CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-107

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-107
DATE RECEIVED BY CENTER:	March 20, 2007
DRUG PRODUCT:	TEKTURNA® HCT Tablets
DRUG SUBSTANCE:	Aliskiren hemifumarate and Hydrochlorothiazide
INTENDED CLINICAL POPULATION:	Hypertensive
SPONSOR:	Novartis Pharmaceuticals Corporation
REVIEW DIVISION:	Division of Cardiovascular and Renal Products
PHARM/TOX REVIEWER:	G. Jagadeesh, Ph.D.
PHARM/TOX SUPERVISOR:	Charles Resnick, Ph.D.
DIVISION DIRECTOR:	Norman Stockbridge, M.D., Ph.D.
PROJECT MANAGER:	Quynh Nguyen

Date of review submission to Division File System (DFS): August 30, 2007

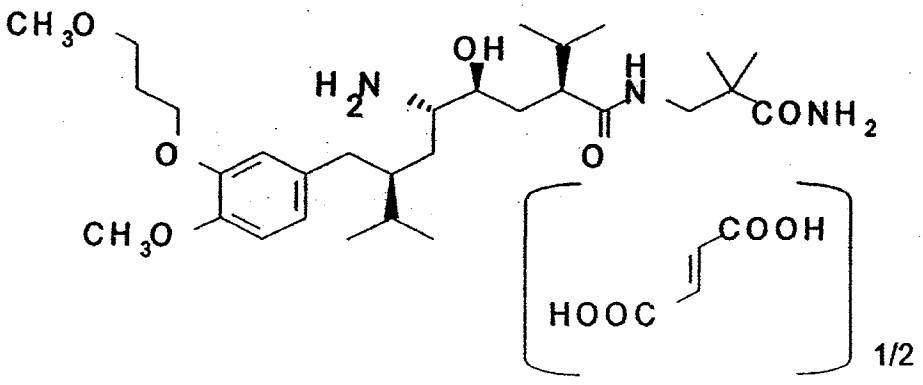
NDA number: 22,107
Date of Submission: 03-20-07
Center Receipt Date: 03-20-07
Sponsor: Novartis Pharmaceuticals Corporation
Manufacturer of Drug Substance: Aliskiren hemifumarate is from Novartis Pharma AG, Basel, Switzerland. Hydrochlorothiazide is from [redacted] b(4)

Reviewer: G. Jagadeesh, Ph.D.
Division: Division of Cardiovascular and Renal products
Review completion date: August 30, 2007

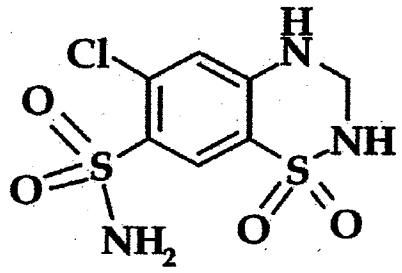
Drug Product: TEKTURNA® HCT Tablets (SPH100)

Drug Substances

Generic name: **Aliskiren hemifumarate**
Code names: SPP 100 (base); SPP 100A (HCl), SPP 100B (hemifumarate)
Chemical name: 2(S),4(S),5(S),7(S)-N-(3-amino-2,2-dimethyl-3-oxopropyl)-2,7-diisopropyl-4-hydroxy-5-amino-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]octanamide hemifumarate.
Chemistry: Aliskiren is a single diastereomer having 4 chiral centers, all S-configured. Aliskiren hemifumarate is a white to off-white crystalline powder and relatively hygroscopic. It is very soluble in aqueous media.
CAS registry number: 173334-58-2
Molecular formula/molecular weight: $C_{30}H_{53}N_3O_6 \cdot 0.5\ C_4H_4O_4$ / 551.8 (free base), 609.8 (hemifumarate)



Generic name: **Hydrochlorothiazide (HCTZ)**
Chemical name: 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
Chemistry: Hydrochlorothiazide is a white, or practically white, crystalline powder which is slightly soluble in water and freely soluble in sodium hydroxide solution.
CAS registry number: 58-93-5
Molecular formula/molecular weight: $C_7H_8ClN_3O_4S_2$ / 297.74



Related INDs/NDAs: Novartis' IND 62,976 and NDA 21,985 for aliskiren hemifumarate for the treatment of hypertension. Novartis' IND [redacted] for aliskiren hemifumarate for the treatment of [redacted] b(4)

Drug Class: Aliskiren hemifumarate is a renin inhibitor and hydrochlorothiazide is a diuretic.
Intended Clinical Population: Hypertensive subjects
Clinical Formulation: The tablets are immediate release dosage forms formulated in four strengths: 150/12.5 mg, 150/25 mg, 300/12.5, 300/25 mg (aliskiren/HCTZ) and the composition is presented in the following table.

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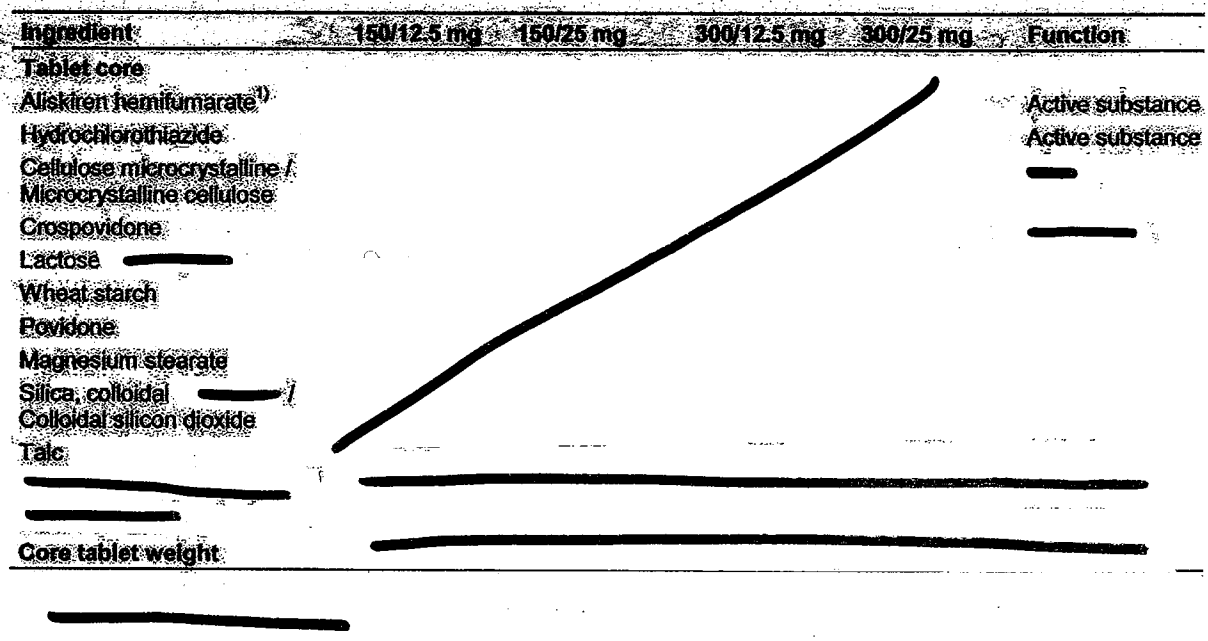
COMPOSITION OF ALISKIREN HEMIFUMARATE AND HCTZ (SPH100) FILM-COATED TABLET
(mg/dosage unit)



Ingredient	150/12.5 mg	150/25 mg	300/12.5 mg	300/25 mg	Function
Tablet core					
Aliskiren hemifumarate[1)]					Active substance
Hydrochlorothiazide					Active substance
Cellulose microcrystalline / Microcrystalline cellulose					
Crospovidone					
Lactose					
Wheat starch					
Povidone					
Magnesium stearate					
Silica, colloidal / Colloidal silicon dioxide					
Talc					
Core tablet weight					

b(4)

Route of Administration: Oral

Proposed Dosage Regimen: One tablet daily.

Disclaimer: Unless indicated otherwise, tables and graphs (some with editorial corrections by the reviewer) are taken directly from the sponsor's submission.

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EXECUTIVE SUMMARY

I. Background

The seventh report (2003) of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends addition of a second drug from a different class when use of a single agent in adequate doses fails to achieve the goal[1]. The current NDA describes the efficacy and safety of the fixed combination of aliskiren hemifumarate and hydrochlorothiazide [Tekturna® HCT (SPH100)] in the treatment of essential hypertension. Aliskiren is a new class of non-peptide, low molecular weight renin inhibitor for the treatment of hypertension. Blockade of the enzyme, renin, at a higher level in the renin angiotensin system (RAS) cascade than the currently available ACE inhibitors blocks the generation of angiotensin I and, consequently, leads to reduced levels of angiotensin II. The latter is the central product of the RAS, a potent vasoconstrictor. HCTZ is an orally active thiazide diuretic. Its antihypertensive effect is believed to be related to its volume/sodium depletion.

HCTZ lowers blood pressure by natriuresis resulting in decreased blood volume, but the reduction in volume stimulates renin release and increases plasma renin activity and, thus, levels of angiotensin II. This counter-regulatory stimulation of the RAS limits the antihypertensive effectiveness of HCTZ. Coadministration of a renin inhibitor such as aliskiren should be able to neutralize the diuretic-mediated increase in plasma renin activity. Thus, it is contemplated that with the combination therapy, both RAS- and volume-dependent mechanisms of hypertension are effectively inhibited. The fixed combination of these drugs should improve patient compliance when compared with non-fixed combination therapy.

HCTZ has been extensively studied and is widely used as monotherapy for the treatment of hypertension. Aliskiren hemifumarate (Tekturna®) is a new drug, first in class, approved in March 2007. The fixed combination which is the subject of this application, is the first of its type.

II. Recommendations

A. **Recommendation on Approvability:** Approvable

B. **Recommendations for Additional Nonclinical Studies:** None

C. **Recommendations for Labeling:** None

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[1] Chobanian, A. V. *et al.* Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* **42**:1206–1252, 2003.

III. Summary of Nonclinical Findings

The sponsor has not performed pharmacology or ADME studies for the combination product.

A. **Brief Overview of Toxicology:** A 13 week toxicity study was conducted in Wistar Hanover rats to support the chronic administration of the aliskiren hemifumarate and hydrochlorothiazide combination to adult hypertensive patients. In this study, aliskiren hemifumarate and hydrochlorothiazide were administered orally, by gavage, separately and together (at a ratio of 12:1). (All doses of aliskiren hemifumarate are presented in terms of the aliskiren base.)

Daily administration of aliskiren hemifumarate and hydrochlorothiazide at doses of 100:8 or 150:12 mg/kg/day for 13 weeks resulted in a moderate decrease in body weight gain of male rats relative to control. Alterations in kidney function as evidenced by minimal to mild decreases (non-dose-dependent) in serum potassium and serum chloride, and increases in urine volume relative to control were noted at all doses of the combination (50:4 or more mg/kg/day) and with aliskiren hemifumarate (150 mg/kg/day) or HCTZ (12 mg/kg/day) alone. These are expected pharmacological findings and were absent in the recovery group animals. A minimal increase in cellular vacuolation in the zona glomerulosa was noted in the adrenal glands of all but one animal given HCTZ alone or in combination with aliskiren hemifumarate. The increased vacuolation was still evident following the 4 week recovery period in animals receiving the highest dose of the combination. A no observed adverse effect level was not established in this study. The combined administration of aliskiren hemifumarate and HCTZ did not augment any existing toxicities of the individual agents, nor induce any new toxicities, and resulted in no toxicologically synergistic effects. No significant difference in exposure to aliskiren or HCTZ was observed when the compounds were administered together, suggesting no effect of one on the absorption and disposition of the other.

B. **Nonclinical Safety Issues Relevant to Clinical Use**

The combined administration of aliskiren hemifumarate and HCTZ did not augment any existing toxicities of the individual agents in the 13 week toxicology study. The minor changes in water and electrolyte balance observed with the highest combination dose probably resulted from decreases in aldosterone secretion by the adrenal zona glomerulosa, a pharmacological effect of both aliskiren and hydrochlorothiazide. The increase in (non-reversible) vacuolation in the adrenal zona glomerulosa, noted at all dose levels of the combination, was attributed to administration of HCTZ. Higher doses were not included in the 13 week study since a dose of 300:25 mg/kg/day during a preliminary 2 week study resulted in morbidity and early group sacrifice. Previous studies with aliskiren alone in rats have demonstrated, at doses as low as 250 mg/kg/day, an increased incidence of mucosal hyperplasia in the small and large intestine. The onset was rapid, occurring within 1 to 3 days of treatment. Cecal erosion and ulceration at 750 mg/kg/day and one colonic

adenoma and one cecal adenocarcinoma at 1500 mg/kg/day ($p > 0.05$) were noted in rats treated chronically with aliskiren hemifumarate (see NDA 21,985 review). Plasma concentrations of aliskiren measured at the highest combination dose used in the current study were far below those anticipated clinically, indicating the absence of a safety margin for humans. On the other hand, rats were substantially exposed to HCTZ in the same study, providing rat to human exposure multiples for HCTZ in the range of 6 to 9. The absence of a safety margin for aliskiren may not be a concern for humans since, according to the sponsor, the combination has demonstrated good clinical tolerance.

IV. Administrative

Reviewer's Signature

Supervisor Signature: Concurrence

PHARMACOLOGY/TOXICOLOGY REVIEW

1.0. PHARMACODYNAMICS: NO STUDIES CONDUCTED

2.0. DRUG DISPOSITION: NO STUDIES CONDUCTED

3.0. TOXICOLOGY

3.1. Repeat Dose Toxicity

3.1.1. 13 Week Oral Gavage Study in Wistar Rats

Key Study Findings: A statistically significant dose-dependent reduction in mean body weight gain relative to control was noted for males at 100:8 or more mg (aliskiren:HCTZ)/kg/day. Mean body weight of the high dose male group was, however not significantly lower than control (8%, $p > 0.05$) at the end of the treatment or recovery periods. Alterations in kidney function were noted in all treated groups as demonstrated by reversible decreases in serum potassium and chloride concentrations relative to control and, in males receiving the combination, increased urine volume; there were no corresponding histopathological alterations. Minimally increased cellular vacuolation in the zona glomerulosa was noted in the adrenal glands of both sexes given HCTZ alone or in combination with aliskiren hemifumarate. Increased vacuolation was still evident following a 4 week recovery period in animals receiving the highest dose of the combination. A no observed adverse effect level was not established in this study.

Study No.: 802218, Sponsor #0670321
Location of Report: EDR
Conducting Laboratory and Location: [redacted] b(4)

Dates of Study: The animals were dosed on August 31, 2006 and necropsied between November 30 and December 28, 2006.
GLP Compliance: Yes
QA'd Report: yes (X) no ( )
Drug, Lot #: Aliskiren hemifumarate, batch #0544033, 98.9% pure; Hydrochlorothiazide, batch #1030035000, 99.9% pure
Formulation: [redacted] b(4)

Animals

Species/Strain: Rats, IGS Wistar Hanover, :WI (from [redacted])
#/Animals/Group: 10/sex. An additional 5 animals/sex/group were included for the control and the high dose combination to serve as recovery animals to be sacrificed after a 4 week recovery period (see Table 3.1.1.1). b(4)
Age: 8 weeks old at initiation of dosing
Weight: Males: 204-272 gm, Females: 157-193 gm, at initiation of dosing

Husbandry: Animals of the same sex and same dosing group were housed 3 per cage. Food and water were available *ad libitum* except for study defined fasting procedures

TABLE 3.1.1.1
STUDY DESIGN

Group no. Identification	Dose level SPP100 (mg/kg/day)	Dose level HCT (mg/kg/day)	Animal number			
			Main study		Recovery study	
1 Vehicle control	0	0	1001-1010	1501-1510	1011-1015	1511-1515
2 SPH100[a]	50	4	2001-2010	2501-2510	-	-
3 SPH100[a]	100	8	3001-3010	3501-3510	-	-
4 SPH100[a]	150	12	4001-4010	4501-4510	4011-4015	4511-4515
5 SPP100	150	0	5001-5010	5501-5510	-	-
6 HCT	0	12	6001-6003, 6005-6011	6501-6510	-	-

[a]: SPH100 is a combination of aliskiren hemifumarate (SPP100) and hydrochlorothiazide (HCT)
The doses of aliskiren hemifumarate are expressed in terms of the base.

Dosing

Doses: Aliskiren hemifumarate and HCTZ were administered (at a dose ratio of 12:1) at three dose levels: 50:4, 100:8 or 150:12 mg (aliskiren:HCTZ)/kg/day. Two additional groups of rats received either aliskiren hemifumarate or HCTZ at 150 or 12 mg/kg/day, respectively (Table 3.1.1.1). Control animals received the vehicle. Doses were selected on the basis of a 2 week dose range-finding oral toxicity study in the same rat strain in which the high dose of 300:25 mg (aliskiren:HCTZ)/kg/day resulted in the early sacrifice (study day 8) of all animals (5 males and 5 females) due to test substance-related moribundity. Animals in this group demonstrated abdominal distention, decreased locomotor activity, piloerection, rales, a statistically significant decrease in mean body weights between day 4 and day 8, decreased food intake, and increased blood urea nitrogen and creatinine. Notable histopathological changes in these animals were tubular necrosis in the kidney, epithelial hyperplasia in the gastrointestinal tract, decreased cellularity in the bone marrow, lymphoid depletion in the spleen and thymus. Minimal tubular basophilia and minimal lymphocytic infiltration of the medulla in the thymus were noted in animals receiving 100:8 mg (aliskiren:HCTZ)/kg/day.

Route, Mode and Duration of Administration: Orally by gavage (10 ml/kg), once daily, for 13 weeks. Recovery phase animals were treated for the same duration but were killed 4 weeks later. Control animals received the vehicle.

Observations and Measurements

Clinical Signs: All animals were observed twice daily for clinical signs and mortality.

Body Weight and Food Consumption: Recorded prior to dosing and once weekly during the dosing and recovery periods.

Ophthalmology: Conducted once pretest and in week 13.

Urinalysis: Overnight urine samples were collected from individual animals at the end of the treatment and recovery periods during which time the animals were deprived of food and water. The following parameters were assessed: color and appearance, urine volume, specific gravity, pH, protein, bilirubin, blood, nitrite, glucose, ketones and urobilinogen.
Hematology[2] and Clinical Biochemistry[3]: Blood samples were collected at the end of the treatment (from the jugular vein) and recovery periods (from the abdominal aorta) from all surviving animals under anesthesia. The animals were fasted overnight.
Pathology: Animals were fasted overnight prior to terminal necropsy. A complete necropsy was conducted on all animals, including those found dead, with a detailed internal examination. Representative samples of the protocol tissues (Table 3.1.1.2) were collected from all study animals and processed for microscopic examination which was performed on the tissues from all animals in the control and high dose combination groups, from one unscheduled death in group 5, and all gross lesions, kidney, adrenal glands, liver, bone marrow, sternum, spleen, thymus, large and small intestine and urinary bladder from all animals in the remaining groups.

TABLE 3.1.1.2
TISSUES SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

adrenals [π]	lacrimal glands	sciatic nerve
aorta (thoracic)	larynx	seminal vesicles
bone marrow (in bone)	liver [π]	skeletal muscle
brain [π]	lymph node, mandibular	skin
cecum	lymph node, mesenteric	spinal cord
colon	lungs [π]	spleen [π]
duodenum	mammary gland	sternum
epididymides [π]	optic nerves	stomach
esophagus	ovaries [π]	testes [π]
eyes	oviducts	thymus [π]
gross lesions	pancreas,	thyroid [π]
Harderian glands	parathyroid [π]	tongue
heart [π]	Pituitary [π]	trachea,
ileum,	prostate [π]	urinary bladder
jejunum	rectum	uterus [π]
kidneys [π]	salivary gland	vagina

[π]: Organ weighed

[2] erythrocytes, hematocrit, hemoglobin, red cell distribution width, Wintrobe indices, blood cell morphology, reticulocytes, white blood cell count, white blood cell differential, platelets, prothrombin time, activated partial thromboplastin time and fibrinogen.

[3] ALT, AST, AP, creatine kinase, total bilirubin, direct bilirubin, indirect bilirubin, total protein, albumin, globulins, A/G ratio, glucose, BUN, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, triglycerides, cholesterol

Toxicokinetics: Blood samples for determination of levels of aliskiren and HCTZ were collected from the jugular vein of the non-recovery animals on study day 1 (1st dose) and in week 13 at 0.5, 1, 3, 7 and 24 hr after dosing (2 rats/sex/treatment group/time point).

Results

Analysis of Formulations: The dosing formulations were stable for at least 24 hr at room temperature and for at least 12 days at 6°C. Mean concentrations of all samples analyzed were in the range of 86% to 113% of target concentrations.

Mortality: Two animals died during the study. One female (#5507) receiving 150 mg aliskiren/kg/day died on day 14. Macroscopic examination revealed that the animal had a fractured C2 vertebra and the death was considered the result of a mechanical trauma. A female (#1511) from the vehicle control group was found dead on day 109 because of gavage error.

Clinical Signs: There were no test substance-related clinical signs in any of the groups.

Body Weights: A moderate and dose-dependent reduction in mean body weight gain was noted for males at 100:8 or 150:12 (aliskiren:HCTZ) mg/kg/day relative to concurrent control from study day 1 to the end of the dosing period (mean reduction of 11 and 14%*, respectively, (*$p < 0.05$)). Mean body weights at the end of the treatment period for these two combination groups were 7 and 8% ($p > 0.05$) lower than control. Mean body weight at the end of the recovery period for the high dose males was still 7% ($p > 0.05$) below control (Fig. 3.1.1.1, top figure). There were no treatment-related effects on body weight for females (Fig. 3.1.1.1, lower figure). Neither aliskiren hemifumarate nor HCTZ alone had any effect on body weights of males or females.

Food Consumption: A mild decrease in mean food consumption relative to control was noted for males at 100:8 or 150:12 (aliskiren:HCTZ) mg/kg/day for the entire duration of the study. The decrease correlated with the lower body weights of animals in these groups during the treatment period.

Ophthalmoscopy: No remarkable ocular changes.

Urinalysis: A mean increase in urine volume relative to control was noted for treated males (21%, 47%, 30%) at 100:8, 150:12 or 150:0 mg (aliskiren:HCTZ)/kg/day at the end of the treatment period; the difference from control, however, was statistically significant ($p < 0.05$) only at the middle dose level. A small increase (11%) seen for females receiving the high dose combination also did not reach statistical significance. There were no differences in urine volume at the end of the recovery period.

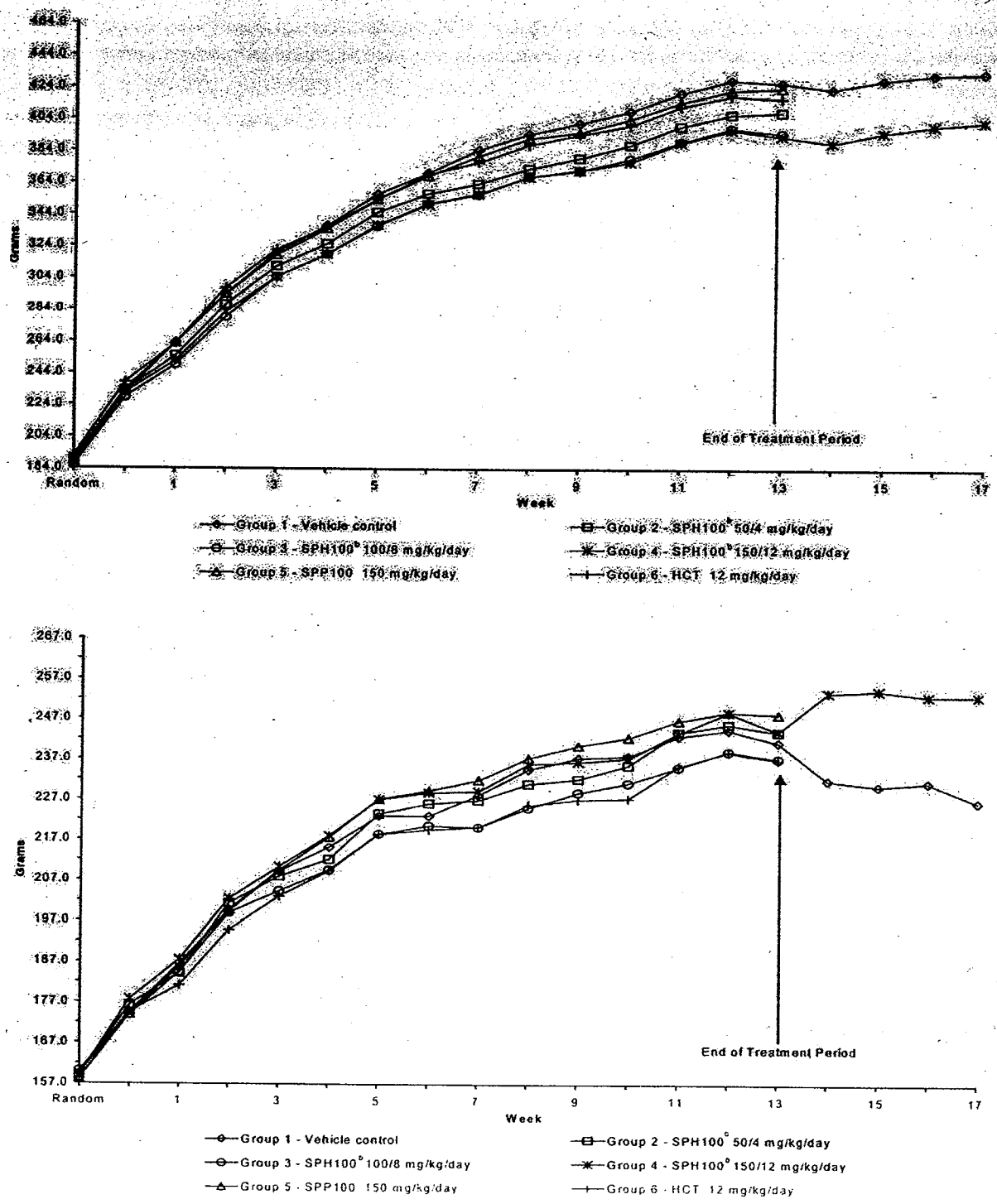

Fig. 3.1.1.1.: Group mean body weights, males (top) and females (bottom).
SPP100: aliskiren hemifumarate; HCT: hydrochlorothiazide; SPH100: aliskiren hemifumarate and HCT

Hematology: No significant treatment-related findings were noted for any of the dose groups.

Clinical Chemistry: At the end of treatment period, mild to moderate, non-dose-dependent decreases ($p < 0.05$) in serum potassium (4-21%) relative to control were noted in animals of both sexes treated with combination doses, aliskiren hemifumarate or HCTZ alone. In addition, minimal decreases in serum chloride (2 to 5%) relative to control ($p < 0.05$) were noted in animals receiving the combination at all doses or HCTZ alone. These differences were no longer seen at the end of recovery.

Organ Weights: There were no changes in organ weights that were considered related to treatment.

Gross Pathology: No treatment-related findings

Histopathology: A minimal increase in cellular vacuolation in the zona glomerulosa of the adrenal was observed in all but one animal given aliskiren hemifumarate and HCTZ combinations or HCTZ alone and necropsied at the end of treatment. Increased vacuolation was also noted in the adrenals of animals treated with the high dose combination sacrificed at the end of the recovery period. No other microscopic findings were seen in any other tissues or organs from any of the treated groups.

Toxicokinetics: Based on dose normalized AUC values, in the combination groups, exposures to the individual drug components increased with increase in dose but were not dose proportional (Tables 3.1.1.3 and 3.1.1.4). A moderate inter-animal variability existed for concentrations measured on day 1 and in week 13. Thus, any gender differences in any groups or accumulation in week 13 over day 1 is not consistent. Based on $AUC_{0\text{-}24h}$, a trend to higher exposure to both drugs was noted in week 13 in comparison with on day 1. Exposure to aliskiren on day 1 and in week 13 was higher in the absence of HCTZ than in the presence of HCTZ. On the other hand, exposure to HCTZ was similar in the presence and absence of aliskiren hemifumarate. Any effect of HCTZ on the exposure to aliskiren and *vice versa* is difficult to interpret since the number of animals used per time point was only 2. Apparent peak plasma concentrations of aliskiren or HCTZ were reached between 0.5 and 3 hr post dose.

TABLE 3.1.1.3
13 WEEK TOXICITY STUDY IN RATS
MEAN TOXICOKINETIC PARAMETERS FOR ALISKIREN IN RAT PLASMA

Dose group (SPP100:HCTZ)	Group 2: (50:4) mg/kg/day		Group 3: (100:8) mg/kg/day		Group 4: (150:12) mg/kg/day		Group 5: (150:0) mg/kg/day	
Parameters	Male (n = 2)	Female (n = 2)	Male (n = 2)	Female (n = 2)	Male (n = 2)	Female (n = 2)	Male (n = 2)	Female (n = 2*)
Day 1								
t_{max}	1	3	3	3	0.5	0.5	3	3
C_{max}	19.1	5.55	17.0	125	42.2	63.6	81.5	147
C_{max}/Dose	0.381	0.111	0.170	1.25	0.281	0.424	0.544	0.979
$AUC_{(0-24h)}$	38.7	31.0	92.3	441	210	247	374	1120
$AUC_{(0-24h)}$ /Dose	0.775	0.620	0.923	4.41	1.40	1.65	2.49	7.47
Week 13								
t_{max}	3	0.5	3	1	1	1	1	1
C_{max}	8.06	7.67	24.0	140	108	138	186	192
C_{max}/Dose	0.161	0.153	0.240	1.40	0.718	0.920	1.24	1.28
$AUC_{(0-24h)}$	57.8	45.6	185	406	351	478	760	872
$AUC_{(0-24h)}$ /Dose	1.16	0.912	1.85	4.06	2.34	3.19	5.07	5.82

t_{max} in hours; C_{max} in ng/mL, C_{max}/dose in (ng/ml)/(mg/kg/day); $AUC_{(0-24h)}$ in ng*hours/mL; $AUC_{(0-24h)}$/dose in (ng*hours/mL)/(mg/kg/day)
* except for the 7 hours post-dose timepoint in Week 13 where n = 1.

TABLE 3.1.1.4
13 WEEK TOXICITY STUDY IN RATS
MEAN TOXICOKINETIC PARAMETERS FOR HCTZ IN RAT PLASMA

Dose group (SPP100:HCTZ)	Group 2: (50:4) mg/kg/day		Group 3: (100:8) mg/kg/day		Group 4: (150:12) mg/kg/day		Group 6: (0:12) mg/kg/day	
Parameters	Male (n = 2)	Female (n = 2)	Male (n = 2)	Female (n = 2)	Male (n = 2)	Female (n = 2)	Male (n = 2)	Female (n = 2)
Day 1								
t_{max}	1	0.5	3	1	1	0.5	1	1
C_{max}	282	419	800	650	764	1130	924	1040
C_{max}/Dose	70.4	105	100	81.2	63.7	94.4	77.0	86.5
$AUC_{(0-24h)}$	1720	1720	4980	3220	6570	5950	5730	6370
$AUC_{(0-24h)}$ /Dose	430	431	623	403	548	496	478	531
Week 13								
t_{max}	0.5	0.5	3	0.5	1	0.5	1	1
C_{max}	352	570	854	863	1070	1320	854	875
C_{max}/Dose	87.9	143	107	108	89.0	110	71.1	72.9
$AUC_{(0-24h)}$	2040	2160	5500	4110	6100	7250	3990	4580
$AUC_{(0-24h)}$ /Dose	510	541	687	514	509	604	333	381

t_{max} in hours; C_{max} in ng/mL, C_{max}/dose in (ng/ml)/(mg/kg/day); $AUC_{(0-24h)}$ in ng*hours/mL; $AUC_{(0-24h)}$/dose in (ng*hours/mL)/(mg/kg/day)

SPH100 is a combination of aliskiren hemifumarate (SPP100) and hydrochlorothiazide (HCT)
The doses of aliskiren hemifumarate are expressed in terms of the base.

4.0. OVERALL SUMMARY AND EVALUATION

Tekturna® HCT is a fixed dose combination of aliskiren hemifumarate and hydrochlorothiazide proposed for the treatment of hypertension. Aliskiren hemifumarate is a renin inhibitor, recently approved (March 2007) for the treatment of hypertension (Novartis Pharmaceuticals NDA 21,985). Hydrochlorothiazide, a diuretic, has been approved for the treatment of hypertension since 1959. Because of their different modes of action, the combination of these drugs is expected to provide better blood pressure control than the component monotherapies. b(4)

A 13 week oral toxicity study in rats was performed with aliskiren hemifumarate and HCTZ. The animals were treated with either drug alone or both drugs in combination at a dose ratio of 12:1. The oral gavage administration of 150 mg/kg/day aliskiren in combination with 12 mg/kg/day HCTZ to Wistar Hannover rats for 13 weeks resulted in the death of a female on day 14. Necropsy revealed the death to be the result of mechanical trauma. A control female was found dead on day 109 because of gavage error. Moderate and dose-dependent reductions in body weight gain and food consumption, relative to control, were noted for males dosed at 100:8 or 150:12 mg (aliskiren:HCTZ)/kg/day ($p < 0.05$). Minimal to mild decreases (non-dose-dependent) in serum potassium and chloride relative to control were noted for both males and females receiving aliskiren hemifumarate, HCTZ or both. Additionally, minimal increases in urine volume, relative to control, were noted for males receiving the combination. However, there was no corresponding histopathology and differences from control were not observed at the end of the recovery period. A minimal increase in cellular vacuolation in the zona glomerulosa was noted in the adrenal glands of all but one animal given HCTZ alone or in combination with aliskiren hemifumarate. Since this effect was not observed in the animals treated with aliskiren hemifumarate alone, the increased vacuolation was considered to be related to administration of HCTZ. Adrenal zona glomerulosa vacuolation was still evident in high dose combination animals allowed a 4 week recovery period prior to sacrifice. A no observed adverse effect level was not established in this study since alterations in serum electrolytes and increased cellular vacuolation in the adrenal glands were noted at the lowest combination dose, 50:4 mg (aliskiren:HCTZ)/kg/day. These findings were attributed by the sponsor to excessive pharmacological effects of aliskiren and/or hydrochlorothiazide. However, only minimal increases in urine volume were observed (and only in males) in this study and blood pressures were not measured.

The highest dose in the 13 week study was limited to 150:12 mg (aliskiren:HCTZ)/kg/day due to the moribund condition and early sacrifice of all animals treated at a dose of 300:25 mg (aliskiren:HCTZ)/kg/day in a 2 week dose range-finding study. The plasma concentrations of aliskiren at the highest dose used in the 13 week toxicity study were below those anticipated clinically (0.3 to 0.5 times based on AUC or Cmax values) (Table 4.1), indicating the absence of a safety margin for humans. On the other hand, rats were substantially exposed to HCTZ in the same study, with rat:human exposure multiples ranging from 6 to 9 (Table 4.2). No significant difference in exposure to aliskiren or HCTZ was observed when the compounds were administered together, suggesting no effect of one on the absorption and disposition of the other.

TABLE 4.1
ALISKIREN HEMIFUMARATE: HCTZ
EXPOSURE MULTIPLES FOR ALISKIREN IN TOXICITY STUDIES

Species	Study number/ Rev section	Dose (aliskiren:HCTZ) mg/kg/day	Gender	$AUC_{0\text{-}24h}$ (ng·h/ml)	C_{max} (ng/ml)	Exposure multiples based on	
						$AUC_{0\text{-}24h}$	C_{max}
2-wk rat	0670118[a] 3.1.1	100:8[b]	male	567	169	0.4	0.6
			female	560	508	0.4	1.9
13-wk rat	0670321 3.1.1	150:12[c]	male	351	108	0.3	0.4
			female	478	138	0.4	0.5
		50:4[d]	male	58	8	0.05	0.03
			female	46	7	0.04	0.03

Aliskiren exposure multiples are based on the human $AUC_{0\text{-}tlast}$ = 1282 ng·h/ml (t= 96 hr) and C_{max} = 271 ng/ml after a single oral dose of 300:25 mg (aliskiren:HCTZ) to male and female healthy subjects (Study #CSPH100A2103)

TABLE 4.2
ALISKIREN HEMIFUMARATE: HCTZ
EXPOSURE MULTIPLES FOR HCTZ IN TOXICITY STUDIES

Species	Study number/ Rev section	Dose (aliskiren:HCTZ) mg/kg/day	Gender	$AUC_{0\text{-}24h}$ (ng·h/ml)	C_{max} (ng/ml)	Exposure multiples based on	
						$AUC_{0\text{-}24h}$	C_{max}
2-wk rat	0670118[a] 3.1.1	100:8[b]	male	3490	840	3.5	5.7
			female	3080	828	3.1	5.6
13-wk rat	0670321 3.1.1	150:12[c]	male	6100	1070	6.1	7.3
			female	7250	1320	7.3	9.0
		50:4[d]	male	2040	352	2.1	2.4
			female	2160	570	2.2	3.9

HCTZ exposure multiples are based on the human $AUC_{0\text{-}tlast}$ = 995 ng·h/ml (t= 96 hr) and C_{max} = 147 ng/ml after a single oral dose of 300:25 mg (aliskiren:HCTZ) to male and female healthy subjects (Study #CSPH100A2103)
a: A dose range-finding study.
b: Minimal adverse effects (reductions in body weight gain, minimal renal tubular basophilia and lymphocytic infiltration in the thymus) were noted at this dose; it was, however, regarded as a NOAEL by the sponsor
c: Although this highest study dose resulted in a few adverse effects (significant reduction in body weight gain, alterations in serum electrolytes, increased adrenal vacuolation) it was regarded as a NOAEL by the sponsor
d: This lowest study dose still produced a few adverse effects (alterations in serum electrolytes)

Evaluation

Although the combined administration of aliskiren hemifumarate and HCTZ did not augment any existing toxicities of the individual agents in the 13 week toxicology study, and although no new toxicities were identified, we note that the highest dose used in the toxicology study, 150:12 mg (aliskiren:HCTZ)/kg/day, was not high enough to demonstrate toxic effects that had been seen in other studies with aliskiren hemifumarate alone. In rats, this drug increased the incidence of mucosal epithelial hyperplasia in the small and large intestine at 250 or more mg aliskiren/kg/day and cecal erosion and ulceration at 750 or more mg aliskiren/kg/day. One

colonic adenoma and one cecal adenocarcinoma (rare tumors in the rat strain studied) were observed in males receiving 1500 mg/kg/day for 24 months (see NDA 21,985 review). In addition, systemic exposure for aliskiren at the highest dose in the combination toxicology study was lower than the anticipated clinical exposure. This may not be a concern for humans, based on the apparent tolerance when the combination was administered in clinical trials.

Recommendations on Labeling: None

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