TABLE 8.4.5.3.2c
TREATMENT EMERGENT ADVERSE EVENTS THAT RESULTED IN DISCONTINUATION
OF 2 OR MORE TOTAL CS-866 PLUS HCTZ TREATED PATIENTS
ALL CLINICAL TRIALS IN PATIENTS

BODY SYSTEM AE PREFERRED TERM	TOTAL PLACEBO ALONE (N = 342) N (%)	TOTAL HCTZ ALONE (N = 188) N (%)	TOTAL CS-866 ALONE (N = 1888) N (%)	TOTAL CS-866 + HCTZ (N = 1243) N (%)
NO AE	335 (98.0%)	181 (96.3%)	1827 (96.8%)	1218 (98.0%)
AT LEAST ONE AE	7 (2.0%)	7 (3.7%)	61 (3.2%)	25 (2.0%)
BODY AS A WHOLE - GENERAL DISORDERS TOTAL	2 (0.6%)	2 (1.1%)	4 (0.2%)	3 (0.2%)
SYNCOPE	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
CARDIOVASCULAR DISORDERS, GENERAL TOTAL	0 (0.0%)	0 (0.0%)	4 (0.2%)	4 (0.3%)
HYPERTENSION AGGRAVATED	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
HYPOTENSION	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
CENTR & PERIPH NERVOUS SYSTEM DISORDERS TOTAL	0 (0.0%)	0 (0.0%)	11 (0.6%)	5 (0.4%)
DIZZINESS	0 (0.0%)	0 (0.0%)	7 (0.4%)	4 (0.3%)
LIVER AND BILIARY SYSTEM DISORDERS TOTAL	0 (0.0%)	1 (0.5%)	3 (0.2%)	3 (0.2%)
GAMMA-GT INCREASED	0 (0.0%)	1 (0.5%)	2 (0.1%)	3 (0.2%)
SGPT INCREASED	0 (0.0%)	1 (0.5%)	1 (0.1%)	3 (0.2%)
SGOT INCREASED	0 (0.0%)	1 (0.5%)	1 (0.1%)	2 (0.2%)
METABOLIC AND NUTRITIONAL DISORDERS TOTAL	0 (0.0%)	1 (0.5%)	3 (0.2%)	3 (0.2%)
HYPERURICAEMIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)

SOURCE: TABLE 66

Overall, the rate of discontinuation for an adverse event in the combination group (2.0%) was identical to the rate for the placebo group. The most common events resulting in discontinuation in the combination group that had a higher rate than the placebo group were dizziness (0.3%), syncope (0.2%), aggravated hypertension (0.2%), hypotension (0.2%), increased gamma GT, SGOT/SGPT, and hyperuricemia (0.2% each).

5.3 Serious adverse events

In the first year cohort group, there were 13 (1.2%) patients in the combination group who reported at least 1 serious adverse event. The incidence rates for placebo, hct monotherapy, and olmesartan monotherapy and were 1.5%, 1.6%, and 2.5%, respectively. No individual event was reported by more than 1 patient in the combination group.

In the second year cohort group, there were 3 (2.2%) patients in the combination group who reported at least 1 serious adverse event. The incidence rates for placebo were 14.8%, hct monotherapy 10.7%, and 3.5% olmesartan monotherapy. No individual event was reported by more than 1 patient in the combination group.

In the all clinical trials combined, there were 18 (1.4%) patients in the combination group who reported at least one serious adverse event. This is similar to the incidence rates for the placebo group (2.6%), hct monotherapy (3.2%), and olmesartan monotherapy (2.9%). The events that were reported by more than 1

combination patient included surgical intervention and renal calculus (2 patients, 0.2% for both events with placebo rates being 0%).

There were 6 patients with reports of serious adverse events that resulted in IND safety reports. These patients are described in the table below.

Table 8.4.5.4a: Serious Adverse Events that Resulted in IND Safety Reports All Studies

Study #	Drug Regimen	AE #	Rand. #	Preferred Term	Drug Relation	FDA Serial #	Initial Report Date
866-305	CS-866 20 mg QD	018	2619	Pancreatitis	Remote	068	Aug 12, 1998
866-306	CS-866 20 mg QD	006	3246	Cerebrovascular Disorder	Possible	049	Feb 3, 1998
866-321	CS-866 20 mg QD plus HCTZ 12.5 mg QD	001	8207	Transient Ischemic Attack	Possible	137	Oct 2, 2000
SE-866/10-01	Placebo and HCTZ 12.5 mg QD	005	0162	GI Neoplasm Malignant	Possible	093	May 26, 1999
SE-866/19	CS-866 20 mg QD plus HCTZ 25 mg QD	005	093	Death Myocardial Infarction Post Study Drug	Possible	080	Nov 2, 1998
SE-866/19	CS-866 20 mg QD	011	0291	Migraine Cerebrovascular Disorder	Possible	092	Apr 26, 1999
SE-866 CMB/02	Blinded	005	0374	Inflicted Injury	Possible	143	Dec 19, 2000
ST-866/146-006	CS-866 10 mg QD plus Amlodipine 5 mg QD	001	T-1	Hepatic Function Abnormal	Possible	136	Sep 1, 2000

This is a diverse list of adverse events that are not unexpected in a hypertensive population. The 2 patients receiving combination therapy in the above list reported experiencing a TIA (20/12.5 dose) and MI (20/25 dose).

6.0 All adverse events

In the first year cohort group, the reporting of adverse events during the first year of treatment was 65.2% for the combination group (average exposure time 4.8 months) compared to 56.4% for the placebo group (average exposure time 3.5 months), 54.1% for the hct monotherapy group and 60.7% for olmesartan monotherapy group.

Body systems that had at least 10% of patients in the combination group reporting adverse events (and at least 1% of combination patients reporting a particular adverse event in the system) are shown below.

Table 8.4.5.2.2a: ADVERSE EVENTS[a] IN MOST FREQUENTLY AFFECTED BODY SYSTEMS[b] LONG-TERM COHORT -- FIRST YEAR

BODY SYSTEM / AE PREFERRED TERM	TOTAL PLACEBO ALONE (N = 342) N (%)	TOTAL HCTZ ALONE (N = 185) N (%)	TOTAL CS-866 ALONE (N = 1888) N (%)	TOTAL CS-866 + HCTZ (N = 1063) N (%)
NO AE	149 (43.6%)	85 (45.9%)	742 (39.3%)	370 (34.8%)
AT LEAST ONE AE	193 (56.4%)	100 (54.1%)	1146 (60.7%)	693 (65.2%)
RESPIRATORY SYSTEM DISORDERS				
TOTAL	63 (18.4%)	27 (14.6%)	395 (20.9%)	228 (21.4%)
UPPER RESP TRACT INFECTION	26 (7.6%)	11 (5.9%)	135 (7.2%)	92 (8.7%)
BRONCHITIS	14 (4.1%)	7 (3.8%)	90 (4.8%)	43 (4.0%)
SINUSITIS	11 (3.2%)	4 (2.2%)	48 (2.5%)	34 (3.2%)
RHINITIS	10 (2.9%)	4 (2.2%)	78 (4.1%)	31 (2.9%)
COUGHING	4 (1.2%)	1 (0.5%)	43 (2.3%)	29 (2.7%)
PHARYNGITIS	5 (1.5%)	2 (1.1%)	43 (2.3%)	23 (2.2%)
BODY AS A WHOLE - GENERAL DISORDERS				
TOTAL	48 (14.0%)	30 (16.2%)	342 (18.1%)	197 (18.5%)
BACK PAIN	12 (3.5%)	8 (4.3%)	98 (5.2%)	54 (5.1%)
INFLUENZA-LIKE SYMPTOMS	7 (2.0%)	6 (3.2%)	83 (4.4%)	40 (3.8%)
FATIGUE	4 (1.2%)	1 (0.5%)	36 (1.9%)	35 (3.3%)
CHEST PAIN	6 (1.8%)	5 (2.7%)	37 (2.0%)	19 (1.8%)
OEDEMA PERIPHERAL	9 (2.6%)	1 (0.5%)	39 (2.1%)	18 (1.7%)
PAIN	3 (0.9%)	5 (2.7%)	34 (1.8%)	17 (1.6%)
CENTR & PERIPH NERVOUS SYSTEM DISORDERS				
TOTAL	44 (12.9%)	29 (15.7%)	274 (14.5%)	161 (15.1%)
HEADACHE	29 (8.5%)	14 (7.6%)	139 (7.4%)	66 (6.2%)
DIZZINESS	6 (1.8%)	9 (4.9%)	84 (4.4%)	59 (5.6%)
METABOLIC AND NUTRITIONAL DISORDERS				
TOTAL	33 (9.6%)	24 (13.0%)	149 (7.9%)	140 (13.2%)
HYPERURICAEMIA	6 (1.8%)	5 (2.7%)	20 (1.1%)	37 (3.5%)
HYPERGLYCAEMIA	11 (3.2%)	4 (2.2%)	22 (1.2%)	27 (2.5%)
CREATINE PHOSPHOKINASE INCREASED	6 (1.8%)	6 (3.2%)	30 (1.6%)	19 (1.8%)
HYPERLIPAEMIA	0 (0.0%)	1 (0.5%)	13 (0.7%)	14 (1.3%)
GASTRO-INTESTINAL SYSTEM DISORDERS				
TOTAL	30 (8.8%)	11 (5.9%)	228 (12.1%)	129 (12.1%)
DIARRHOEA	5 (1.5%)	3 (1.6%)	52 (2.8%)	25 (2.4%)
NAUSEA	4 (1.2%)	1 (0.5%)	35 (1.9%)	22 (2.1%)
ABDOMINAL PAIN	4 (1.2%)	1 (0.5%)	31 (1.6%)	17 (1.6%)
DYSPEPSIA	5 (1.5%)	6 (3.2%)	36 (1.9%)	15 (1.4%)
VOMITING	1 (0.3%)	1 (0.5%)	13 (0.7%)	13 (1.2%)
GASTROENTERITIS	2 (0.6%)	0 (0.0%)	28 (1.5%)	12 (1.1%)

Source: Table 24

[a] ADVERSE EVENTS REPORTED IN >1% OF PATIENTS IN THE TOTAL CS-866 PLUS HCTZ TREATMENT GROUP.

[b] BODY SYSTEMS IN WHICH 10% OR MORE OF PATIENTS IN THE TOTAL CS-866 PLUS HCTZ TREATMENT GROUP EXPERIENCED EVENTS, AND IN WHICH AT LEAST ONE EVENT WAS REPORTED IN >1% OF PATIENTS IN THIS SAME GROUP.

The events from the above list that had a higher reporting rate in the combination group compared to the other groups included dizziness (3.8% placebo subtracted), fatigue (2.1%), hyperuricemia (1.7%), coughing (1.5%), hyperlipidemia (1.3%), URI (1.1%), nausea (0.9%), and vomiting (0.9%). The events reported by the combination group that had a comparison with the placebo group that resulted in a p value< 0.05 included fatigue, dizziness, and hyperlipidemia.

Adverse events reported more frequently by the combination group compared to olmesartan monotherapy included fatigue (1.4% olmesartan monotherapy subtracted), hyperuricemia (2.4%), and hyperglycemia (1.3%).

In the second year cohort group, selected events that were reported only during the second year of treatment are shown in the table below.

Table 8.4.5.2.2d ADVERSE EVENTS[a] IN MOST FREQUENTLY AFFECTED BODY SYSTEMS[b]
LONG-TERM COHORT -- SECOND YEAR

BODY SYSTEM AE PREFERRED TERM	TOTAL PLACEBO ALONE (N = 27)	TOTAL HCTZ ALONE (N = 28)	TOTAL CS-866 ALONE (N = 289)	TOTAL CS-866 + HCTZ (N = 134)
	N (%)	N (%)	N (%)	N (%)
NO AE	7 (25.9%)	13 (46.4%)	131 (45.3%)	43 (32.1%)
AT LEAST ONE AE	20 (74.1%)	15 (53.6%)	158 (54.7%)	91 (67.9%)
BODY AS A WHOLE - GENERAL DISORDERS	7 (25.9%)	5 (17.9%)	54 (18.7%)	27 (20.1%)
BACK PAIN	3 (11.1%)	2 (7.1%)	35 (12.1%)	15 (11.2%)
INFLUENZA-LIKE SYMPTOMS	2 (7.4%)	2 (7.1%)	15 (5.2%)	10 (7.5%)
PAIN	0 (0.0%)	0 (0.0%)	2 (0.7%)	2 (1.5%)
METABOLIC AND NUTRITIONAL DISORDERS	4 (14.8%)	4 (14.3%)	21 (7.3%)	14 (10.4%)
HYPERURICAEMIA	0 (0.0%)	0 (0.0%)	8 (2.1%)	6 (4.5%)
HYPERTRIGLYCERIDAEMIA	1 (3.7%)	1 (3.6%)	6 (2.1%)	3 (2.2%)
BUN INCREASED	0 (0.0%)	0 (0.0%)	3 (1.0%)	2 (1.5%)
DIABETES MELLITUS	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.5%)
HYPERGLYCAEMIA	3 (11.1%)	2 (7.1%)	1 (0.3%)	2 (1.5%)
NPN INCREASED	0 (0.0%)	0 (0.0%)	2 (0.7%)	2 (1.5%)
MUSCULO-SKELETAL SYSTEM DISORDERS	2 (7.4%)	4 (14.3%)	20 (6.9%)	14 (10.4%)
ARTHRITIS	0 (0.0%)	0 (0.0%)	4 (1.4%)	5 (3.7%)
ARTHRALGIA	0 (0.0%)	0 (0.0%)	3 (1.0%)	3 (2.2%)
MYALGIA	1 (3.7%)	1 (3.6%)	3 (1.0%)	3 (2.2%)
RESPIRATORY SYSTEM DISORDERS	9 (33.3%)	3 (10.7%)	50 (17.3%)	32 (23.9%)
BRONCHITIS	6 (22.2%)	2 (7.1%)	38 (13.1%)	25 (18.7%)
PHARYNGITIS	1 (3.7%)	1 (3.6%)	9 (3.1%)	4 (3.0%)
COUGHING	0 (0.0%)	0 (0.0%)	1 (0.3%)	2 (1.5%)
LARYNGITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.5%)
SINUSITIS	2 (7.4%)	0 (0.0%)	2 (0.7%)	2 (1.5%)

Source: Table 42
[a]ADVERSE EVENTS REPORTED IN >1% OF PATIENTS IN THE TOTAL CS-866 PLUS HCTZ TREATMENT GROUP.
[b] BODY SYSTEMS IN WHICH 10% OR MORE OF PATIENTS IN THE TOTAL CS-866 PLUS HCTZ TREATMENT GROUP EXPERIENCED EVENTS, AND IN WHICH AT LEAST ONE EVENT WAS REPORTED IN >1% OF PATIENTS IN THIS SAME GROUP.

Events from the above table that were reported more often in the combination group compared to placebo include pain (1.5% placebo subtracted), hyperuricemia (4.5%), BUN increase (1.5%), diabetes (1.5%), NPN increased (1.5%), arthritis (3.7%), arthralgia (2.2%), coughing (1.5%), and laryngitis (1.5%). No comparison with placebo had a p value < 0.05.

Adverse events reported in the second year

The incidence rates of patients who reported an adverse event for the first time during their second year of treatment were 58.2% (78/134) for the combination group. 74.1% (20/27) for the placebo group, 42.9% for the hct monotherapy group (12/28), and 46.0% (133/289). Compared to placebo, the most notable events reported by the combination group were back pain (4.5%, placebo subtracted) and hyperuricemia (4.5%).

The incidence rate of reporting an adverse event for all combination patients was 62.7% (779/1243). This rate is similar to the rates for the placebo (57.0%), hct monotherapy (56.9%), and olmesartan monotherapy (61.9%) with dizziness (3.5%, placebo subtracted), hematuria (2.0%), hyperuricemia (1.7%), being the notable events.

6.1 Selected adverse events

Dizziness
The table below shows the percent of patients reporting dizziness for all clinical trials by randomized dose.

Table 8.4.10a
Dose Response
Percents of Patients with Dizziness
All Clinical Trials

	CS-866 Dose (mg)					
HCTZ Dose (mg)	0	2.5	5	10	20	40
0	N=342 1.8%	N=91 3.3%	N=603 4.1%	N=536 3.2%	N=999 3.6%	N=464 1.9%
12.5	N=145 2.1%	N=51 2.0%	N=115 1.7%	N=136 2.9%	N=489 4.9%	N=301 3.3%
25	N=113 5.3%	N=29 0.0%	N=58 3.4%	N=249 4.0%	N=194 5.2%	N=160 6.9%

Source: Table 65

The group with the highest reporting rate was 40/25 mg; a rate that was higher than the placebo rate (1.8%), but similar to the 25 mg hct monotherapy rate (5.3%).

Hypotension
There were 10 patients (0.8%) receiving the combination who reported hypotension (including 6 who reported postural hypotension). The event rate was identical for the losartan or atenolol combination group. The placebo rate was 0%.

Of the 10 combination patients reporting hypotension, all but 2 completed the study. One patient (40/25 dose) was reported as having a hypotensive episode on day 3 (no blood pressure recordings available). He was discontinued on the same day. The other patient (20/12.5) reported dizziness on day 38. She temporarily stopped study drug, restarted, and again reported dizziness. She permanently discontinued study drug on day 43 because of hypotension.

Syncope
There were 7 patients (0.6%) receiving combination who reported syncope (doses used 2.5/25, 5/12.5/ 40/12.5, 40/25, and 20/12.5 (3 patients). Of these 7, 2 discontinued study drug (1 patient (5/12.5) reported syncope on day 563 and was found to have stenosis of left and right external carotid arteries; the second patient (40/25) reported syncope on day 37 and recovered soon after discontinuation.

7.0 Laboratory
In the placebo controlled trial (866-318), there were the expected minor decreases in mean hemoglobin/hematocrit, increases in BUN and uric acid and creatinine, and decreases in potassium and chloride (see discussion of this study for details).

Long term cohort—first year[9]

Hematology

Mean changes from baseline at months 6 and 12 for hematology parameters are shown in the table below.

TABLE 8.4.6.2.2a: MEAN CHANGE FROM BASELINE
HEMATOLOGY VARIABLES FOR WHICH WITHIN GROUP PAIRED T-TEST RESULTED IN P-VALUE <0.05
IN TOTAL CS-866 PLUS HCTZ GROUP
LONG-TERM COHORT -- FIRST YEAR

	CHANGE[1] FROM BASELINE							
VARIABLE	TOTAL PLACEBO ALONE	TOTAL HCTZ ALONE	TOTAL CS-866 ALONE	TOTAL CS-866 +HCTZ	TOTAL CS-866 +HCTZ 12.5 mg	TOTAL CS-866 +HCTZ 25 mg	TOTAL LOSARTAN ALONE	TOTAL LOSARTAN +HCTZ
HEMOGLOBIN (g/Dl)								
MONTH 6	0.0	0.1	-0.3	-0.2	-0.2	-0.3	-0.3	-0.3
MONTH 12	0.0	-0.2	-0.4	-0.3	-0.3	-0.3	-	-
HEMATOCRIT (%)								
MONTH 6	0	1	0	-1	-1	-1	-1	-1
MONTH 12	-1	-1	-1	-1	-1	-2	-	-
RBC (x10^6/μL)								
MONTH 6	0.1	0.1	-0.1	-0.1	-0.1	-0.1	-0.1	-0.1
MONTH 12	0.3	0.3	0.2	0.1	0.1	0.2	-	-
WBC (x10^3/μL)								
MONTH 6	0.0	0.2	0.0	0.1	0.0	0.3	0.0	0.1
MONTH 12	-0.3	0.4	0.1	0.4	0.4	0.3		
EOSINOPHILS (%)								
MONTH 12	-0.2	-0.2	-0.1	-0.3	-0.3	-0.3	-	-
BASOPHILS (%)								
MONTH 6	0.0	0.0	0.0	0.1	0.1	0.0	-	-
PLATELETS (x10^3/μL)								
MONTH 6	-5	7	0	11	11	10	0	22
MONTH 12	-5	6	2	5	7	3	-	-

SOURCE: TABLE 85
[1]MEAN VALUE FOR CHANGE
SHADED VALUES INDICATE WITHIN-GROUP PAIRED T-TEST P-VALUE RESULTS OF <0.05.
- SIGNIFIES TEST NOT DONE FOR THIS TREATMENT GROUP

There were decreases in hemoglobin, hematocrit, and red cell count for most groups except placebo. The other parameters appear to be unchanged.

Chemistry

Mean changes from baseline at months 6 and 12 for chemistry parameters are shown in the table below.

[9] The numbers of subjects per treatment group were 47, 62, 494, 303, 186, 117 for placebo, hct monotherapy, olmesartan monotherapy, all combination, combination with 12.5 mg hct, and combination with 25 mg hct, respectively. Not all parameters had the same number of patients.

TABLE 8.4.6.2.2c: MEAN CHANGE FROM BASELINE
CHEMISTRY VARIABLES FOR WHICH WITHIN GROUP PAIRED T-TEST RESULTED IN P-VALU
IN TOTAL CS-866 PLUS HCTZ GROUP
LONG-TERM COHORT -- FIRST YEAR

	CHANGE[1] FROM BASELINE					
VARIABLE	TOTAL PLACEBO ALONE	TOTAL HCTZ ALONE	TOTAL CS-866 ALONE	TOTAL CS-866 +HCTZ	TOTAL CS-866 +HCTZ 12.5 mg	TOTAL CS-866 +HCTZ 25 mg
SGPT (U/L)						
MONTH 6	2	3	-1	2	2	2
MONTH 12	-1	0	1	4	3	6
SGOT (U/L)						
MONTH 6	0	1	-1	1	1	1
MONTH 12	0	1	0	1	1	2
GGT (U/L)						
MONTH 6	7	3	2	3	3	3
MONTH 12	-3	-2	4	6	4	8
UREA NITROGEN (BUN) (mg/dL)						
MONTH 6	1	1	1	2	2	3
MONTH 12	0	0	0	1	1	1
CREATININE (mg/dL)						
MONTH 6	0.01	0.00	0.00	0.03	0.03	0.04
SODIUM (mEq/L)						
MONTH 6	0	0	-1	-1	-1	-1
MONTH 12	0	-1	-1	-1	1	-1
POTASSIUM (mEq/L)						
MONTH 6	-0.2	-0.1	0.1	-0.1	-0.1	-0.1
MONTH 12	0.2	-0.2	0.1	-0.2	-0.2	-0.1
URIC ACID (mg/dL)						
MONTH 6	0.0	0.7	0.2	0.8	0.8	1.0
MONTH 12	-0.2	0.5	0.2	0.6	0.7	0.6
CALCIUM (mg/dL)						
MONTH 6	0.1	0.2	0.1	0.2	0.2	0.2
MONTH 12	0.2	0.1	0.1	0.2	0.1	0.2
CHLORIDE (mEq/L)						
MONTH 6	-1	-3	-2	-2	-2	-3
MONTH 12	-2	-4	-2	-3	-3	-4
CHOLESTEROL (mg/dL)						
MONTH 6	1	12	3	7	5	10
MONTH 12	6	8	5	7	5	9
TRIGLYCERIDES (mg/dL)						
MONTH 6	-12	29	8	35	27	47
HDL (mg/dL)						
MONTH 6	0	-1	-1	-2	-2	-2
MONTH 12	1	0	-2	-3	-3	-3
LDL (mg/dL)						
MONTH 6	2	1	1	3	1	5
MONTH 12	3	-4	1	5	5	5

There were minor increases in GGT and SGPT in the combination group compared to the other groups, but less so for SGPT. There were minor increases in BUN and creatinine. Sodium and potassium values tended to decrease for the combination as did chloride. Uric acid tended to rise as did calcium. All of these changes with the exception of uric acid were minor.

Compared to placebo, cholesterol, triglycerides, and LDL were elevated in the combination group, and there were declines in HDL.

Urinalysis

There were more patients with normal baseline urine and increased urine blood at endpoint in the combination groups (8.8% for omlesartan/12.5, and 11.4% for omlesartan/25) compared to placebo (4.3%).

Long term cohort—second year

Hematology

Mean change from baseline at 18 months for selected hematology parameters are shown below by treatment group.

TABLE 8.4.6.2.2h: MEAN CHANGE FROM BASELINE
HEMATOLOGY VARIABLES FOR WHICH WITHIN GROUP PAIRED T-TEST RESULTED IN P-VALUE <0.05
IN TOTAL CS-866 PLUS HCTZ GROUP
LONG-TERM COHORT -- SECOND YEAR

	CHANGE[1] FROM BASELINE					
VARIABLE	TOTAL PLACEBO ALONE	TOTAL HCTZ ALONE	TOTAL CS-866 ALONE	TOTAL CS-866 +HCTZ	TOTAL CS-866 +HCTZ 12.5 mg	TOTAL CS-866 +HCTZ 25 mg
HEMOGLOBIN (g/dL)						
MONTH 18	-0.3	-0.7	-0.3	-0.3	-0.2	-0.3
HEMATOCRIT (%)						
MONTH 18	-2	-3	-2	-1	-1	-2
RBC (x10^6/μL)						
MONTH 18	0.6	0.5	0.6	0.5	0.6	0.5
MONTH 24	0.6	0.5	0.6	0.5	0.5	0.6

SOURCE: TABLE 97.
[1]MEAN VALUE FOR CHANGE
SHADED VALUES INDICATE WITHIN-GROUP PAIRED T-TEST P-VALUE RESULTS OF <0.05.

There was little difference between treatment groups in hematology, although hct alone had the largest decrease in hemoglobin and hematocrit.

Chemistry

Mean changes from baseline at month 18 are shown below by treatment group.

TABLE 8.4.6.2.2j: MEAN CHANGE FROM BASELINE
CHEMISTRY VARIABLES FOR WHICH WITHIN GROUP PAIRED T-TEST RESULTED IN P-VALUE <0.05
IN TOTAL CS-866 PLUS HCTZ GROUP
LONG-TERM COHORT -- SECOND YEAR

	CHANGE[1] FROM BASELINE					
VARIABLE	TOTAL PLACEBO ALONE	TOTAL HCTZ ALONE	TOTAL CS-866 ALONE	TOTAL CS-866 +HCTZ	TOTAL CS-866 +HCTZ 12.5 mg	TOTAL CS-866 +HCTZ 25 mg
SGPT (U/L)						
MONTH 24	1	3	3	4	5	3
SGOT (U/L)						
MONTH 18	0	-1	-1	-1	-2	0
UREA NITROGEN (BUN) (mg/dL)						
MONTH 18	0	0	0	1	1	2
MONTH 24	1	0	0	1	0	2
SERUM GLUCOSE (mg/dL)						
MONTH 18	-11	2	5	7	5	10
MONTH 24	-16	-10	8	11	12	9
URIC ACID (mg/dL)						
MONTH 18	-0.1	-0.2	-0.1	0.4	0.1	0.8
CALCIUM (mg/dL)						
MONTH 18	0.3	0.1	0.1	0.2	0.2	0.2
MONTH 24	0.2	0.2	0.2	0.3	0.2	0.4
SODIUM (mEq/L)						
MONTH 24	1	0	0	1	0	1
CHOLESTEROL (mg/dL)						
MONTH 24	0	10	7	12	17	3
TRIGLYCERIDES (mg/dL)						
MONTH 24	-17	24	9	26	35	13

SOURCE: TABLE 9B
[1]MEAN VALUE FOR CHANGE
SHADED VALUES INDICATE WITHIN-GROUP PAIRED T-TEST P-VALUE RESULTS OF <0.05.

The most striking differences between placebo and the combination groups were for glucose, uric acid, cholesterol and triglycerides. For the most part, however, the changes for the combination groups were similar to those for hct alone.

More patients in the combination groups had increases in total protein, cholesterol, triglycerides, and/or glucose compared to placebo group but similar to the hct monotherapy group.

7.1 Selected laboratory parameters

Liver function

Elevated LFTs: Of the 1243 patients who received the combination, 12 (0.97%) had SGOT or SGOT values >3xULN or 3X baseline value if baseline was above normal. This compares to 2 (0.58%) for the placebo group, 1 (0.53%) for the hct monotherapy, and 9 (0.48%) for the olmesartan monotherapy.[10]

[10] from table 8.4.7.1a

Examining the 12 combination patients, there were 7 with elevated enzymes at baseline, 4 had transient increases during the study, 3 had history of alcohol use, 1 had received anesthesia, and 2 had received HMG-CoA reductase inhibitors.

Discontinuations: there were 7 patients who discontinued study drug because of abnormal hepatic function. Three received the combination, 3 received olmesartan monotherapy, 1 received hct monotherapy. All 3 combination patients had elevated enzymes at baseline. One patient was suspected of alcohol use and another had a viral infection (with reports of diarrhea and vomiting) and the third had enzyme elevations at baseline and was taking ibuprofen, cortisone injections and Nyquil.

Renal function

With the placebo controlled trials, there were increases in serum creatinine of 0.02 and 0.08 mg/dl for combination groups with 12.5 mg hct and 25 mg hct, respectively (placebo was –0.01 mg/dl and hct monotherapy was 0.03 mg/dl). Small elevations in creatinine were also seen in the higher hct combination group at 18 and 24 months of treatment. There were 2 patients in the combination with 25 mg hct group with a marked abnormality, but no patient was discontinued for elevations in serum creatinine.

With the placebo controlled trials, there were also larger mean increases in BUN (2 – 3 mg/dl) compared to placebo (1 mg/dl), but similar to hct monotherapy (2 mg dl). There were no discontinuations for elevations in BUN.

Hyperuricemia

Table 8.4.10b
Dose Response
Percents of Patients with Adverse Events of Hyperuricemia
All Clinical Trials

	CS-866 Dose (mg)					
HCTZ Dose (mg)	0	2.5	5	10	20	40
0	N=342 1.8%	N=91 1.1%	N=603 1.2%	N=536 1.1%	N=999 1.2%	N=464 0.2%
12.5	N=145 2.1%	N=51 3.9%	N=115 2.6%	N=136 5.9%	N=489 3.7%	N=301 1.0%
25	N=113 3.5%	N=29 6.9%	N=58 6.9%	N=249 2.8%	N=194 3.6%	N=160 3.1%

Source: Table 65

The reporting rates for elevated uric acid levels are higher in the combination groups compared to placebo and olmesartan monotherapy groups. While the largest reporting rates for the combination tended to reflect the rates for the hct monotherapy groups (and the higher rates were associated with the higher dose of hct), there is no evidence of association with higher doses of olmesartan.

Drug-drug interactions

8.0 Drug-demographic interactions
There were no studies specifically designed to investigate a drug-age, drug-gender, or drug-race interaction.

Age
An adverse events review, limited to dizziness, hyperuricemia, and hypotension (including postural), was based on age (< 65 years and ≥ 65 years).

	< 65 years			≥ 65 years		
Event	Total placebo alone N=269	Total combo N=878	% Pl subtracted	Total placebo alone N=73	Total combo N=185	Pl subtracted
dizziness	4 (1.5)	51 (5.8)	4.3	2 (2.7)	8 (4.3)	1.6
hyperuricemia	4 (1.5)	28 (3.2)	1.7	2 (2.7)	9 (4.9)	2.2
hypotension	0	9 (1.0)	1.0	0	1 (0.5)	0.5

From tables 31A and 31 B

The above table gives some reassurance that older patients are not more susceptible to dizziness, hyperuricemia, or hypotension compared to younger patients.

Gender

	males			females		
Event	Total placebo alone N=209	Total combo N=597	% Pl subtracted	Total placebo alone N=133	Total combo N=466	Pl subtracted
Hyperuricemia	6 (2.9)	28 (4.7)	1.8	0	9 (1.9)	1.9

From tables 32A and 32B

Of the commonly occurring adverse events, only hyperuricemia was reported >1% more often by one or the other gender. There is no difference between the placebo subtracted rates.

Race
There are no data indicating that one race (black versus non black) taking the combination is more susceptible to a particular adverse event compared to the same race taking placebo.

9.0 Clinical pharmacology
All clinical pharmacology studies were randomized, open-label, crossover with healthy volunteers.

Study	Type	Number of subjects	Dose olme/hct	Safety reports
SE-866CMB/01	Dose tolerance	24	20/25	no reported deaths; one withdrawal because of an adverse event (fracture of nasal bone requiring hospitalization); no other reported serious adverse events.
866-126	Bioavailability	33	20/12.5	no reported deaths; one withdrawal because of an adverse event (dizziness, vomiting, nausea, heartburn, headache); no other reported serious adverse events
866-127	Bioavailability, dose proportionality	18	10-40/12.5	no reported deaths, serious adverse events, or adverse events leading to withdrawal.
866-134	Bioequivalence	30	Hct 12.5	no reported deaths, serious adverse events, or adverse events leading to withdrawal.

10.0 Longterm safety
Adverse events that were reported for the first time in an individual subject during the second year were examined.

Events reported by more than 3 combination patients and the reporting rate was higher in the combination group compared to the placebo group are shown below.

No. and (percent) of patients reporting an adverse event

Event	Placebo N=27	Hct monotherapy N=28	Olm monotherapy N=289	Combination N=134
At least 1 report	20 (74.1)	12 (42.9)	133 (46.0)	78 (58.2)
hyperuricemia	0	0	4 (1.4)	6 (4.5)
Back pain	1 (3.7)	2 (7.1)	19 (6.6)	11 (8.2)
Arthritis	0	0	3 (1.0)	4 (3.0)

The incidence rate for reporting an adverse event for the first time during the second year of therapy was higher for the placebo group (74.1%) compared to combination group (58.2%). The sample sizes were different so the relevance of this is unknown. Of the selected individual adverse events, hyperuricemia and back pain had the highest placebo subtracted reporting rate (4.5% each). While the relationship of combination therapy to back pain is unknown, the link between combination and hyperuricemia is well established.

11.0 Withdrawal effects

The sponsor added a placebo period to the beginning of study 10-01 (the extension to study 10) to investigate the potential effects of abrupt withdrawal of olmesartan therapy (doses 5, 10, 20mg), with or without hct, compared to placebo. All willing patients who completed study 10 with a mean sitting diastolic blood pressure $\leq$ 90 mmHg were given placebo for 2 weeks.

The table below shows the number of patients with blood pressure and/or heart rate greater than baseline after abrupt withdrawal of olmesartan or placebo followed by 2 weeks of placebo treatment.

Table I: Numbers of patients with blood pressure and pulse rate at visit 2 of study SE-866/10-01 equal to or above baseline values of study SE-866/10 or with AEs suggestive of sympathetic overactivity.

Treatment	5 mg CS-866	10 mg CS-866	20 mg CS-866	Placebo
N	136	134	134	50
Number of patients with sitting dBP ≥ baseline (%)	4 (2.9)	4 (3.0)	7 (5.2)	3 (6.0)
Number of patients with sitting sBP ≥ baseline (%)	31 (22.8)	30 (22.4)	27 (20.1)	10 (20.0)
Number of patients with sitting PR ≥ baseline (%)	67 (49.3)	66 (49.3)	57 (42.5)	21 (42.0)
Number of patients with standing dBP ≥ baseline (%)	14 (10.3)	17 (12.7)	18 (13.4)	8 (16)
Number of patients with AEs suggestive of sympathetic overactivity (EFS Population)	0 (136)	1 (137)	1 (136)	0 (53)

There is no evidence of a rebound effect on blood pressure.

There were no deaths reported during the 2 week placebo treatment period. The one reported serious event was a compression fracture of spinal vertebra. There is no evidence of a withdrawal effect with the combination.

12.0 Safety Update

Safety data from studies that were ongoing as of Jan 1, 2002 consist of serious adverse events reported to the sponsor by that date, and all deaths reported by June 15, 2002. As of January 1, 2002, six studies were ongoing (see section 1.3 of this review for listing of the studies).

Deaths

There were 4 deaths reported from the ongoing studies. One patient (20/25 mg) died of a hemorrhagic stroke. The other 3 deaths (study drug blinded) were attributed to cerebellar hemorrhage, sudden death, and myocardial infarction.

Serious adverse events

There were 31 patients reporting serious adverse events; 29 of the 31 are still blinded to study drug. The reported events include decreased hearing, cerebellar hemorrhage, prostate disorder, surgery (6), traumatic injury (3), lumbar pain, unstable angina, gastritis, chest pain and hypertension, osterochondrosis, varicose vein, tachycardia and ischemic heart disease, Hodgkin's disease, myocardial infarction (2), hematuria and abdominal pain, stroke and hemiparesis (2), malaise, renal colic, stroke, hypertension and angina, hernia, cholelithiasis and pancreatitis, atrial fibrillation, abnormal hepatic function (10 mg olmesartan/5 mg amlodipine, myocardial infarction (10 mg olmesartan).

13.0 Heart Rate

There is no effect on mean sitting heart rate as shown by results from the placebo controlled trial 866-318.

Mean sitting heart rate (bpm)

	0/0 1 (n=42)	0/12.5 (n=35)	10/25@ (n=39)	20/12.5# (n=44)	20/25 (n=46)	40/12.5 (n=42)	40/20 (n=39)
baseline	75.3	74.2	75.1	73.6	73.2	75.2	75.9
LOCF^	74.4	72.1	74.0	73.8	74.0	73.3	73.7
change	-0.9	-2.1	-1.1	0.2	0.8	-1.9	-2.2

^last observation carried forward
@missing 1 subject at endpoint
#missing 2 subjects at endpoint

14.0 ECG abnormalities

ECG abnormalities were reported as treatment emergent adverse events. The table below shows the results from the placebo controlled trial 866-318 (combination groups are combined).

No. and (percent) of patients reporting an abnormality

	placebo (n=42)	HCT only (n=88)	Olme alone (n=125)	combin (n=247)
ECG abnormal	0	0	1 (0.8)	1 (0.4)

There were 2 reports of ECG abnormalities: 1 in the olmesartan monotherapy group and 1 in the combination group.

Safety Update Review

The Safety Update Review was included in Dr. Gordon's medical review of February 28, 2003 (see page 31).

NDA 21-532

Benicar HCT™

Sankyo Pharma Inc.

Monica D. Cooper
Division of Cardio-Renal Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-532

2. REVIEW NUMBER: #2

3. REVIEW DATE: 23-Apr-2003

4. REVIEWER: Monica D. Cooper, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission (000)	05-Aug-2002
Amendment (N000 BC)	05-Sep-2002
Amendment (N000 BC)	22-Jan-2003
Amendment (N000 BC)	10-Mar-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (N000 BC)	28 -Mar-2003
Amendment (N000 BC)	03-Apr-2003
Amendment (N000 BC)	17-Apr-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Sankyo Pharma Inc.
Address:	399 Thornall Street, 11th Floor Edison, New Jersey 08837
Representative:	Albert S. Yehaskel, MS, MBA
Telephone:	732-590-5009

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Benicar HCT™
b) Non-Proprietary Name (USAN): olmesartan medoxomil and hydrochlorothiazide
c) Code Name/# (ONDC only): CS-866HCTZ
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antihypertensive

11. DOSAGE FORM: Film-Coated Immediate Release Tablets

12. STRENGTH/POTENCY: 20/12.5 mg, 40/12.5 mg, and 40/25 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _✔_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

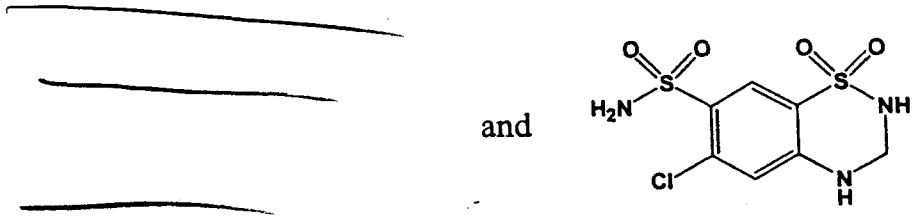
_____SPOTS product – Form Completed

__✔__Not a SPOTS product

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

Olmesartan medoxomil: 2,3-Dihydroxy-2-butenyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[p-(o-1*H*-tetrazole-5-ylphenyl)benzyl]imidazole-5-carboxylate, cyclic 2,3 carbonate

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



and

$C_{29}H_{30}N_6O_6$
558.6

$C_7H_8ClN_3O_4S_2$
297.7

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II	Sankyo Co., Ltd.	Drug Substance, Benicar (olmesartan medoxomil)	1	Adequate	11-Mar-2003 and 31-Mar-2003	Amendments Reviewed by Monica Cooper, Initial by Florian Zelinski
	II			1	Adequate	11-Mar-2003	Annual Update Reviewed by Monica Cooper
	II			3	Adequate	19-Feb-2002	Reviewed by RD' Costa
	II	Sankyo Pharma Inc.	Drug Product, Benicar HCT Tablets	1	Adequate	10-Apr-2003	Reviewed by Monica Cooper
	II	Sankyo Co., Ltd.	Drug Substance, Benicar (olmesartan medoxomil)	7	N/A		production will not be used.
	III			7	N/A		
	III			3	Adequate	26-Sep-2000	Reviewed by Donald N. Klein
	III			3	Adequate	20-Aug-2001 and 06-Aug-2002	Reviewed by Raj Uppoor and Stuart Zimmerman
	III			1	Adequate	18-Dec-2002	Amendments Reviewed by Monica Cooper

Chemistry Review Data Sheet

	III			3	Adequate	14-Jun-2002	Both were Reviewed by Lorenzo Rocca
	III			3	Adequate	24-Apr-2000 and 18-Aug-2000	Reviewed by Xavier Ysern, Reviewed by Raymond Frankewich

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		
NDA	21-286	Benicar™ (approval 25-Apr-2002)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	09-Jan-2003	S. Adams
Pharm/Tox	N/A		
Biopharm	Acceptable	10-Apr-2003	N. Nguyen
LNC	N/A		
Methods Validation	Pending		
DMETS	Acceptable for Proprietary Name "Benicar HCT"	25-Oct-2002	K. Dermanoski
EA	Acceptable (Categorical Exclusion)		
Microbiology	N/A		

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 21-532

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This new drug application (21-532) is recommended for **APPROVAL** ~~from the~~ perspective of chemistry, manufacturing and controls. The applicant and the DMF holders provided responses to our information requests/deficiency letters and these responses were found acceptable.

The overall evaluation from the Office of Compliance for cGMP compliance was ACCEPTABLE. See the attachment at the end of Review #1 for the Establishment Evaluation Report.

The action letter should state – "Based on the provided stability data, the expiration date for Benicar HCT™ tablets packaged in HDPE bottles and Aluminum/Aluminum blisters is 18 months, when stored at 20 – 25°C."

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No Phase 4 Commitments, Agreements, and/or Risk Management Steps have been made.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Benicar HCT™ is a combination drug product consisting of two synthetic drug substances: olmesartan medoxomil and hydrochlorothiazide. Previously, both of these drug substances were approved individually in drug product formulations (see NDA 21-286 for Benicar™/olmesartan medoxomil tablets and see NDA 11-793 for the first approval of hydrochlorothiazide tablets). Olmesartan medoxomil (as Benicar™ tablets) was approved for the treatment of hypertension and is an ester prodrug of olmesartan, an angiotensin II receptor blocker. Hydrochlorothiazide is a thiazide diuretic and has been used alone and in combination with other anti-hypertensive drugs for the treatment of high blood pressure. Olmesartan medoxomil (CS-866) was clinically investigated under IND [redacted] Some information regarding the study of the

combination of CS-866 and hydrochlorothiazide (HCTZ) was also included in IND — However, in those studies CS-866 and HCTZ were administered separately. Thus, bioequivalence studies were initiated to show comparability.

Benicar HCT™ immediate-release, film-coated tablets are packaged in HDPE bottles containing —30, 90, or 1000 tablets and in aluminum/aluminum blisters containing 10 tablets per card. **Note:** In the original submission, the use of — count HDPE bottles was planned; however, the applicant has since decided that the — count bottles will not be marketed. The aluminum blisters will be used for Hospital Unit Dose purposes. Use of the — HDPE bottle with tamper-evident seal and child-resistant closure is planned for all 30-tablet and 90-tablet dose strengths. For the 1000-tablet dose strengths, the 20/12.5 mg will be packaged in — HDPE bottles, and the 40/12.5 mg and 40/25 mg will be packaged in — HDPE bottles, all with tamper-evident seals and non-child-resistant closures. Physician's samples will be packaged in — HDPE bottles with tamper-evident seals and child-resistant closures, each containing —

This application provided information on Benicar HCT™ tablets available in —fixed-combination strengths: — 20/12.5 mg, 40/12.5 mg, — and 40/25 mg. However, subsequent to the filing of the original NDA, the applicant made a decision to seek approval for only three strengths: 20/12.5 mg, 40/12.5 mg, and 40/25 mg The first number corresponds to the amount of olmesartan medoxomil (CS-866) and the second number corresponds to the amount of hydrochlorothiazide (HCTZ). For example, the 20/12.5 mg CS-866HCTZ tablet contains 20 mg of olmesartan medoxomil and 12.5 mg of hydrochlorothiazide. The CS-866HCTZ tablets are manufactured by a

— The different tablet dose strengths are physically distinguishable based on size, shape, color, and identifying debossed markings.

Olmesartan medoxomil drug substance is a white to light yellowish-white powder that is practically insoluble in water, sparingly soluble in methanol and acetone —

— CS-866 is not hygroscopic and no evidence of polymorphism has been demonstrated following recrystallization from various solvents. All information regarding the synthetic manufacture of CS-866 drug substance is referenced to DMF — As approved in NDA 21-286, a retest date of — is recommended for the CS-866 bulk drug substance.

Hydrochlorothiazide drug substance is a white or almost white crystalline powder, very slightly soluble in water, soluble in — and sparingly soluble in — It dissolves readily in — HCTZ is listed in both the U.S. Pharmacopeia and the European Pharmacopeia and all synthetic manufacturing information is referenced to DMFs # — and # — A retest date of — has been

established for the HCTZ bulk drug substance supplied by [redacted] and a retest date of [redacted] has been established for HCTZ bulk drug substance supplied by [redacted]. Per Amendment N000 BC (28-Mar-2003) in which the applicant submitted batch release data and some limited stability data for drug product batches manufactured using [redacted] hydrochlorothiazide drug substance, [redacted] is approved as a supplier of hydrochlorothiazide drug substance for the manufacture of olmesartan medoxomil/hydrochlorothiazide tablets. This data demonstrated that the drug product manufactured using [redacted] hydrochlorothiazide is comparable to the drug product manufactured using [redacted] hydrochlorothiazide. Also, it should be noted that the applicant is not currently able to obtain hydrochlorothiazide from [redacted] because the facility is being relocated.

B. Description of How the Drug Product is Intended to be Used

Benicar HCT™ is proposed for the treatment of hypertension. This new drug application is for an immediate release tablet formulation combining the two active ingredients, olmesartan medoxomil and hydrochlorothiazide. Benicar HCT™ tablets are intended for once-daily oral administration and are available in the following combination strengths: 20/12.5 mg, 40/12.5 mg, and 40/25 mg. The maximum daily dose of olmesartan medoxomil is 40 mg and the maximum daily dose of hydrochlorothiazide is 25 mg. The drug product should be stored at 20 – 25°C (68 – 77°F) [See USP Controlled Room Temperature]. The applicant originally proposed an expiration date of [redacted] for Benicar HCT™ packaged in [redacted] bottles and [redacted] blisters and [redacted] packaged in aluminum/aluminum blisters. However, stability problems arose with the [redacted] blisters at [redacted] and this packaging configuration was withdrawn mid-review. The cumulative long-term stability data submitted mid-review for aluminum blisters totaled [redacted] and for HDPE bottles, [redacted]. Taking into account the statistical analysis and the recommendations of the ICH stability guidances, an expiration date of 18 months for Benicar HCT™ tablets packaged in HDPE bottles and aluminum/aluminum blisters stored at 20 – 25°C (See DMF [redacted] Review and Section II.H below for more details) is granted. This expiration date has been finalized taking into consideration the revised dissolution specification limits agreed upon by the chemistry review team and the Office of Clinical Pharmacology and Biopharmaceutics.

C. Basis for Approvability or Not-Approval Recommendation

This new drug application (21-532) is recommended for **APPROVAL**. There are no outstanding issues with regard to chemistry, manufacturing, and controls.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName:	Monica D. Cooper, Ph.D.
ChemistryTeamLeaderName:	Kasturi Srinivasachar, Ph.D.
ProjectManagerName:	Edward Fromm

C. CC Block

Orig. NDA 21-532
HFD-110/Division File
HFD-110/Team Leader/K. Srinivasachar
HFD-110/Review Chemist/M. Cooper
HFD-110/Project Manager/E. Fromm

14 Page(s) Withheld

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Monica Cooper
4/23/03 04:11:51 PM
CHEMIST

Kasturi Srinivasachar
4/23/03 04:35:40 PM
CHEMIST

CDER CHEMISTRY REVIEW CDER

NDA 21-532

Benicar HCT™

Sankyo Pharma Inc.

Monica D. Cooper
Division of Cardio-Renal Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-532

2. REVIEW NUMBER: #1

3. REVIEW DATE: 03-Apr-2003

4. REVIEWER: Monica D. Cooper, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission (000)	05-Aug-2002
Amendment (N000 BC)	05-Sep-2002
Amendment (N000 BC)	22-Jan-2003
Amendment (N000 BC)	10-Mar-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Sankyo Pharma Inc.
Address:	399 Thornall Street, 11th Floor Edison, New Jersey 08837
Representative:	Albert S. Yehaskel, MS, MBA
Telephone:	732-590-5009

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Benicar HCT™
b) Non-Proprietary Name (USAN): olmesartan medoxomil and hydrochlorothiazide
c) Code Name/# (ONDC only): CS-866HCTZ
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antihypertensive

11. DOSAGE FORM: Film-Coated Immediate Release Tablets

12. STRENGTH/POTENCY: 20/12.5 mg, 40/12.5 mg, and 40/25 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _✔_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

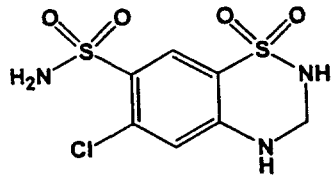
_____SPOTS product – Form Completed

___✔___Not a SPOTS product

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

Olmesartan medoxomil: 2,3-Dihydroxy-2-butenyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[p-(o-1*H*-tetrazole-5-ylphenyl)benzyl]imidazole-5-carboxylate, cyclic 2,3 carbonate

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

[redacted] and 

$C_{29}H_{30}N_6O_6$
558.6

$C_7H_8ClN_3O_4S_2$
297.7

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II	Sankyo Co., Ltd.	Drug Substance, Benicar (olmesartan medoxomil)	1	Adequate	11-Mar-2003 and 31-Mar-2003	Amendments Reviewed by Monica Cooper, Initial by Florian Zelinski
	II			1	Adequate	11-Mar-2003	Annual Update Reviewed by Monica Cooper
	II			3	Adequate	19-Feb-2002	Reviewed by RD' Costa
	II	Sankyo / Pharma Inc.	Drug Product, Benicar HCT Tablets	1	Not Adequate	13-Mar-2003	Reviewed by Monica Cooper
	II	Sankyo Co., Ltd.	Drug Substance, Benicar (olmesartan medoxomil)	7	N/A		production will not be used.
	III			7	N/A		Packaging protocols and standard operating procedures (no CMC info).
	III			3	Adequate	26-Sep-2000	Reviewed by Donald N. Klein
	III			3	Adequate	20-Aug-2001 and 06-Aug-2002	Reviewed by Raj Uppoor and Stuart Zimmerman
	III			1	Adequate	18-Dec-2002	Amendments Reviewed by Monica Cooper

Chemistry Review Data Sheet

[redacted]	III	[redacted]	[redacted]	3	Adequate	14-Jun-2002	Both [redacted] were Reviewed by Lorenzo Rocca
[redacted]	III	[redacted]	[redacted]	3	Adequate	24-Apr-2000 and 18-Aug-2000	[redacted] Reviewed by Xavier Ysern, [redacted] Reviewed by Raymond Frankewich

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	[redacted]	[redacted]
NDA	21-286	Benicar™ (approval 25-Apr-2002)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	09-Jan-2003	S. Adams
Pharm/Tox	N/A		
Biopharm	Pending		
LNC	N/A		
Methods Validation	Pending		
DMETS	Acceptable Proprietary Name "Benicar HCT"	25-Oct-2002	K. Dermanoski
EA	Acceptable (Categorical Exclusion)		
Microbiology	N/A		

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 21-532

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This new drug application (21-532) is recommended as **APPROVABLE** from the perspective of chemistry, manufacturing and controls. Information requests/deficiency letters have been sent to the applicant and DMF holders outlining the information that is needed to complete this application.

The overall evaluation from the Office of Compliance for cGMP compliance is ACCEPTABLE. The Establishment Evaluation Report is attached at the end of this review.

Methods validation will be submitted after all CMC information requests and deficiencies have been addressed.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No Phase 4 Commitments, Agreements, and/or Risk Management Steps have been made.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Benicar HCT™ is a combination drug product consisting of two drug substances: olmesartan medoxomil and hydrochlorothiazide. Previously, both of these drug substances were approved individually in drug product formulations (see NDA 21-286 for Benicar™/olmesartan medoxomil tablets and see NDA 11-793 for the first approval of hydrochlorothiazide tablets). Olmesartan medoxomil (as Benicar™ tablets) was approved for the treatment of hypertension and is an ester prodrug of olmesartan, an angiotensin II receptor blocker. Hydrochlorothiazide is a thiazide diuretic and has been used alone and in combination with other anti-hypertensive drugs for the treatment of high blood pressure. Olmesartan medoxomil (CS-866) was clinically investigated under IND ——— Some information regarding the study of the combination of CS-866 and hydrochlorothiazide (HCTZ) was also included in IND ——— However, in

those studies CS-866 and HCTZ were administered separately. Thus, bioequivalence studies were initiated to show comparability.

Benicar HCT™ immediate-release, film-coated tablets are packaged in HDPE bottles containing — 30, 90 —, or 1000 tablets and in aluminum/aluminum blisters containing 10 tablets per card. The aluminum blisters will be used for Hospital Unit Dose purposes. Use of the — HDPE bottle with tamper-evident seal and child-resistant closure is planned for all 30-tablet and 90-tablet dose strengths. For the — tablet dose strengths, the 20/12.5 mg will be packaged in — HDPE bottles with tamper-evident seals and child-resistant closures, and the 40/12.5 mg and 40/25 mg will be packaged in —HDPE bottles with tamper-evident seals and non-child-resistant closures. For the 1000-tablet dose strengths, the 20/12.5 mg will be packaged in — HDPE bottles, and the 40/12.5 mg and 40/25 mg will be packaged in bottles, all with tamper-evident seals and non-child-resistant closures. Physician's samples will be packaged in —HDPE bottles with tamper-evident seals and child-resistant closures, each containing —

This application provided information on Benicar HCT™ tablets available in — fixed-combination strengths: — 20/12.5 mg, 40/12.5 mg, — and 40/25 mg. However, subsequent to the filing of the original NDA, the applicant made a decision to seek approval for only three strengths: 20/12.5 mg, 40/12.5 mg, and 40/25 mg The first number corresponds to the amount of olmesartan medoxomil (CS-866) and the second number corresponds to the amount of hydrochlorothiazide (HCTZ). For example, the 20/12.5 mg CS-866HCTZ tablet contains 20 mg of olmesartan medoxomil and 12.5 mg of hydrochlorothiazide. The CS-866HCTZ tablets are manufactured by a

Olmesartan medoxomil drug substance is a white to light yellowish-white powder that is practically insoluble in water, sparingly soluble in methanol — — CS-866 is not hygroscopic and no evidence of polymorphism has been demonstrated following recrystallization from various solvents. All information regarding the manufacture of CS-866 drug substance is referenced to DMF — As approved in NDA 21-286, a retest date of — is recommended for the CS-866 bulk drug substance.

Hydrochlorothiazide drug substance is a white or almost white crystalline powder, very slightly soluble in water, soluble in —, and sparingly soluble in — dissolves readily in — HCTZ is listed in both the U.S. Pharmacopeia and the European Pharmacopeia and all manufacturing information

is referenced to DMFs # [redacted] and # [redacted] A retest date of [redacted] has been established for the HCTZ bulk drug substance supplied by [redacted] At this time, we cannot approve [redacted], as a supplier of hydrochlorothiazide drug substance for the manufacture of olmesartan medoxomil/hydrochlorothiazide tablets due to an absence of data using this supplier for the manufacture of Benicar HCT™ tablets.

B. Description of How the Drug Product is Intended to be Used

Benicar HCT™ is proposed for the treatment of hypertension. This new drug application is for an immediate release tablet formulation combining the two active ingredients olmesartan medoxomil and hydrochlorothiazide. Benicar HCT™ tablets are intended for once-daily oral administration and are available in the following combination strengths: 20/12.5 mg, 40/12.5 mg, and 40/25 mg. The maximum daily dose of olmesartan medoxomil is 40 mg and the maximum daily dose of hydrochlorothiazide is 25 mg. The drug product should be stored at 20 – 25°C (68 – 77°F) [See USP Controlled Room Temperature]. The applicant originally proposed an expiration date of [redacted], for Benicar HCT™ packaged in HDPE bottles and [redacted] blisters and [redacted], packaged in aluminum/aluminum blisters. However, stability problems arose with the [redacted] blisters at [redacted] and this packaging configuration was withdrawn mid-review. The cumulative long-term stability data submitted mid-review for aluminum blisters totaled [redacted] and for HDPE bottles. [redacted] Taking into account the statistical analysis and the recommendations of the ICH stability guidances, we recommend a tentative expiration date for Benicar HCT™ tablets in HDPE bottles and aluminum/aluminum blisters of 18 months at 25°C (See DMF [redacted] Review and Section II.H below for more details). However, this recommended expiration date will not be final until the dissolution specification limit is determined in concordance with the Office of Clinical Pharmacology and Biopharmaceutics.

C. Basis for Approvability or Not-Approval Recommendation

The "approvable" recommendation is based on noted concerns and deficiencies in the chemistry, manufacturing, and controls section of this NDA and in the DMF [redacted] for the manufacture of the drug product. Information requests were sent to the applicant and DMF holder outlining the concerns and deficiencies that should be addressed to ensure the safety and quality of the drug product. This application is recommended as "approvable" rather than "not approvable" because the applicant should be able to resolve the deficiencies readily without the need for additional studies.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name:	Monica D. Cooper, Ph.D.
Chemistry Team Leader Name:	Kasturi Srinivasachar, Ph.D.
Project Manager Name:	Edward Fromm

C. CC Block

Orig. NDA 21-532
HFD-110/Division File
HFD-110/Team Leader/K. Srinivasachar
HFD-110/Review Chemist/M. Cooper
HFD-110/Project Manager/E. Fromm

45 Page(s) Withheld

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21532/000
Org Code : 110
Priority : 4S

Sponsor: SANKYO PHARMA
399 THORNALL ST 7TH FLOOR
EDISON, NJ 08837

Stamp Date : 05-AUG-2002
PDUFA Date : 05-JUN-2003
Action Goal :
District Goal: 06-APR-2003

Brand Name : BENICAR HCT (OLMESARTAN MEDOXOMIL/HYDRO
Estab. Name:
Generic Name: OLMESARTAN MEDOXOMIL/HYDROCHLOTHIAZIDE
Dosage Form: (TABLET)
Strength : 10/12.5MG(SEE COMMENTS)

FDA Contacts:			
E. FROMM	Project Manager	(HFD-110)	301-594-5300
M. COOPER	Review Chemist	(HFD-110)	301-594-5300
K. SRINIVASACHAR	Team Leader	(HFD-110)	301-594-5376

Overall Recommendation: ACCEPTABLE on 09-JAN-2003by S. ADAMS (HFD-322) 301-827-9051

Establishment : CFN : [redacted] FEI : 3002808449

[redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile : CSN
Last Milestone: OC RECOMMENDATION
Milestone Date: 09-SEP-02
Decision : ACCEPTABLE

OAI Status: NONE

Reason : BASED ON PROFILE

Establishment : CFN : FEI : 1000522077

DMF No: AADA:

Responsibilities:

Profile : TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-SEP-02

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : FEI : 3002807904

DMF No: AADA:

Responsibilities:

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-OCT-02

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : 2129896

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-JAN-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9611913 FEI : 3002808056

SANKYO CO LTD

ODAWARA (KANAGAWA), , JA

DMF No: [redacted] AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-SEP-02

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CBN : 9617684 FEI : 3003282622

SANKYO PHARMA INC

D 85276

PFAFFENHOFEN, , GM

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

Profile : TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-SEP-02

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Monica Cooper
4/3/03 01:41:16 PM
CHEMIST

Kasturi Srinivasachar
4/4/03 03:12:45 PM
CHEMIST