardiovascular system".

Under "body as a whole", headache was most frequent, 0.8% of all NDA cases and 0.7% of the update ones. Most of these ocurred in Q/H or Q cases in controlled trials.

Most of the cases reported under "respiratory system" had cough (1.2% of NDA; 1.0%of the update group). Dyspnea was reported in n=1 case.

The third most frequent category, "nervous system" had 0.4% "paresthesia" of which n=2 cases occurred in the Q monotherapy group only. "Dizziness" occurred in 0.3% of all cases in the NDA and in the update ones.

"Cardiovascular system" withdrawal- ADEs occurred in 1.3% of "all cases" in the NDA and 1.1% of the update group. The largest category in the NDA group was angina pectoris (0.3%, 0.2% in the update). Hypotension was noted in 0.2% of "all cases" in both the NDA and update groups.

The remaining body systems each had percentages of ADE- withdrawal of less than 1%. N=1 cases (0.1%) of cases had hematemesis (n=1 case in the QUIN controlled trial group). Laboratory deviations were the basis for withdrawal in n=1 case each for elevated , creatinine, BUN, uric acid,LDH, Na, Cl, and K.

SUMMARY OF ASSOCIATED ADVERSE EVENTS RESULTING IN WITHDRAWAL OF PATIENTS FROM CONTROLLED AND ALL STUDIES

BODY SYSTEM ADVERSE EVENT	NDA CONTROLLED Q/H (N=820) N	%	NDA CONTROLLED QUIN (N=698) N	%	NDA CONTROLLED HCTZ (N=256) N	%	NDA CONTROLLED PLACEBO (N= 85) N	%	NDA ALL Q/H (N=1452) N	%	SECOND SAFETY UPDATE CONTROLLED Q/H (N=943) N	%	SECOND SAFETY UPDATE CONTROLLED QUIN (N=804) N	%	SECOND SAFETY UPDATE CONTROLLED HCTZ (N=365) N	%	SECOND SAFETY UPDATE CONTROLLED PLACEBO (N=100) N	%	SECOND SAFETY UPDATE ALL Q/H (N=1656) N	%
BODY AS A WHOLE	6	0.7	12	1.7	0	0.0	1	1.2	15	1.0	6	0.6	12	1.5	0	0.0	1	1.0	15	0.9
ASTHENIA	1	0.1	3	0.4	0	0.0	0	0.0	4	0.3	1	0.1	3	0.4	0	0.0	0	0.0	4	0.2
DEHYDRATION	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
FATIGUE	1	0.1	3	0.4	0	0.0	0	0.0	2	0.1	1	0.1	3	0.4	0	0.0	0	0.0	2	0.1
HEADACHE	4	0.5	2	0.3	0	0.0	1	1.2	8	0.6	4	0.4	2	0.2	0	0.0	1	1.0	8	0.5
MALAISE	1	0.1	1	0.1	0	0.0	0	0.0	1	0.1	1	0.1	1	0.1	0	0.0	0	0.0	1	0.1
LASSITUDE	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
CHEST PAIN	1	0.1	1	0.1	0	0.0	0	0.0	1	0.1	1	0.1	1	0.1	0	0.0	0	0.0	1	0.1
STRESS	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
PERIPHERAL EDEMA	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
VIRAL INFECTION	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
CARDIOVASCULAR SYSTEM	5	0.6	8	1.1	0	0.0	1	1.2	11	0.8	5	0.5	8	1.0	1	0.3	1	1.0	11	0.7
HYPOTENSION	1	0.1	4	0.6	0	0.0	0	0.0	3	0.2	1	0.1	4	0.5	0	0.0	0	0.0	3	0.2
HEART FAILURE	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	0	0.0
ANGINA PECTORIS	1	0.1	0	0.0	0	0.0	0	0.0	2	0.1	1	0.1	0	0.0	0	0.0	0	0.0	2	0.1
CARDIOVASCULAR DISORDER	0	0.0	2	0.3	0	0.0	0	0.0	0	0.0	0	0.0	2	0.2	0	0.0	0	0.0	0	0.0
VASODILATATION	1	0.1	0	0.0	0	0.0	1	1.2	2	0.1	1	0.1	0	0.0	0	0.0	1	1.0	2	0.1
PERIPH VASCULAR DISORDER	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
PALPITATION	1	0.1	1	0.1	0	0.0	0	0.0	1	0.1	1	0.1	1	0.1	0	0.0	0	0.0	1	0.1
TACHYCARDIA	1	0.1	0	0.0	0	0.0	0	0.0	2	0.1	1	0.1	0	0.0	0	0.0	0	0.0	2	0.1
MIGRAINE	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
HYPERLIPIDEMIA	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
HYPERTENSIVE CRISIS	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
DIGESTIVE SYSTEM	2	0.2	9	1.3	0	0.0	0	0.0	7	0.5	2	0.2	9	1.1	0	0.0	0	0.0	7	0.4
MOUTH OR THROAT DRY	0	0.0	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	1	0.1	0	0.0	0	0.0	1	0.1
DYSPEPSIA	0	0.0	2	0.3	0	0.0	0	0.0	0	0.0	0	0.0	2	0.2	0	0.0	0	0.0	0	0.0
NAUSEA &/OR VOMITING	2	0.2	2	0.3	0	0.0	0	0.0	6	0.4	2	0.2	2	0.2	0	0.0	0	0.0	6	0.4
HEMATEMESIS	1	0.1	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	1	0.1
DIARRHEA	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
CONSTIPATION	0	0.0	2	0.3	0	0.0	0	0.0	1	0.1	0	0.0	2	0.2	0	0.0	0	0.0	1	0.1
ABDOMINAL PAIN	2	0.2	3	0.4	0	0.0	0	0.0	2	0.1	2	0.2	3	0.4	0	0.0	0	0.0	2	0.1
MUSCULOSKELETAL SYSTEM	1	0.1	0	0.0	0	0.0	0	0.0	3	0.2	1	0.1	0	0.0	0	0.0	0	0.0	3	0.2
MYALGIA	1	0.1	0	0.0	0	0.0	0	0.0	3	0.2	1	0.1	0	0.0	0	0.0	0	0.0	3	0.2
NERVOUS SYSTEM	8	1.0	11	1.6	0	0.0	0	0.0	16	1.1	8	0.8	11	1.4	0	0.0	0	0.0	16	1.0
DIZZINESS	2	0.2	4	0.6	0	0.0	0	0.0	4	0.3	2	0.2	4	0.5	0	0.0	0	0.0	4	0.2
TREMOR	1	0.1	1	0.1	0	0.0	0	0.0	1	0.1	1	0.1	1	0.1	0	0.0	0	0.0	1	0.1

SUMMARY OF ASSOCIATED ADVERSE EVENTS RESULTING IN WITHDRAWAL OF PATIENTS FROM CONTROLLED AND ALL STUDIES

BODY SYSTEM ADVERSE EVENT	NDA CONTROLLED Q/H (N=820) N	%	QUIN (N=698) N	%	HCTZ (N=256) N	%	PLACEBO (N= 85) N	%	NDA ALL Q/H (N=1452) N	%	SECOND SAFETY UPDATE CONTROLLED Q/H (N=943) N	%	QUIN (N=804) N	%	HCTZ (N=365) N	%	PLACEBO (N=100) N	%	SECOND SAFETY UPDATE ALL Q/H (N=1656) N	%
NERVOUS SYSTEM																				
INSOMNIA	1	0.1	2	0.3	0	0.0	0	0.0	1	0.1	1	0.1	2	0.2	0	0.0	0	0.0	1	0.1
SOMNOLENCE	2	0.2	0	0.0	0	0.0	0	0.0	3	0.2	2	0.2	0	0.0	0	0.0	0	0.0	3	0.2
VERTIGO	1	0.1	0	0.0	0	0.0	0	0.0	3	0.2	1	0.1	0	0.0	0	0.0	0	0.0	3	0.2
SYNCOPE	0	0.0	3	0.4	0	0.0	0	0.0	0	0.0	0	0.0	3	0.4	0	0.0	0	0.0	0	0.0
AMNESIA	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
PARESTHESIA	2	0.2	0	0.0	0	0.0	0	0.0	4	0.3	2	0.2	0	0.0	0	0.0	0	0.0	4	0.2
DYSTONIA	0	0.0	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	1	0.1	0	0.0	0	0.0	1	0.1
PSYCHOBIOLOGIC FUNCTION	0	0.0	5	0.7	0	0.0	0	0.0	2	0.1	0	0.0	5	0.6	0	0.0	0	0.0	2	0.1
DEPRESSION	0	0.0	4	0.6	0	0.0	0	0.0	0	0.0	0	0.0	4	0.5	0	0.0	0	0.0	0	0.0
NERVOUSNESS	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
THINKING ABNORMAL	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
DECREASE/LOSS,LIBIDO	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
HOSTILITY	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
NERVOUS BREAKDOWN	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
RESPIRATORY SYSTEM	1	0.1	2	0.3	0	0.0	0	0.0	21	1.4	1	0.1	2	0.2	0	0.0	0	0.0	21	1.3
RHINITIS	0	0.0	0	0.0	0	0.0	0	0.0	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0	2	0.1
SINUSITIS	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
BRONCHITIS	0	0.0	0	0.0	0	0.0	0	0.0	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0	2	0.1
COUGHING	1	0.1	2	0.3	0	0.0	0	0.0	16	1.1	1	0.1	2	0.2	0	0.0	0	0.0	16	1.0
ASTHMA	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
SKIN AND APPENDAGES	1	0.1	1	0.1	0	0.0	0	0.0	6	0.4	1	0.1	1	0.1	0	0.0	0	0.0	6	0.4
RASH	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
RASH-ERYTHEMATOUS	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
RASH-MACULOPAPULAR	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
RASH VESICULOBULLOUS	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
SKIN DRY	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
SWEATING INCREASED	1	0.1	1	0.1	0	0.0	0	0.0	1	0.1	1	0.1	1	0.1	0	0.0	0	0.0	1	0.1
URTICARIA	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
UROGENITAL SYSTEM	0	0.0	0	0.0	0	0.0	0	0.0	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0	2	0.1
ALBUMINURIA	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
IMPOTENCE	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
SPECIAL SENSES	1	0.1	2	0.3	0	0.0	0	0.0	3	0.2	1	0.1	2	0.2	0	0.0	0	0.0	3	0.2
AMBLYOPIA	1	0.1	1	0.1	0	0.0	0	0.0	2	0.1	1	0.1	1	0.1	0	0.0	0	0.0	2	0.1
TASTE LOSS	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1

SUMMARY OF ASSOCIATED ADVERSE EVENTS RESULTING IN WITHDRAWAL OF PATIENTS FROM CONTROLLED AND ALL STUDIES

BODY SYSTEM ADVERSE EVENT	NDA CONTROLLED Q/H (N=820) N	%	NDA CONTROLLED QUIN (N=698) N	%	NDA CONTROLLED HCTZ (N=256) N	%	NDA CONTROLLED PLACEBO (N= 85) N	%	NDA ALL Q/H (N=1452) N	%	SECOND SAFETY UPDATE CONTROLLED Q/H (N=943) N	%	SECOND SAFETY UPDATE CONTROLLED QUIN (N=804) N	%	SECOND SAFETY UPDATE CONTROLLED HCTZ (N=365) N	%	SECOND SAFETY UPDATE CONTROLLED PLACEBO (N=100) N	%	SECOND SAFETY UPDATE ALL Q/H (N=1656) N	%
SPECIAL SENSES																				
UNUSUAL TASTE	0	0.0	1	0.1	0	0.0	0	0.0	1	0.1	0	0.0	1	0.1	0	0.0	0	0.0	1	0.1
BAD BREATH	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
LABORATORY DEVIATIONS	1	0.1	1	0.1	0	0.0	0	0.0	1	0.1	1	0.1	1	0.1	0	0.0	0	0.0	1	0.1
ELEVATED CREATININE	1	0.1	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	1	0.1
ELEVATED BUN	1	0.1	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	1	0.1
ELEVATED URIC ACID	1	0.1	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	1	0.1
HYPOKALEMIA	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0

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Narrative summaries of withdrawals :

Appendix I of this review provides case histories of withdrawals considered to be due to adverse events, serious or not. These summaries also include those for withdrawals associated with serious ADEs in the NDE or previous safety update.

Clinical laboratory changes:

These data are evaluated on the basis of their possible significance; median change, and shifts to above or below a reference level. Table 9, below, shows the NDA and update groups compare favorably for percentages of possibly- clinically important deviations. Except for eosinophils, the largest percentages are in thiazide- type responses (K,Cl,C02). App A.19, on the next page gives details for controlled studies.

TABLE 9. Percentage of Quinapril/HCTZ Patients With Possibly Clinically Important Deviations of Laboratory Values in Controlled and Uncontrolled Studies

Test	NDA		Second Safety Update	
	%	N	%	N
Hemoglobin	6	1043	5	1230
Hematocrit	9	760	8	947
Platelets	7	951	6	1136
WBC	9	1042	8	1229
Eosinophils	10	1010	9	1142
Calcium	0	761	1	939
Creatinine	3	1046	3	1231
CPK	0	102	0	183
Glucose	16	454	14	555
Urea (BUN)	4	613	4	794
Blood Urea	9	383	9	383
Uric Acid	3	976	3	1160
Total Protein	2	760	2	938
Albumin	2	719	1	893
Bilirubin	3	929	3	1114
Alk Phosphatase	0	1042	1	1226
LDH	0	724	0	897
AST	0	1041	0	1227
ALT	0	959	0	1144
Sodium	9	1063	9	1253
Potassium	11	1062	10	1252
Chloride	10	920	9	1099
Carbon Dioxide	13	578	13	660
Cholesterol	6	332	6	432
Triglycerides	58	218	58	218

APPENDIX A.19.

Summary of Possibly Clinically Important Deviations in Clinical Laboratory Values by Treatment Group for All Controlled Studies

Test	NDA												Second Safety Update											
	Placebo			HCTZ			Quinapril			Quinapril + HCTZ			Placebo			HCTZ			Quinapril			Quinapril + HCTZ		
	N	(%)	Total	N	(%)	Total	N	(%)	Total	N	(%)	Total	N	(%)	Total	N	(%)	Total	N	(%)	Total	N	(%)	Total
Hemoglobin	6	(7)	80	6	(2)	244	25	(4)	615	50	(7)	764	6	(6)	94	10	(3)	337	27	(4)	711	50	(6)	882
Hematocrit	6	(7)	80	13	(5)	239	15	(5)	311	52	(10)	537	6	(6)	94	19	(6)	332	19	(5)	407	53	(8)	655
Platelets	7	(9)	79	9	(4)	242	38	(7)	517	41	(6)	679	8	(9)	93	11	(3)	333	41	(7)	611	46	(6)	795
WBC	9	(11)	80	9	(4)	245	57	(9)	614	64	(8)	763	11	(12)	94	11	(3)	339	58	(8)	710	66	(7)	881
Eosinophils	7	(9)	80	15	(7)	228	50	(9)	588	68	(9)	734	8	(9)	94	19	(6)	310	53	(8)	670	72	(9)	838
Calcium	0	(0)	78	0	(0)	238	0	(0)	388	2	(0)	539	0	(0)	92	0	(0)	327	1	(0)	477	8	(1)	648
Creatinine	1	(1)	80	3	(1)	246	16	(3)	619	25	(3)	769	1	(1)	94	3	(1)	344	16	(2)	716	25	(3)	885
CPK	0	(0)	0	0	(0)	101	0	(0)	96	0	(0)	102	0	(0)	0	0	(0)	176	0	(0)	175	0	(0)	183
Glucose	0	(0)	0	10	(9)	116	68	(17)	401	40	(12)	337	0	(0)	0	17	(8)	212	70	(14)	495	44	(10)	438
Urea (BUN)	1	(2)	63	4	(2)	175	5	(2)	299	17	(4)	407	1	(1)	77	7	(3)	269	6	(2)	392	20	(4)	519
Blood Urea	1	(7)	15	6	(10)	59	19	(6)	308	30	(9)	320	1	(7)	15	6	(10)	59	19	(6)	308	30	(9)	320
Uric Acid	2	(2)	80	5	(2)	244	15	(2)	616	26	(3)	761	2	(2)	94	5	(1)	340	16	(2)	712	27	(3)	876
Total Protein	2	(2)	80	2	(1)	243	5	(2)	317	12	(2)	538	2	(2)	94	3	(1)	334	10	(2)	408	15	(2)	647
Albumin	1	(1)	78	3	(1)	230	2	(1)	299	8	(2)	501	1	(1)	92	3	(1)	320	5	(1)	388	8	(1)	606
Bilirubin	0	(0)	79	6	(3)	237	12	(3)	436	20	(3)	660	0	(0)	93	7	(2)	329	14	(3)	525	22	(3)	776
Alkaline Phosphatase	0	(0)	80	6	(2)	241	11	(2)	614	4	(1)	764	0	(0)	94	6	(2)	335	11	(2)	708	6	(1)	879
LDH	0	(0)	79	1	(0)	231	1	(0)	306	0	(0)	503	0	(0)	93	1	(0)	315	1	(0)	389	0	(0)	607
AST	1	(1)	80	0	(0)	240	2	(0)	615	1	(0)	766	1	(1)	94	1	(0)	335	2	(0)	711	2	(0)	883
ALT	3	(4)	79	0	(0)	238	0	(0)	552	2	(0)	702	3	(3)	93	2	(1)	333	0	(0)	648	3	(0)	818
Sodium	6	(7)	82	24	(10)	252	51	(8)	628	75	(10)	786	6	(6)	96	30	(8)	353	61	(8)	728	83	(9)	907
Potassium	7	(9)	82	44	(17)	252	80	(13)	630	88	(11)	786	7	(7)	96	58	(16)	353	89	(12)	730	98	(11)	907
Chloride	6	(7)	82	23	(10)	220	48	(9)	529	68	(10)	704	6	(6)	96	30	(10)	308	53	(9)	617	77	(9)	814
Carbon Dioxide	5	(7)	71	11	(12)	92	44	(14)	317	60	(13)	447	5	(6)	85	11	(12)	92	44	(14)	317	60	(13)	462
Cholesterol	3	(5)	56	12	(8)	158	19	(7)	262	14	(5)	295	3	(5)	56	18	(7)	253	25	(7)	356	19	(5)	395
Triglycerides	26	(46)	56	30	(68)	44	79	(53)	150	98	(54)	181	26	(46)	56	30	(68)	44	79	(53)	150	98	(54)	181

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Table T2 (App A.18) and App A20 give median differences from baseline for all studies, controlled or uncontrolled. For Table T2 the median is indicated as the "Q50" column. Hemoglobin, and to a lesser extent hematocrit, tend to be reduced, eosinophils increased. Creatinine, BUN, blood urea, urine protein, urine wbc, and rbc are increased.

App A20, on the two pages following Table T2, shows median differences for the controlled trials only. These tables are useful to examine since they provide results for the different treatment groups. There are changes in hemoglobin but not hematocrit, in QUIN or QUIN/HCTZ- treated cases. The median creatinine change was 0 in both the NDA and update groups while both showed increases in BUN and blood urea though these were smaller than in the placebo and HCTZ groups. Median values for urine protein, rbc,wbc are not given probably because of the problem of units. Glucose increased only in the HCTZ monotherapy groups. Uric acid was increased in HCTZ and in HCTZ/QUIN.

APPENDIX A.18.

TAB.T2:Quinapril Combined Hypertension Trials - Double-Blind and Open-Label Quin-HCTZ Experience (NDA vs Second Safety Update)

SUMMARY OF MINIMUM, MEDIAN AND MAXIMUM DIFFERENCES BETWEEN BASELINE AND FINAL VALUES FOR CLINICAL LABORATORY TESTS
CENTER: Multicenter

TEST	UNIT	NDA MIN	NDA Q50	NDA MAX	NDA N	Second Safety Update MIN	Second Safety Update Q50	Second Safety Update MAX	Second Safety Update N
HEMOGLOBIN	G/L	-64	-1	150	1043	-64	-1	150	1230
HEMATOCRIT	%	-15	0	45	760	-15	0	45	947
ERYTHROCYTES	X10E12/L	-40.4	-0.03	1.6	771	-40.4	-0.03	1.6	956
PLATELETS	X10E9/L	-556	5	331	951	-556	4	331	1136
WBC	X10E9/L	-5.9	0.2	7.8	1042	-5.9	0.1	7.8	1229
POLYMORPHS	%	-33	0	71	999	-34	0	71	1131
STABS	%	-61	0	31	658	-61	0	31	658
LYMPHOCYTES	%	-31	0	33	1015	-31	0	33	1147
MONOCYTES	%	-9	0	21	1010	-9	0	21	1142
EOSINOPHILS	%	-12	0	14	1010	-12	0	14	1142
BASOPHILS	%	-5	0	5	983	-5	0	5	1115
CALCIUM	MMOL/L	-1.5	0	2.3	761	-11	0	2.3	939
CREATININE	UMOL/L	-9800	0	18800	1046	-9800	0	18800	1231
CPK	U/L	-74	0	128.2	102	-225	-1	128.2	183
GLUCOSE	MMOL/L	-7.7	0	7.7	454	-7.7	0	7.7	555
N.F. GLUCOSE	MMOL/L	-8.2	0	10.7	300	-55466	0	8100	664
UREA (BUN)	MMOL/L	-8.7	0.4	8.6	613	-8.7	0.4	8.6	794
BLOOD UREA	MMOL/L	-66.8	0.2	11.8	383	-66.8	0.2	11.8	383
URIC ACID	UMOL/L	-5710	20	410	976	-5710	20	410	1160
TOTAL PROTEIN	G/L	-678	1	78	760	-678	1	78	938
ALBUMIN	G/L	-28800	0	46500	719	-28800	0	46500	893
BILIRUBIN	UMOL/L	-120	0	43	929	-120	0	43	1114
ALK. PHOSPHATAS	IU/L	-612	-1	135	1042	-612	-2	135	1226
LDH	U/L	-241	-2.5	421	724	-309	-2	421	897
AST	U/L	-105	0	104	1041	-105	0	104	1227
ALT	U/L	-94	0	131	959	-94	0	131	1144
PROTA1	G/L	-440	-10	700	23	-440	-10	700	23
PROTB	G/L	-490	-80	440	23	-490	-80	440	23
SODIUM	MMOL/L	-109	-1	21	1063	-109	0	21	1253
POTASSIUM	MMOL/L	-2.6	0	2.2	1062	-2.6	0	2.2	1252
CHLORIDE	MMOL/L	-80	-1	18	920	-80	-1	18	1099
CARBON DIOXIDE	MMOL/L	-50	1	13	578	-50	1	13	660
CHOLESTEROL	MMOL/L	-4.33	0	5.97	332	-4.33	0	5.97	432
TRIGLYCERIDES	MMOL/L	-37.42	0.05	8.73	218	-37.42	0.05	8.73	218
HDL-CHOLESTEROL	MMOL/L	-0.62	0.06	5.04	198	-0.62	0.06	5.04	198
LDL-CHOLESTEROL	MMOL/L	-5.79	-0.1	2.09	162	-5.79	-0.1	2.09	162
URINE SPEC. W.	G/L	-21	0	53	556	-21	0	53	685

(END)

Summary of Median Differences Between Baseline and Final Clinical Laboratory Values by Treatment Group for All Controlled Studies

Parameter	Units	NDA				Second Safety Update			
		Placebo	HCTZ	Quinapril	Quinapril + HCTZ	Placebo	HCTZ	Quinapril	Quinapril + HCTZ
Hemoglobin	g/L	2	1	-1	-1	1.5	0	-1	-1
Hematocrit	%	1	0	0	0	1	0	0	0
Erythrocytes	$x10^{12}/L$	0.035	0	-0.05	-0.04	0.045	0	-0.03	-0.04
Platelets	$x10^{9}/L$	5	5	4	5	0	6	4	4
WBC	$x10^{9}/L$	0.05	0.25	0.1	0.1	0	0.2	0.1	0.1
Polymorphs	%	-3	0	0	0	-2.5	1	0	0
Stabs	%	0	0	0	0	0	0	0	0
Lymphocytes	%	2.5	0	0	0	2	0	0	0
Monocytes	%	0	0	0	0	0	0	0	0
Eosinophils	%	0	0	0	0	0	0	0	0
Basophils	%	0	0	0	0	0	0	0	0
Calcium	mmol/L	0	0	0	0	0	0	0	0
Creatinine	µmol/L	0	0	0	0	0	0	0	0
CPK	U/L		3	0	0		2	-1	-1
Glucose	mmol/L		0.1	0	0		0.2	0	0
Nonfasting Glucose	mmol/L	0.1	-0.1	0	0	0.2	0.1	0	0
Urea (BUN)	mmol/L	0.4	0.4	0.1	0.3	0.3	0.3	0.2	0.3
Blood Urea	mmol/L	0.9	0.9	0.15	0.1	0.9	0.9	0.15	0.1
Uric Acid	µmol/L	0	20	0	20	0	20	0	12

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Summary of Median Differences Between Baseline and Final Clinical Laboratory Values by Treatment Group for All Controlled Studies

Parameter	Units	NDA				Second Safety Update			
		Placebo	HCTZ	Quinapril	Quinapril + HCTZ	Placebo	HCTZ	Quinapril	Quinapril + HCTZ
Total Protein	g/L	1	1	1	0	1	0.5	0	0
Albumin	g/L	1	0	1	0	1	0	1	0
Bilirubin	µmol/L	0	0	0	0	0	0	0	0
Alkaline Phosphatase	IU/L	2	-1	-1.5	-1	1	0	-1	-2
LDH	U/L	6	1	-1	-1	6	1	-2	-1
AST	U/L	3	0.5	0	0	2	0	0	0
ALT	U/L	0	1	0	0	0	1	0	0
Apolipoprotein A1	g/L			-40	-10			-40	-10
Apolipoprotein B	g/L			0	-90			0	-90
Sodium	mmol/L	0	0	0	0	0	0	0	0
Potassium	mmol/L	-0.1	-0.1	0	0	-0.1	-0.1	0	0
Chloride	mmol/L	-1	-2	-1	-1	-0.5	-2	0	-1
Carbon dioxide	mmol/L	0	1	0	1	0	1	0	1
Cholesterol	mmol/L	0	0	0	0	0	0	0	0
Triglycerides	mmol/L	0.085	0.37	0.12	0.01	0.085	0.37	0.12	0.01
HDL-cholesterol	mmol/L	0.08	0.05	0.02	0.06	0.08	0.05	0.02	0.06
LDL-cholesterol	mmol/L	-0.05	0.19	0	-0.1	-0.05	0.19	0	-0.1
Urine Specific Weight	g/L	0	0	0	0	0	0	0	0

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Table 10 on the next three pages gives the percentages of cases changing to low or high values of various tests in the QUIN/HCTZ group only. App A21, on the following four pages, allows one to see in which Rx groups the changes occurred.

Table 10 shows that both hemoglobin and hematocrit tended to decrease. Serum creatinine increased in 4% of both the NDA and the update group (table 10) while A21 shows this occurred in the HCTZ monotherapy group as well. BUN and blood urea increased also increased in the HCTZ monoRx group as well as in Quin and QUIN/HCTZ. Table 10 shows that urine protein, urine blood, and urine wbc increased in the QUIN/HCTZ group. A21 shows that urine protein, blood, and rbc/hpf increased in both the QUIN and QUIN/HCTZ groups while A21 shows that wbc/hpf did not increase in these groups in the controlled studies.

n.b. In considering the interpretation of these data, note that the "shifts" occur to or from levels that are deemed significant according to the Sponsor's and laboratories' definitions. Therefore, shifts within the normal range, as occur for example with creatinine, would not be detected. This is also true of the urine sediment changes as well as all other tests. The median changes would not be affected by this bias.

TABLE 10. Percentage of Quinapril/HCTZ Patients Changing to "Low" or "High" Values at the End of the Study for Controlled and Uncontrolled Studies
(Page 1 of 3)

Test	Change Summarized	NDA		Second Safety Update	
		%	N at Risk	%	N at Risk
Hemoglobin	H	3	988	3	1173
	L	5	935	5	1104
Hematocrit	H	4	703	4	887
	L	5	705	5	877
Erythrocytes	H	2	732	2	913
	L	6	705	6	870
Platelets	H	2	912	2	1088
	L	1	918	1	1100
WBC	H	5	994	4	1176
	L	2	980	3	1159
Polymorphs	H	5	821	5	937
	L	5	836	5	960
Stabs	H	3	629	3	629
	L	1	621	1	621
Lymphocytes	H	7	883	8	1000
	L	5	945	5	1064
Monocytes	H	7	939	7	1070
	L	6	896	7	997
Eosinophils	H	8	911	8	1035
	L	6	891	6	1001
Basophils	H	4	918	4	1051
	L	0	981	0	1113
Calcium	H	1	749	1	920
	L	1	737	2	912
Creatinine	H	4	982	4	1162
	L	1	1029	1	1198
CPK	H	10	90	7	175
	L	3	90	8	154
Glucose	H	14	331	13	421
	L	2	441	2	540

L = "Normal" or "High" range at baseline and "Low" at the end of the study
H = "Low" or "Normal" range at baseline and "High" at the end of the study

TABLE 10. Percentage of Quinapril/HCTZ Patients Changing to "Low" or "High" Values at the End of the Study for Controlled and Uncontrolled Studies
(Page 2 of 3)

Test	Change Summarized	NDA		Second Safety Update	
		%	N at Risk	%	N at Risk
NF Glucose	H	0	1	2	88
	L	0	1	1	93
Urea (BUN)	H	8	581	9	749
	L	1	586	1	755
Blood Urea	H	13	326	13	326
	L	1	368	1	368
Uric Acid	H	13	821	12	987
	L	0	922	0	1103
Total Protein	H	2	736	2	911
	L	1	738	1	910
Albumin	H	1	704	1	871
	L	2	685	2	845
Bilirubin	H	3	880	3	1056
	L	1	919	1	1072
Alk Phosphatase	H	2	971	2	1131
	L	1	1007	1	1180
LDH	H	2	694	3	855
	L	1	700	1	843
AST	H	6	945	5	1121
	L	0	1033	1	1159
ALT	H	6	813	6	979
	L	1	948	1	1075
Apolipoprotein A1	H	21	19	21	19
	L	0	23	0	23
Apolipoprotein B	H	8	13	8	13
	L	0	22	0	22
Sodium	H	2	1034	2	1219
	L	3	1049	3	1230
Potassium	H	1	1044	1	1231
	L	5	987	5	1169

L = "Normal" or "High" range at baseline and "Low" at the end of the study
H = "Low" or "Normal" range at baseline and "High" at the end of the study

TABLE 10. Percentage of Quinapril/HCTZ Patients Changing to "Low" or "High" Values at the End of the Study for Controlled and Uncontrolled Studies
(Page 3 of 3)

Test	Change Summarized	NDA		Second Safety Update	
		%	N at Risk	%	N at Risk
Chloride	H	2	840	3	1002
	L	4	896	4	1071
Carbon Dioxide	H	7	517	7	597
	L	5	483	6	559
Cholesterol	H	7	217	8	291
	L	1	282	4	363
HDL-Cholesterol	H	1	135	2	122
	L	6	126	7	114
LDL-Cholesterol	H	3	101	3	96
	L	1	112	1	107
Triglycerides	H	16	122	16	122
	L	0	198	0	197
Urine Specific Weight	H	2	547	1	676
	L	0	549	0	678
Urine Ketones	H	2	684	2	869
	L	0	572	0	656
Urine Protein	H	9	912	8	1093
	L	2	769	2	854
Urine Glucose	H	3	969	2	1155
	L	1	762	1	846
Urine Blood	H	6	702	5	877
	L	1	625	1	714
Urine WBC	H	13	689	12	848
	L	8	646	9	750
Urine RBC	H	7	648	7	648
	L	3	610	3	610
Casts	H	0	0	4	68
	L	0	0	0	80
Hyaline Casts	H	1	606	1	606
	L	0	516	0	516

L = "Normal" or "High" range at baseline and "Low" at the end of the study
H = "Low" or "Normal" range at baseline and "High" at the end of the study

APPENDIX A.21.
(Page 1 of 4)

Summary of Percentage of Patients Changing to Low or High Values at the End of the Study by Treatment Group for All Controlled Studies

Test	Change Summarized	NDA								Second Safety Update							
		Placebo		HCTZ		Quinapril		Quinapril + HCTZ		Placebo		HCTZ		Quinapril		Quinapril + HCTZ	
		Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk
Hemoglobin	H	5	74	5	239	3	601	3	723	5	88	4	322	3	689	3	839
	L	6	71	4	221	3	574	5	685	5	83	4	309	4	664	5	794
Hematocrit	H	9	76	3	226	4	298	4	492	8	90	3	313	3	389	3	608
	L	8	76	6	225	4	288	5	494	8	88	6	311	5	379	6	603
Erythrocytes	H	4	76	4	237	2	377	2	516	3	90	3	327	2	469	2	631
	L	5	74	4	214	9	321	7	503	6	84	4	299	8	408	6	609
Platelets	H	3	77	3	233	1	500	2	652	2	89	3	322	1	592	2	763
	L	1	77	2	238	2	504	1	654	1	91	2	327	2	596	1	767
WBC	H	1	77	3	233	4	588	5	725	2	91	3	322	4	680	4	840
	L	3	77	3	234	2	590	2	715	2	91	2	327	2	680	2	825
Polymorphs	H	1	75	7	213	4	489	4	583	1	89	7	298	4	566	4	686
	L	5	70	6	217	4	486	5	574	4	92	5	298	4	560	5	672
Stabs	H	1	76	6	106	2	263	4	387	1	76	6	106	2	263	4	387
	L	0	75	2	112	1	194	1	378	0	75	2	112	1	194	1	378
Lymphocytes	H	7	75	7	200	5	541	7	642	6	89	8	276	6	608	8	734
	L	1	77	5	213	5	549	5	691	1	91	6	288	5	626	5	787
Monocytes	H	5	79	3	217	9	533	7	682	6	90	3	304	8	614	6	780
	L	1	74	4	200	5	532	7	641	1	88	7	261	6	598	7	722
Eosinophils	H	7	76	9	213	6	543	8	670	6	89	9	292	6	619	8	767
	L	1	78	5	201	8	504	6	643	1	92	7	280	8	588	6	743
Basophils	H	3	75	5	207	5	543	4	671	2	89	6	288	5	624	4	776
	L	0	78	0	223	0	578	0	719	0	92	1	305	0	662	0	823
Calcium	H	0	77	0	234	0	381	1	529	0	90	1	322	1	469	1	633
	L	0	77	3	227	2	367	2	521	0	91	3	311	2	452	2	623

H = High; L = Low

Summary of Percentage of Patients Changing to Low or High Values at the End of the Study by Treatment Group for All Controlled Studies

Test	Change Summarized	NDA								Second Safety Update							
		Placebo		HCTZ		Quinapril		Quinapril + HCTZ		Placebo		HCTZ		Quinapril		Quinapril + HCTZ	
		Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk
Creatinine	H	1	76	5	221	5	579	4	712	1	90	4	311	5	674	4	826
	L	0	80	2	243	0	614	1	756	0	94	2	324	1	692	1	856
CPK	H	0	0	5	92	7	84	10	90	0	0	7	174	7	183	7	175
	L	0	0	3	92	2	85	3	90	0	0	5	146	6	141	8	154
Glucose	H	0	0	18	83	13	309	13	245	0	0	14	155	12	385	12	335
	L	0	0	1	115	5	371	2	324	0	0	1	210	4	465	2	423
Nonfasting Glucose	H	0	0	0	0	14	7	0	1	0	15	0	0	13	8	5	21
	L	0	0	0	0	0	7	0	1	0	14	0	3	0	8	0	24
Urea (BUN)	H	0	63	6	168	5	283	8	385	0	77	7	244	6	368	9	484
	L	0	63	1	174	1	290	1	402	0	76	2	259	1	374	1	503
Blood Urea	H	20	15	17	52	11	269	13	269	20	15	17	52	11	269	13	269
	L	0	15	4	56	1	305	1	313	0	15	4	56	1	305	1	313
Uric Acid	H	6	72	13	209	8	546	12	629	5	86	11	294	7	629	11	732
	L	0	79	0	239	1	604	0	716	0	93	1	333	1	699	0	829
Total Protein	H	1	79	1	236	3	311	2	517	1	93	2	322	3	395	2	623
	L	0	78	0	238	2	308	1	518	0	92	1	327	3	398	1	625
Albumin	H	0	76	1	222	2	292	2	487	0	90	1	310	2	376	2	587
	L	1	76	2	219	2	292	2	469	1	90	2	296	2	371	2	560
Bilirubin	H	3	75	6	227	3	410	2	618	2	89	6	317	3	495	2	727
	L	3	78	0	236	1	431	0	659	2	92	0	297	1	493	0	743
Alkaline Phosphatase	H	1	75	3	225	4	576	2	708	1	89	3	315	3	667	2	815
	L	0	79	0	240	1	605	1	743	0	93	0	327	1	687	1	847
LDH	H	3	77	3	221	2	286	3	479	2	91	4	296	4	362	3	571
	L	0	78	3	217	1	292	1	483	0	92	3	276	2	345	1	557

H = High; L = Low

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Summary of Percentage of Patients Changing to Low or High Values at the End of the Study by Treatment Group for All Controlled Studies

Test	Change Summarized	NDA								Second Safety Update							
		Placebo		HCTZ		Quinapril		Quinapril + HCTZ		Placebo		HCTZ		Quinapril		Quinapril + HCTZ	
		Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk
AST	H	5	74	5	220	3	568	7	688	6	87	5	314	3	664	7	798
	L	0	80	0	235	0	608	0	758	0	94	2	278	1	649	1	815
ALT	H	6	70	7	208	5	485	6	598	5	81	7	299	5	576	6	705
	L	0	79	0	233	0	545	1	692	0	93	4	279	2	587	1	750
Apolipoprotein A1	H	0	0	0	0	0	9	22	18	0	0	0	0	0	9	22	18
	L	0	0	0	0	0	11	0	21	0	0	0	0	0	11	0	21
Apolipoprotein B	H	0	0	0	0	22	9	0	11	0	0	0	0	22	9	0	11
	L	0	0	0	0	0	13	0	20	0	0	0	0	0	13	0	20
Sodium	H	0	80	2	249	3	606	2	762	0	94	1	346	4	705	2	878
	L	2	81	5	250	2	618	3	774	2	95	5	348	2	715	3	887
Potassium	H	1	82	2	248	2	611	1	776	1	96	3	347	3	711	1	895
	L	1	82	9	245	2	606	5	730	1	96	9	342	2	702	5	843
Chloride	H	3	72	3	194	5	476	2	639	5	86	4	268	6	557	3	736
	L	0	81	5	220	3	520	3	682	0	95	5	303	3	606	4	789
Carbon Dioxide	H	0	67	3	80	3	305	7	396	1	80	3	80	3	305	7	411
	L	12	57	6	71	10	240	5	371	10	71	6	71	10	240	5	386
Cholesterol	H	6	49	11	104	8	198	6	220	6	49	12	177	9	275	6	298
	L	2	54	3	155	2	249	1	285	2	54	9	238	6	330	4	371
Triglycerides	H	16	37	30	23	22	79	15	111	16	37	30	23	22	79	15	111
	L	0	56	0	44	1	150	0	180	0	56	0	44	1	150	0	180
HDL-Cholesterol	H	0	44	5	43	0	127	2	159	0	44	5	43	0	127	2	159
	L	6	36	8	39	7	107	7	148	6	36	8	39	7	107	7	148
LDL-Cholesterol	H	3	39	8	39	8	88	3	119	3	39	8	39	8	88	3	119
	L	0	42	5	42	1	95	2	130	0	42	5	42	1	95	2	130

H = High; L = Low

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Summary of Percentage of Patients Changing to Low or High Values at the End of the Study by Treatment Group for All Controlled Studies

Test	Change Summarized	NDA								Second Safety Update							
		Placebo		HCTZ		Quinapril		Quinapril + HCTZ		Placebo		HCTZ		Quinapril		Quinapril + HCTZ	
		Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk	Percent	N at Risk
Urine Specific Weight	H	3	67	1	148	1	224	1	355	2	81	1	191	1	268	1	415
	L	0	68	0	147	0	225	0	353	0	82	0	190	0	269	0	413
Ketones	H	0	70	2	218	2	288	1	472	0	84	2	317	2	383	1	590
	L	0	72	0	107	0	185	0	363	0	86	0	107	0	185	0	378
Urine Protein	H	11	72	5	223	4	489	7	670	9	86	5	321	4	586	7	788
	L	0	79	4	130	1	429	2	545	0	93	7	134	1	430	2	561
Urine Glucose	H	0	73	3	232	2	513	3	708	0	87	2	332	1	610	2	826
	L	0	79	4	130	0	428	1	538	0	93	5	131	0	428	1	553
Urine Blood	H	8	75	4	225	5	289	5	494	8	89	4	325	5	385	5	612
	L	0	78	4	126	1	203	1	410	0	92	7	130	2	205	2	430
WBC/HPF	H	2	65	14	188	9	280	12	487	1	79	12	278	9	364	11	593
	L	0	73	15	124	8	230	11	435	0	87	27	143	16	251	14	470
RBC/HPF	H	3	70	3	98	5	199	7	412	3	70	3	98	5	199	7	412
	L	0	73	0	105	0	211	4	399	0	73	0	105	0	211	4	399
Hyaline Casts	H	0	72	2	102	1	202	1	433	0	72	2	102	1	202	1	433
	L	0	73	0	103	0	209	0	369	0	73	0	103	0	209	0	369

H = High; L = Low

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Conclusions:

The findings in the safety update are quite similar to those in the NDA, which is not surprising since the sample size is not very much increased for the update.

The proposal for the adverse effects section of the package insert listing ADE occurring in >1% of subjects in controlled trials, while arbitrary, tends to be balanced by including clinically significant though less frequent ADE (see page 1 of this Review and Table 3).

/S/

Philip L. Dern M.D.

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APPENDIX I

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Case Histories of Withdrawals Due to Adverse Events[a]

1. Albuminuria

Patient 1 (Study 906-12X, Center 13), a 62-year-old man with hypertension, had been treated with quinapril/HCTZ (20/50) when proteinuria (albuminuria) was reported on Day 231. Urine protein levels were 1+ on Day 231, however the levels were 2+ at baseline and on Day 336. The patient had been treated with acetaminophen with codeine, indomethacin, and choline theophyllinate (oxtriphylline) and had a history of a colostomy and myocardial infarction. Quinapril/HCTZ therapy was discontinued on Day 335 and the patient was withdrawn from the study. The investigator indicated this event was related to quinapril/HCTZ therapy.

2. Headache, Nausea &/or Vomiting, Paresthesia

Patient 1 (Study 906-12X, Center 20), a 39-year-old man with hypertension, had been treated with quinapril/HCTZ (30/50) when he experienced headache, nausea and/or vomiting, and paresthesia on Day 171. Quinapril/HCTZ therapy was discontinued and the patient was withdrawn from the study. The investigator indicated the headache and nausea and/or vomiting were related to quinapril/HCTZ therapy; however, the relationship of the paresthesia to therapy was unknown.

[a] Where applicable the investigator's term for adverse events are used with the corresponding preferred term (modified COSTART) in parentheses.

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Case Histories of Withdrawals Due to Adverse Events

3. Coughing, Asthma

Patient 1 (Study 906-82X, Center 82), a 69-year-old woman with hypertension, had been treated with quinapril/HCTZ (80/25) when she experienced coughing on Day 632. She had reported asthma on Day 191 of the study. In addition to quinapril/HCTZ the patient had been also taking prazosin for hypertension. Quinapril/HCTZ therapy was discontinued on Day 687 and the patient was withdrawn from the study. The investigator indicated that these events were related to quinapril/HCTZ therapy.

4. Rash

Patient 18 (Study 906-82X, Center 84), a 47-year-old man with hypertension, had been treated with quinapril/HCTZ (40/50) when he experienced an itching rash (rash) on Day 35 in the double-blind phase of the study. The rash persisted and quinapril/HCTZ was discontinued and the patient was withdrawn on Day 785. The patient had been taking diphenhydramine and alprazolam at the time of withdrawal. The investigator indicated that this event was related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

5. Hypotension

Patient 12 (Study 906-82X, Center 85), a 60-year-old man, withdrew from captopril treatment during the double-blind phase of the study due to dizziness and lightheadedness that led to a loss of consciousness. This event was attributed to cerebellar diseases however, the patient was entered into the open-label phase of the study. Four hours after the first dose of quinapril/HCTZ (10/25), the patient's blood pressure decreased from 155/103 mm Hg to 112/84 mm Hg and the patient was withdrawn from the study. Further management of this patient was not specified. This event was considered possibly related to quinapril/HCTZ by the investigator.

6. Angina Pectoris, Coronary Artery Disease

Patient 4 (Study 906-82X, Center 86), a 60-year-old man with hypertension, had been treated with quinapril/HCTZ (80/25) when he experienced angina pectoris on Day 557 with coronary artery disease subsequently reported on Day 560. Quinapril/HCTZ therapy was discontinued on Day 559 and the patient was withdrawn from the study. The investigator indicated that these events were not related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

7. Impotence

Patient 14 (Study 906-82X, Center 90), a 59-year-old man with hypertension, had been treated with quinapril/HCTZ (80/25) when he reported impotence on Day 184. Quinapril/HCTZ therapy was discontinued on Day 196 and the patient was withdrawn from the study. The investigator indicated that the relationship of this event to the quinapril/HCTZ therapy was unknown.

8. Rash - Erythematous, Skin Dry

Patient 7 (Study 906-82X, Center 91), a 56-year-old man with hypertension, had been treated with quinapril/HCTZ (40/25) when he presented with an erythematous rash and dry skin on Day 303. The patient was treated with a clotrimazole preparation and hydrocortisone cream. Quinapril/HCTZ therapy was discontinued on Day 659 and the patient was withdrawn from the study. The investigator indicated that these events were related to quinapril/HCTZ therapy.

9. Somnolence, Libido Decrease/Loss

Patient 14 (Study 906-82X, Center 91), a 46-year-old man with hypertension, had been treated with quinapril/HCTZ (20/25) when he experienced somnolence and a decrease and/or loss of libido on Days 60 and 13 of double-blind, respectively. Quinapril/HCTZ therapy was discontinued on Day 251 and the patient was withdrawn from the study. The investigator indicated that these events were related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

10. Myalgia, Desquamation

Patient 18 (Study 906-82, Center 91), a 53-year-old man with hypertension, had been treated with quinapril/HCTZ (20/25) when he experienced myalgia and desquamation on Day 3 of the double-blind phase. Quinapril/HCTZ therapy was discontinued on Day 14 and the patient was withdrawn from the study. The investigator indicated that the relationship of these events to quinapril/HCTZ therapy was unknown.

11. Peripheral Edema, Paresthesia

Patient 22 (Study 906-82X, Center 91), a 44-year-old woman with hypertension, had been treated with quinapril/HCTZ (20/25) when she experienced peripheral edema and numbness in hands (paresthesia) on Days 95 and 110, respectively. The patient had been treated with aspirin, terfenadine, and nadolol. Quinapril/HCTZ therapy was discontinued on Day 147 and the patient was withdrawn from the study. The investigator indicated that these events were related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

12. Taste Loss, Unusual Taste, Bad Breath

Patient 15 (Study 906-82X, Center 94), a 57-year-old man with hypertension, had been treated with quinapril/HCTZ (40/25) when he experienced a decreased sense of taste (taste loss), bad taste in mouth (unusual taste), and mouth odor (bad breath), on Days 31, 31, and 46 of open-label, respectively. The patient had previously reported the same events while being treated with captopril and HCTZ in the double-blind phase of the study for which the patient was withdrawn from the study. The patient was then entered into the open-label phase for a trial of quinapril/HCTZ. Quinapril/HCTZ therapy was discontinued on Day 56 and the patient was withdrawn from the study. The investigator indicated that these events were related to quinapril/HCTZ therapy.

13. Headache, Rhinitis

Patient 3 (Study 906-82X, Center 95), a 65-year-old man with hypertension, had been treated with quinapril/HCTZ (20/25) when he experienced headache and rhinitis on Day 102. Quinapril/HCTZ therapy was discontinued on Day 112 and the patient was withdrawn from the study. The investigator indicated that these events were related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

14. Hemorrhoids, Coughing

Patient 6 (Study 906-82X, Center 96), a 56-year-old woman with hypertension, had been treated with quinapril/HCTZ (40/25) when she experienced hemorrhoids and coughing on Days 45 and 14, respectively, during double-blind treatment with captopril/HCTZ. The events continued into open label while she received quinapril/HCTZ (40/25). The patient had a history of constipation and had previously reported coughing and sinusitis. She was treated with amoxicillin, chlor-trimeton, and dextromethorphan. Quinapril/HCTZ therapy was discontinued on Day 267 and the patient was withdrawn from the study. The investigator indicated that the coughing was related to quinapril/HCTZ therapy however the hemorrhoids were unrelated to therapy.

15. Rash - Vesiculobullous

Patient 6 (Study 906-114X, Center 114), a 62-year-old woman with hypertension, had been treated with quinapril/HCTZ (40/25) when she presented with a vesiculobullous rash on Day 290. Quinapril/HCTZ therapy was discontinued on Day 330 and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

16. Gout

Patient 9 (Study 906-114X, Center 114), a 71-year-old man with hypertension, had been treated with open-label quinapril/HCTZ (40/25) when he experienced gout on Day 174. The patient was hospitalized on Day 266 for a severe gout attack. HCTZ was discontinued on Day 273 and allopurinol and indomethacin were prescribed. Two weeks later quinapril therapy was discontinued and the patient was withdrawn from the study. The investigator indicated that these events were not related to quinapril/HCTZ therapy, but rather to concurrent illness.

17. Chest Pain, Gout

Patient 16 (Study 906-114, Center 114), a 51-year-old man with hypertension, had been treated with double-blind quinapril/HCTZ (40/25) when he experienced gout on Day 113 and chest pain on Day 183. The patient had a history of gout. Quinapril/HCTZ therapy was discontinued on Day 186. The investigator indicated the events were not related to quinapril/HCTZ.

18. Impotence

Patient 21 (Study 906-114X, Center 115), a 61-year-old man with hypertension, had been treated with quinapril/HCTZ (40/25) when he experienced impotence on Day 257. The patient had previously reported impotence during quinapril therapy in the double-blind phase of the study. Quinapril/HCTZ therapy was discontinued on Day 277 and the patient was withdrawn from the study. The investigator indicated that the relationship of this event to quinapril/HCTZ therapy was unknown.

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Case Histories of Withdrawals Due to Adverse Events

19. Bronchitis

Patient 1 (Study 906-114, Center 116), a 60-year-old man with hypertension, had been treated with quinapril/HCTZ (40/25) when he experienced bronchitis on Day 58. The patient did not report a history of asthma or bronchitis. HCTZ was subsequently titrated to 50 mg at Day 126. Therapy was discontinued on Day 280 and the patient was withdrawn from the study. The investigator indicated this event was related to quinapril/HCTZ therapy.

20. Colon Cancer

Patient 9 (Study 906-114X, Center 118), a 68-year-old man with hypertension, had been treated with open-label quinapril/HCTZ (40/25) for 206 days prior to being diagnosed with colon cancer. Quinapril/HCTZ therapy was discontinued and the patient was withdrawn from the study. The investigator indicated that this event was not related to quinapril/HCTZ therapy but rather to a concurrent illness.

21. Libido Disorder

Patient 4 (Study 906-114X, Center 120), a 36-year-old woman with hypertension, had been treated with quinapril/HCTZ (10/25) when she experienced sexual dysfunction on Day 389. Quinapril/HCTZ was discontinued on Day 454 and the patient was withdrawn from the study. The investigator indicated the relationship of this event to quinapril/HCTZ therapy was unknown.

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Case Histories of Withdrawals Due to Adverse Events

22. Myalgia

Patient 8 (Study 906-114X, Center 120), a 39-year-old man with hypertension, had been treated with quinapril/HCTZ (40/25) when he experienced pain in toe (myalgia) on Day 154. The patient was treated with indomethacin and sulindac. The patient did not report a history of toe pain. Quinapril/HCTZ therapy was discontinued on Day 175 and the patient was withdrawn from the study. The investigator indicated this event was related to quinapril/HCTZ therapy.

23. Peripheral Edema, Flatulence

Patient 11 (Study 906-114, Center 120), a 38-year-old woman with hypertension had been treated with quinapril/HCTZ (40/25) when she experienced peripheral edema and flatulence on Days 49 and 56, respectively. The patient was taking glyburide for diabetes mellitus. Quinapril/HCTZ therapy was discontinued on Day 88 and the patient was withdrawn from the study. The investigator indicated this event was not related to quinapril/HCTZ therapy.

24. Face Edema, Sinusitis, Rash - Maculopapular, Vision Loss

Patient 12 (Study 906-114X, Center 120), a 62-year-old woman with hypertension had been treated with quinapril/HCTZ (10/25) when she experienced face edema on Day 133. The patient discontinued quinapril/HCTZ therapy on Day 133 and was withdrawn from the study. Five days later, the patient returned to the investigator's office and reported sinusitis and vision loss. The patient subsequently developed a rash. The patient had been taking ceclor, ampicillin, medrol, and Benadryl® to treat these poststudy events. The investigator indicated

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Case Histories of Withdrawals Due to Adverse Events

that the relationship of the face edema to quinapril/HCTZ therapy was unknown and that all the poststudy events were not related to quinapril/HCTZ therapy.

25. Pyelonephritis

Patient 13 (Study 906-114X, Center 121), a 49-year-old woman with hypertension, had been treated with quinapril/HCTZ (40/50) when she presented with pyelonephritis on Day 298. The patient experienced a urinary tract infection prior to the pyelonephritis as well as back pain, abdominal discomfort (dyspepsia), arthritis flare-up, and anxiety. The patient was taking sulindac, sulfisoxazole, chlordiazepoxide, piroxicam, acetaminophen with codeine, and alprazolam. Quinapril/HCTZ therapy was discontinued on Day 298 and the patient was withdrawn from the study. The investigator indicated this event was not related to quinapril/HCTZ therapy.

26. Headache

Patient 18 (Study 906-114X, Center 123), a 58-year-old man with hypertension, had been treated with quinapril (10 mg) when he experienced headache on Day 44 of the double-blind phase of the study. The patient discontinued double-blind and entered open-label quinapril/HCTZ treatment (40/25) where he again reported headaches. The patient was subsequently withdrawn on Day 340. The investigator indicated that the relationship of this event to quinapril/HCTZ therapy was unknown.

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Case Histories of Withdrawals Due to Adverse Events

27. Dizziness

Patient 21 (Study 906-114X, Center 123), a 44-year-old man with hypertension, had been treated with quinapril/HCTZ (40/25) when he experienced dizziness on Day 109. Quinapril/HCTZ therapy was discontinued on Day 109 and the patient was withdrawn from the study. The investigator indicated this event was related to quinapril/HCTZ therapy.

28. Coughing

Patient 5 (Study 906-114, Center 124), a 59-year-old man with hypertension, had been treated with quinapril/HCTZ (40/25) when he experienced coughing on Day 64. The patient had an history of tachycardia and laminectomy. Quinapril/HCTZ therapy was discontinued on Day 175 and the patient was withdrawn from the study. The investigator indicated this event was related to quinapril/HCTZ therapy.

29. Asthenia, Paresthesia

Patient 14 (Study 906-114, Center 124), a 37-year-old woman with hypertension, had been treated with quinapril/HCTZ (40/25) when she experienced hand and arm weakness (asthenia) and tingling fingers and toes (paresthesia) on Day 83 and 125 of therapy, respectively. Quinapril/HCTZ therapy was discontinued on Day 152 and the patient was withdrawn from the study. The investigator indicated this event was related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

30. Headache

Patient 7 (Study 906-114X, Center 129), a 54-year-old woman with hypertension, had been treated with quinapril/HCTZ (40/50) when she experienced headache on Day 47. The patient had also been taking atenolol. Quinapril/HCTZ therapy was discontinued and the patient was withdrawn from the study on Day 412. The investigator indicated that this event was related to quinapril/HCTZ therapy.

31. Myocardial Infarction

Patient 5 (Study 906-231X, Center 2), a 42-year-old woman with hypertension, had been treated with open-label quinapril/HCTZ (40/25) when she experienced a myocardial infarction on Day 107. Quinapril/HCTZ therapy was discontinued and the patient was withdrawn from the study. The investigator indicated that the relationship of this event to quinapril/HCTZ therapy was unknown.

32. Coughing

Patient 1 (Study 906-231, Center 9), a 66-year-old woman with hypertension had been treated with quinapril/HCTZ (40/50) when she reported coughing on Day 43. Quinapril/HCTZ therapy was discontinued on Day 127 and the patient was withdrawn from the study. The investigator indicated this event was related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

33. Dystonia

Patient 8 (Study 906-231X, Center 10), a 71-year-old woman with hypertension, had been treated with quinapril/HCTZ (40/50) when she experienced dystonia on Day 34. Quinapril/HCTZ therapy was discontinued on Day 84 and the patient was withdrawn from the study. The investigator indicated this event was related to quinapril/HCTZ therapy.

34. Headache, Mouth/Throat Dry, Lacrimation Disorder

Patient 9 (Study 906-238X, Center 11), a 64-year-old woman with hypertension had been treated with quinapril/HCTZ (40/25) when she experienced headache, dry mouth/throat, and a lacrimation disorder on Days 136, 9, and 112, respectively. Quinapril/HCTZ therapy was discontinued on Day 167 and the patient was withdrawn from the study. The investigator indicated that the dry mouth was related to quinapril/HCTZ therapy while the relationship of therapy to the other events was unknown.

35. Coughing

Patient 1 (Study 906-238X, Center 15), a 47-year-old woman with hypertension, had been treated with quinapril/HCTZ (40/25) when she experienced coughing on Day 14 of double blind. Quinapril/HCTZ therapy was discontinued on Day 152 (open label) and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

36. Hypertensive Crisis

Patient 4 (Study 906-238X, Center 18), a 50-year-old man with hypertension, had been treated with quinapril/HCTZ (40/50) when he experienced a hypertensive crisis on Day 173. Quinapril/HCTZ therapy was discontinued on the same day and the patient was withdrawn from the study. The investigator indicated that this event was possibly related to quinapril/HCTZ therapy.

37. Pancreatitis

Patient 2 (Study 906-238X, Center 26), a 54-year-old man with hypertension, had been treated with open-label quinapril/HCTZ (40/25) for 4 days before being diagnosed with pancreatitis on Day 116. The patient had a history of gout and alcohol abuse. Quinapril/HCTZ therapy was discontinued and the patient was withdrawn from the study on Day 116. The investigator indicated that the relationship of this event to quinapril/HCTZ therapy was unknown.

38. Angina Pectoris, Coronary Artery Disease

Patient 12 (Study 906-241X, Center 1), a 60-year-old woman with hypertension, had been treated with quinapril/HCTZ (20/25) when she experienced angina pectoris on Day 270. The investigator also reported coronary artery disease for this patient on Day 270. The patient had been taking isosorbide mononitrate for coronary heart disease and did not report a history of angina. Quinapril/HCTZ therapy was discontinued the same day and the patient was withdrawn from the study. The investigator indicated that these events were not related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

39. Coughing

Patient 2 (Study 906-241X, Center 2), a 52-year-old man with hypertension, had been treated with quinapril/HCTZ (40/50) when he experienced coughing on Day 332. Quinapril/HCTZ therapy was discontinued on Day 389 and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

40. Transient Ischemic Attack

Patient 5 (Study 906-241, Center 6), a 61-year-old woman with hypertension, had been treated with double-blind quinapril/HCTZ (40/12.5) when she experienced a transient ischemic attack on Day 23. Quinapril/HCTZ therapy was discontinued and the patient was withdrawn from the study on Day 25. An angiogram was performed and the results were normal. The investigator indicated that this event was not related to quinapril/HCTZ therapy.

41. Fatigue, Vertigo

Patient 1 (Study 906-241, Center 8), a 59-year-old woman with hypertension, had been treated with quinapril/HCTZ (40/25) when she experienced fatigue and vertigo on Day 11. The patient did not take any concurrent medications but had concurrent illnesses of arthrosis, hypercalciuria, and hyperlipemia. Quinapril/HCTZ therapy was discontinued on Day 15 and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

42. Vertigo

Patient 5 (906-241X, Center 8), a 23-year-old woman with hypertension, had been treated with quinapril/HCTZ (10/12.5) when she began experiencing intermittent vertigo on Day 133. Quinapril/HCTZ therapy was discontinued on Day 136 and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

43. Coughing

Patient 10 (906-241X, Center 10), a 43-year-old woman with hypertension, had been treated with quinapril/HCTZ (20/25) when she experienced coughing on Day 70. The patient had been taking dextromethorphan, doxycycline, and astemizole for the treatment of cough. Quinapril/HCTZ therapy was discontinued on Day 136 and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

44. Rash - Maculopapular

Patient 16 (906-241X, Center 10), a 46-year-old man with hypertension, had been treated with quinapril/HCTZ (10/12.5) when he experienced a rash (itching papules on the extremities) on Day 64. Quinapril/HCTZ therapy was discontinued on Day 71 and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

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45. Coughing

Patient 6 (906-241X, Center 11), a 50-year-old man with hypertension, had been treated with quinapril/HCTZ (40/50) when he experienced coughing on Day 223. The patient had a history of allergic rhinitis and had been taking brompheniramine, dextromethorphan, doxycycline, and erythromycin. Quinapril/HCTZ therapy was discontinued on Day 266 and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

46. Headache, Malaise

Patient 7 (906-241, Center 11), a 61-year-old man with hypertension, had been treated with quinapril/HCTZ (2.5/6.25) when he experienced headache and malaise on Day 2. Concurrent illnesses reported by the patient were cervical-thoracic osteoarthritis, degenerative cochlea, and cervical spondylarthrosis. Quinapril/HCTZ therapy was discontinued on Day 7 and the patient was withdrawn from the study. The investigator indicated that these events were related to quinapril/HCTZ therapy.

47. Coughing

Patient 16 (906-241X, Center 11), a 48-year-old man with hypertension, had been treated with quinapril/HCTZ (20/25) for 92 days when he experienced coughing. Quinapril/HCTZ therapy was discontinued on Day 196 and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

48. Coughing

Patient 1 (Study 906-241X, Center 12), a 58-year-old woman with hypertension, had been treated with quinapril (2.5 mg) when she reported coughing at the last visit of the open-label phase of the study. She indicated that the coughing had started sometime during double-blind but did not know the exact date. The patient had a history of chronic cough. The patient was treated with 10/12.5 quinapril/HCTZ during open-label for 231 days before therapy was discontinued and the patient was withdrawn from the study. The investigator indicated that this event was related to study medication.

49. Palpitation, Insomnia

Patient 4 (Study 906-241X, Center 12), a 54-year-old woman with hypertension, had been treated with quinapril/HCTZ (2.5/6.25) when she experienced palpitation and insomnia on Day 10. Quinapril/HCTZ therapy was discontinued on Day 14 and the patient was withdrawn from the study. The investigator indicated that these events were related to quinapril/HCTZ therapy.

50. Breast Cancer

Patient 14 (Study 906-241X, Center 12), a 50-year-old woman with hypertension, had been treated with quinapril/HCTZ (20/25) for 132 days when she presented with breast cancer on Day 132. Quinapril/HCTZ treatment was discontinued and the patient was withdrawn from the study on Day 182. The patient recovered following treatment. The investigator indicated that this event was not related to quinapril/HCTZ therapy.

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51. Coughing

Patient 18 (Study 906-241X, Center 12), a 50-year-old woman with hypertension, had been treated with quinapril/HCTZ (20/25) when she experienced coughing on Day 235. Quinapril/HCTZ therapy was discontinued on Day 366 and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

Death[b], Bone Neoplasm, Back Pain, Nausea/Vomiting, Vertigo, Elevated LDH

Patient 19 (906-241X, Center 12), a 60-year-old man with hypertension, had been treated with quinapril/HCTZ (40/50) when he experienced vertigo, back pain and nausea/vomiting, and elevated LDH on Days 58, 111, and 120, respectively. Two months after the patient left the study the patient died. The diagnosis was a malignant neoplasm of the bone as a result of metastases. The primary tumor was not found. The investigator indicated that the patient had been in generally poor health for the 2 months poststudy and stated that these events were not related to quinapril/HCTZ therapy.

[b] Narrative first reported in Second Safety Update, Section 4.1.

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Case Histories of Withdrawals Due to Adverse Events

52. Headache, Angina Pectoris, Nausea/Vomiting

Patient 21 (Study 906-241X, Center 12), a 41-year-old woman with hypertension, had been treated with quinapril/HCTZ (40/50) when she experienced nausea/vomiting and angina on Days 61 and 62, respectively. She also experienced headache while on placebo on Day 27 of the double-blind phase of the study which continued into the open-label phase. The patient had been taking doxycycline for sinusitis. Quinapril/HCTZ therapy was discontinued on Day 85 and the patient was withdrawn from the study. The investigator indicated that these events were related to quinapril/HCTZ therapy.

53. Coughing

Patient 23 (Study 906-241X, Center 12), a 48-year-old man with hypertension, had been treated with quinapril/HCTZ (40/50) when he experienced coughing on Day 89. Quinapril/HCTZ therapy was discontinued on Day 354 and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

54. Angina Pectoris

Patient 29 (Study 906-241, Center 12), a 42-year-old man with hypertension, had been treated with quinapril/HCTZ (40/12.5) when he experienced angina on Day 2. No prior history of angina was reported. Quinapril/HCTZ therapy was discontinued on Day 3 and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

55. Facial Paralysis

Patient 31 (Study 906-241, Center 12), a 41-year-old woman with hypertension, experienced an episode of facial paralysis after the first dose of quinapril/HCTZ (10/12.5). The patient had reported a cold (viral infection) during the placebo baseline period of the study. Quinapril/HCTZ therapy was discontinued and the patient was withdrawn from the study on Day 8. The investigator indicated that this event was unlikely due to quinapril/HCTZ therapy, but rather to possible Bell's Palsy.

56. Neoplasm, General

Patient 4 (Study 906-241X, Center 14), a 62-year-old man with hypertension, had been treated with open-label quinapril/HCTZ (10/12.5) when he presented with a general neoplasm on Day 178. The patient has a history of gastric ulcer (1982) and also of a cholecystectomy. Quinapril/HCTZ treatment was discontinued and the patient was withdrawn from the study on Day 240. The patient recovered. The investigator indicated that this event was definitely not related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

57. Fracture

Patient 6 (Study 906-241, Center 14), a 48-year-old woman with hypertension, had been treated in the double-blind phase with quinapril/HCTZ (2.5/25) when she fell and fractured her lower leg on Day 45. There was no indication of hypotension or fainting. Quinapril/HCTZ therapy was discontinued and the patient withdrawn from the study the same day. The investigator indicated that this event was not related to quinapril/HCTZ therapy.

58. Bronchitis

Patient 16 (Study 906-241X, Center 16), a 55-year-old woman with hypertension, had been treated with quinapril/HCTZ (20/25) when she experienced bronchitis on Day 248. The patient did not report a history of asthma or bronchitis, or chronic obstructive pulmonary disease. Quinapril/HCTZ therapy was discontinued on Day 392 and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

59. Fatigue, Nausea/Vomiting, Myalgia, Rhinitis, Constipation

Patient 10 (Study 906-241X, Center 17), a 69-year-old woman with hypertension, had been treated with quinapril/HCTZ (10/12.5) when she experienced fatigue, nausea/vomiting, myalgia, rhinitis, and constipation on Day 60. Quinapril/HCTZ therapy was discontinued on Day 84 and the patient was withdrawn from the study. The investigator indicated that these events were related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

60. Coughing

Patient 15 (Study 906-241, Center 17), a 62-year-old man with hypertension, had been treated with quinapril/HCTZ (2.5/12.5) when he experienced coughing on Day 31. The dose of quinapril/HCTZ increased to 10/12.5 but therapy was discontinued on Day 67 and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

61. Chest Pain

Patient 24 (Study 906-241, Center 22), a 51-year-old man with hypertension, had been treated with quinapril/HCTZ (40/6.25) when he experienced chest pain on Day 2 (double-blind). No prior history of chest pain was reported. Quinapril/HCTZ therapy was discontinued on Day 5 and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

62. Tachycardia, Dizziness, Somnolence, Increased Sweating

Patient 4 (Study 906-241, Center 23), a 49-year-old man with hypertension, had been treated with quinapril/HCTZ (40/25) when he experienced tachycardia, dizziness, somnolence, and increased sweating on Day 6. Quinapril/HCTZ therapy was discontinued on Day 19 and the patient was withdrawn from the study. The investigator indicated that these events were related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

63. Hypotension

Patient 10 (Study 906-241X, Center 24), a 50-year-old man, was treated with quinapril/HCTZ (10/12.5) when he experienced hypotension upon standing on Day 10. Blood pressure measurements were not specified by the investigator. Therapy was discontinued and the patient recovered but was withdrawn from the study the same day. The investigator indicated that this event was definitely related to the quinapril/HCTZ therapy.

64. Impotence

Patient 10 (Study 906-241X, Center 25), a 51-year-old man with hypertension, had been treated with quinapril/HCTZ (40/50) when he experienced impotence on Day 146. Quinapril/HCTZ therapy was discontinued on Day 308 and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

65. Hypotension

Patient 8 (Study 906-241, Center 27), a 59-year-old man with hypertension, had been treated with quinapril/HCTZ (40/12.5) when he experienced postural dizziness (hypotension) on Day 10. The patient had been receiving aspirin 250 mg daily for prophylaxis of myocardial infarction occurring 3 years prior to the start of the study. Quinapril/HCTZ therapy was discontinued on Day 32, and the patient was withdrawn from the study. The investigator indicated that the event was related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

66. Nausea and/or Vomiting, Abdominal Pain, Tremor

Patient 14 (Study 906-241, Center 28), a 67-year-old man with hypertension, had been treated with quinapril/HCTZ (2.5/12.5) when he experienced intermittent nausea and/or vomiting, epigastric pain (abdominal pain), and shaking (tremor) on Day 2 of the study. Quinapril/HCTZ therapy was discontinued on Day 3, and the patient was withdrawn from the study. The abdominal pain and tremor resolved on Day 6 and the nausea and vomiting on Day 7. The investigator indicated that these events were related to quinapril/HCTZ therapy.

67. Dizziness

Patient 11 (Study 906-241, Center 31), a 40-year-old woman with hypertension, had been treated with quinapril/HCTZ (10/12.5) when she experienced intermittent dizziness on Day 19. Quinapril/HCTZ therapy was discontinued on Day 28, and the patient was withdrawn from the study. The dizziness subsided by Day 36. The investigator indicated that this event was not related to quinapril/HCTZ therapy.

68. Coughing

Patient 1 (Study 906-241X, Center 34), a 62-year-old man with hypertension, had been treated with quinapril/HCTZ (20/25) when he developed a cough on Day 388. Quinapril/HCTZ therapy was discontinued on Day 419, and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

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69. Urticaria

Patient 13 (Study 906-241X, Center 34), a 53-year-old woman with hypertension, had been treated with quinapril/HCTZ (20/25) when she developed urticaria on Day 132. Quinapril/HCTZ therapy was discontinued on Day 179, and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

70. Asthenia, Nausea and/or Vomiting

Patient 8 (Study 906-241X, Center 35), a 46-year-old woman with hypertension, had been treated with quinapril/HCTZ (20/25) when she developed extreme fatigue (asthenia) and nausea on Day 78. Quinapril/HCTZ therapy was discontinued on Day 89, and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

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71. Polyneuritis, Paresthesia, Myalgia, Asthenia

Patient 12 (Study 906-241X, Center 35), a 49-year-old man with hypertension, had been treated with open-label quinapril/HCTZ (40/50) for 286 days when he experienced asthenia, myalgia, paresthesia, and Guillain-Barre Syndrome (polyneuritis) on Day 325, 248, and 360, respectively. Quinapril/HCTZ treatment was temporarily discontinued. Prior to this diagnosis the patient had experienced several episodes of weakness and paresthesia and had cervical fusion surgery on Day 316. Quinapril/HCTZ treatment was discontinued and the patient was withdrawn on Day 360. The patient had not yet recovered at the time of withdrawal from the study. The investigator indicated that the polyneuritis was definitely not related to quinapril/HCTZ therapy, but instead possibly was idiopathic or a result of the anesthesia used when the patient had the cervical fusion.

72. Hyperlipidemia

Patient 13 (Study 906-241X, Center 35), a 52-year-old man with hypertension, had been treated with quinapril/HCTZ (10/12.5) when he developed elevated triglycerides (hyperlipidemia) on Day 85. Quinapril/HCTZ therapy was discontinued on Day 176, and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

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73. Vasodilatation, Tachycardia, Dizziness, Sinusitis, Amblyopia, Abnormal Thinking

Patient 16 (Study 906-241X, Center 35), a 46-year-old female with hypertension, had been treated with quinapril/HCTZ (10/12.5) when she developed sinusitis on Day 57, flushed feeling (vasodilatation), increased heart rate (tachycardia) and dizziness on Day 59, blurred vision (amblyopia) and difficulty in concentrating (abnormal thinking) on Day 77. Quinapril/HCTZ therapy was discontinued on Day 91, and the patient was withdrawn from the study. The investigator indicated that these events were related to quinapril/HCTZ therapy.

74. Asthenia

Patient 6 (Study 906-247, Center 1) a 64-year-old woman with hypertension, had been treated with quinapril/HCTZ (10/25) when she became weak (asthenia) on Day 36 of open-label. Quinapril/HCTZ therapy was discontinued on Day 56, and the patient withdrew herself from the study. The investigator considered the event to be possibly related to quinapril/HCTZ therapy.

75. Coughing

Patient 21 (Study 906-253, Center 1) a 45-year-old woman with hypertension, had been treated with quinapril/HCTZ (40/25) when she reported persistent coughing on Day 56. Quinapril/HCTZ therapy was discontinued on Day 89, and the patient was withdrawn from the study. The investigator indicated that this event was related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

76. Anxiety, impotence

Patient 12 (Study 906-327, Center 9), a 46-year-old man with hypertension had been treated with quinapril/HCTZ (40/25) when he reported anxiety on Day 95 of open label. Impotence was also reported, but was noted prior to the start of the study. Concomitant medications included diazepam, acetaminophen, and nasal aid spray. Quinapril/HCTZ therapy was discontinued on Day 125, and the patient was withdrawn from the study. The investigator indicated that these events were not related to quinapril/HCTZ therapy.

77. Paresthesia, Elevated Creatinine, Elevated BUN, Elevated Uric Acid

Patient 1 (Study 906-286 [I9-033-2], Center 211) a 49-year-old man with hypertension, and a history of hyperuricemia, and renal insufficiency, had been treated with quinapril/HCTZ (40/25) when he developed paresthesia on Day 57. He experienced further increases in creatinine, BUN, and uric acid above elevated or upper normal range levels at baseline. (Baseline and final study values for creatinine, BUN, and uric acid were 97 μmol/L and 133 μmol/L; 6.5 mmol/L and 12 mmol/L; 470 μmol/L and 510 μmol/L, respectively.) Quinapril/HCTZ therapy was discontinued on Day 92, and the patient was withdrawn from the study. The investigator indicated that these events were related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

78. Coughing

Patient 51 (Study 906-287 [9-007], Center 7), a 40-year-old woman with hypertension, had been treated with quinapril/HCTZ (20/25) when she developed a dry cough on Day 148. Quinapril/HCTZ therapy was discontinued on Day 163, and the patient was withdrawn from the study due to lack of efficacy. The investigator indicated that the attributability of the event to quinapril/HCTZ therapy was unknown.

79. Hematemesis, Nausea and/or Vomiting, Abdominal Pain, Paresthesia, Myalgia

Patient 4 (Study 906-141 [9-030], Center 162), a 24-year-old man with hypertension, had been treated with double-blind quinapril/HCTZ (10/25) when he experienced hematemesis, nausea/vomiting, abdominal pain, and paresthesia on Day 8. Quinapril/HCTZ therapy was discontinued and the patient was withdrawn from the study. The investigator indicated that these events were related to quinapril/HCTZ therapy.

80. Asthenia, Headache, Vasodilatation, Somnolence

Patient 9 (Study 906-141 [9-030], Center 166), a 65-year-old woman with hypertension, had been treated with quinapril/HCTZ (10/25) when she developed asthenia, headache, vasodilatation (flushing), and sedation (somnolence) on Day 9. Quinapril/HCTZ therapy was discontinued on Day 13, and the patient was withdrawn from the study. The investigator considered these events to be related to quinapril/HCTZ therapy.

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Case Histories of Withdrawals Due to Adverse Events

81. Headache, Coughing

Patient 10 (Study 906-141 [9-030], Center 192), a 56-year-old man with hypertension and a history of smoking, had been treated with quinapril/HCTZ (40/25) when he experienced a headache and coughing on Day 22. Prior to the start of the study, the patient was receiving diphenhydramine with codeine for a dry cough. Quinapril/HCTZ therapy was discontinued on Day 34, and the patient was withdrawn from the study. The investigator considered these events related to quinapril/HCTZ therapy.

82. Headache, Dizziness, Amblyopia

Patient 13 (Study 906-141 [9-030], Center 192), a 45-year-old woman with hypertension, had been treated with quinapril/HCTZ (20/25) when she developed headache, dizziness, and blurred vision (amblyopia) on Day 26. Physical examination showed a change from Grade I retinopathy at screening to Grade II at end of therapy. Quinapril/HCTZ therapy was discontinued on Day 42, and the patient was withdrawn from the study. The investigator indicated these events were related to quinapril/HCTZ therapy.

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83. Headache

Patient 1 (Study 906-141 [9-030], Center 197), a 47-year-old man with hypertension, had been treated with quinapril/HCTZ (10/25) when he experienced a mild headache on Day 1. The patient reported having headaches prior to the start of the study. Quinapril/HCTZ therapy was discontinued on Day 41, and the patient was withdrawn from the study. The investigator indicated that this event was not related to quinapril/HCTZ therapy.

Bongiovanni

MAY 13

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

NDA: 20- 125

SPONSOR: PARKE- DAVIS

DRUG: QUINAPRIL/HCTZ (ACCURETIC)

INDICATION: HYPERTENSION

DATE SUBMISSION: 4- 24-91

DATE REVIEW: 5- 10- 91

REVIEWER: Philip Dern M.D. PJD

RESUME:

The Sponsor provides an updated safety review ("First Safety Update") covering the period since the NDA submission to 1- 4- 91 and, for serious ADEs, to 4- 1- 91.

No deaths are reported for the interval to 4- 1- 91. Three, non-fatal, serious ADEs are listed (breast cancer, stroke, and "secondary" (second degree?) heart block.

The update provides information on N= 1548 cases whereas the NDA had 1452 cases. Examination of the distribution of the less serious ADEs showed only minor alteration in rates as compared to those for the NDA. One subject withdrew as a result of impotence and anxiety (for the period since the NDA cutoff).

cc Original
HFD- 110
HFD- 110/CSO ✓
HFD- 110/PLD