CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-217

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:	22,217
DATE RECEIVED BY CENTER:	November 26, 2008
DRUG PRODUCT:	VALTURNA® Tablets
DRUG SUBSTANCE:	Aliskiren hemifumarate and Valsartan
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:	Lori Wachter

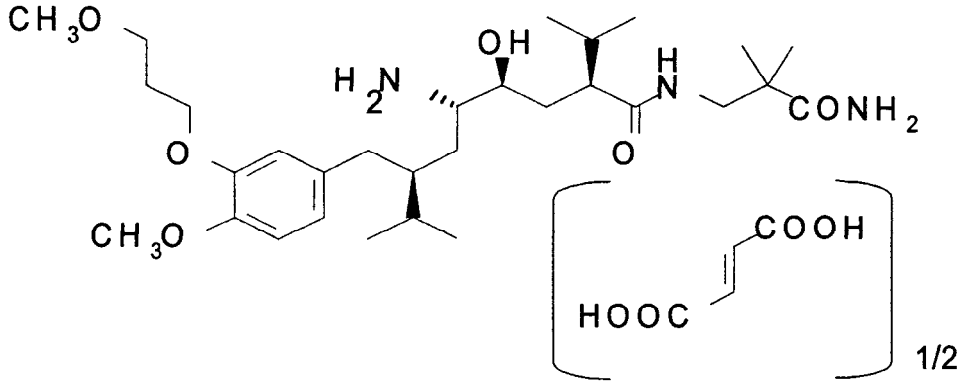
Date of review submission to Division File System (DFS): April 21, 2009

NDA number: 22,217
Date of Submission: 11-25-08
Center Receipt Date: 11-26-08
Reviewer Receipt Date: 12-03-08
Sponsor: Novartis Pharmaceuticals Corporation, USA
Manufacturer of Drug Substance: Aliskiren hemifumarate and valsartan are from Novartis Pharma AG, Basel, Switzerland.
Manufacturer of Drug Product: Novartis Pharma Stein AG, Schaffhauserstrasse, 4332-Stein, Switzerland.
Reviewer: G. Jagadeesh, Ph.D.
Division: Division of Cardiovascular and Renal products
Review completion date: April 20, 2009

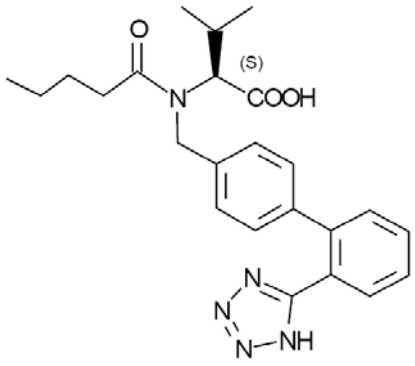
Drug Product: VALTURNA® Tablets (SPV100A)

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: **Valsartan**
Chemical name: (S)-N-Valeryl-N-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}-valine
Chemistry: It contains two acidic functions and includes one asymmetric center. Valsartan is free diacid, hydrophilic and the pure S-enantiomer. The corresponding (R)-enantiomer, which is less active in biological tests, is known as CGP 49309.
CAS registry number: 87333-19-5
Molecular formula/molecular weight: $C_{24}H_{29}N_5O_3$/ 435.5



Related INDs/NDAs: Novartis' IND 62,976 (aliskiren monotherapy), IND 76,046 (SPV100A, aliskiren/valsartan fixed dose combination), NDA 20,665 (valsartan monotherapy) and NDA 21,985 (aliskiren monotherapy) for the treatment of hypertension.
Drug Class: Aliskiren hemifumarate is a renin inhibitor and valsartan is an AT-1 receptor antagonist.
Intended Clinical Population: Hypertensive subjects
Clinical Formulation: The tablets are immediate release dosage forms formulated in two strengths: 150/160 mg and 300/320 mg (aliskiren/VAL) and the composition is presented in the following table provided by the sponsor.

COMPOSITION OF ALISKIREN HEMIFUMARATE AND VALSARTAN (SPV100) FILM-COATED TABLET
(mg/dosage unit)

Ingredient	150/160 mg	300/320 mg	Function	Reference to standards
(b) (4)				
Aliskiren hemifumarate[1)]	165.750	331.500	Active substance	Novartis monograph
(corresponds to Aliskiren hemifumarate base)	(150.000)	(300.000)		
Valsartan	160.000	320.000	Active substance	Novartis monograph
Cellulose microcrystalline / Microcrystalline cellulose			(b) (4)	Ph. Eur. / NF
Crospovidone				Ph. Eur. / NF
Hydroxypropylcellulose				Ph. Eur. / NF
Magnesium stearate				Ph. Eur. / NF
(b) (4) / Colloidal silicon dioxide				Ph. Eur. / NF
Indigotin Blue Lake (b) (4)				95/45/EC / 21CFR[3)]
(b) (4)				Ph. Eur. / USP
(b) (4)				
(b) (4)				
Total film-coated tablet weight	**574.000**	**1148.000**		
(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

Available evidence suggests that the majority of hypertensive individuals will require two or more antihypertensive drugs in order to achieve adequate control of blood pressure. Treatment with a single antihypertensive agent is often insufficient to control hypertension, as monotherapy inhibits only one of several pathophysiological mechanisms of this multifactorial disease.

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 dose combination of aliskiren hemifumarate and valsartan [Valturna® (SPV100)] in the treatment of essential hypertension. Aliskiren is the first of a new class of non-peptide, low molecular weight renin inhibitors to be approved 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. Valsartan is an orally active non-peptide angiotensin II AT-1 receptor antagonist.

Blockade of the renin angiotensin system by an angiotensin II receptor antagonist in combination with a renin inhibitor offers optimal blockade by inhibiting the actions of angiotensin II at the receptor level and inhibiting plasma renin activity (PRA) and subsequent increases in angiotensin I and angiotensin II. Hence, co-administration of aliskiren prevents the reactive rise in PRA observed with valsartan. Because of their different modes of action, the combination of these drugs is expected to provide better blood pressure control than the component monotherapies. The fixed combination of these drugs should improve patient compliance when compared with non-fixed combination therapy.

Valsartan has been extensively studied (approved in 1996) and is widely used as monotherapy and in combination with HCTZ or amlodipine for the treatment of hypertension. Aliskiren hemifumarate (Tekturna®), though a new class drug approved in March 2007, is used as mono therapy or in combination with HCTZ for the treatment of hypertension. The fixed dose combination which is the subject of this application is the first of its type.

II. Recommendations

A. **Recommendation on Approvability:** Approvable

[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.

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

C. **Recommendations for Labeling:** None

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 valsartan combination to adult hypertensive patients. In this study, aliskiren hemifumarate and valsartan were administered orally, by gavage, separately and together (at a ratio of 1:1). (All doses of aliskiren hemifumarate are presented in terms of the aliskiren base.)

Daily administration of aliskiren hemifumarate and valsartan at doses of 300:300 mg/kg/day for 13 weeks resulted in minimal vacuolation of the squamous epithelium at the limiting ridge of the non-glandular stomach in both sexes. It was also noted in a few males treated with valsartan alone at 300 mg/kg/day. A trend to reversibility was seen in recovery group animals. Animals receiving valsartan alone also exhibited increased incidence of renal tubular basophilia and minimal but statistically significant decreases in erythrocyte parameters. Most of the toxic effects noted in previous studies with either drug administered alone were not demonstrated in the present study because of sub-threshold doses. The combined administration of aliskiren hemifumarate and valsartan did not augment any existing toxicities of the individual agents, nor induce any new toxicities.

Toxicokinetics data show that exposure to aliskiren was at least 3-fold higher in absence of valsartan than in combination with valsartan. In contrast, there was no effect of aliskiren on valsartan exposure.

Sponsor proposed specifications for the final product to include limits for three aliskiren hemifumarate degradation products: (b) (4)% for (b) (4), (b) (4)% for (b) (4) and (b) (4)% for (b) (4). In a 4 week oral gavage toxicity study in rats, the drug substance contained (b) (4) and (b) (4) levels of (b) (4)% and (b) (4)%, respectively. Total daily intake for these two impurities achieved at the highest aliskiren dose level (250 mg/kg/day) was, on body surface area basis, 8.7-fold higher than anticipated in humans (3.9 mg/day for a 60 kg individual with combined impurities at the specification limit of (b) (4)%). Similarly, total daily intake for (b) (4) achieved at the highest dose level (600 mg/kg/day) in a 13 week oral gavage toxicity study (impurity level (b) (4)%) was 2.7-fold higher than anticipated in humans (1.5 mg/day for a 60 kg individual with impurity at the specification limit of (b) (4)%). This suggests that animals were adequately exposed to all three impurities and, thus, the proposed specifications for these impurities in the drug product are supported. The toxicity of aliskiren hemifumarate with these impurities is comparable to that of aliskiren hemifumarate without them in these repeat dose toxicity studies. Furthermore, the batches containing the impurities were negative in Ames and chromosome aberration tests.

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

The combined administration of aliskiren hemifumarate and valsartan did not augment any existing toxicities of the individual agents in the 13 week toxicology study. Minimal histopathological changes in the non-glandular stomach were observed in rats treated at 300:300 mg (aliskiren:valsartan)/kg/day and 300 mg valsartan/kg/day and were attributed to administration of valsartan. Although the incidence was higher for the combination, the findings are of limited concern since human beings do not possess this tissue and valsartan has been used safely in the clinics for many years as a monotherapy and in combination with other antihypertensive agents. 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, 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).

Toxicokinetic findings in rats reveal reduced availability (75% and 82% reduction in AUC in females and males, respectively) of aliskiren when given in combination with valsartan. In humans, co-administration of valsartan decreased AUC_{τ} and $C_{max,ss}$ for aliskiren by 26% and 28%, respectively (clinical study #2216). Aliskiren marginally decreased the AUC and Cmax of valsartan in rats and humans. Based on the supporting PK/PD data and safety/efficacy profile in various clinical studies, the sponsor asserts that the effect of valsartan on aliskiren PK is not considered clinically relevant and, further, these changes were within the range of intra-subject variability for AUC_{τ} (20%) and $C_{max\ ss}$ (40%) observed for aliskiren in previous clinical studies.

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 valsartan in the same study, providing 2 to 3-fold multiples of human exposure. The absence of a safety margin for aliskiren may not be a concern since, according to the sponsor, the combination has demonstrated good clinical tolerance.

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 of Aliskiren Hemifumarate:Valsartan in Rats

Key Study Findings: The administration of aliskiren in combination with valsartan by daily oral gavage to the rat for 13 weeks at dose levels of 300/300 mg/kg/day increased the incidence of microscopic changes in the non-glandular stomach. The incidence of this finding was reduced after a 4-week recovery period, indicating a trend to reversibility. A no observed adverse effect level for this study is 150/150 (aliskiren:valsartan) mg/kg/day.

Study No.: Contract lab #802359, Sponsor #0680120
Location of Report: EDR
Conducting Laboratory and Location: (b) (4)
Dates of Study: The animals were initially dosed on September 20, 2006 and necropsied between December 21, 2006 and January 16, 2007.
GLP Compliance: Yes
QA'd Report: yes
Drug, Lot #: Aliskiren hemifumarate, batch #0544033, 98.6% pure; Valsartan, batch #C0657, 99.5% pure
Formulation: Appropriate amounts of the drugs were suspended in 0.5% (w/v) hydroxypropylcellulose aqueous solution under stirring. Suspensions were prepared daily for first 3 days of study, then weekly, and refrigerated and protected from light. Samples of the formulations from weeks 1, 6 and 13 were analyzed for concentration. Samples of the week 1 formulations were taken on the first day and last day of use for stability testing. Additionally, samples of formulation batches prepared for the 1st day of dosing were taken from the top, middle and bottom of the preparation vessels for homogeneity.
Animals
Species/Strain: Rats, IGS Wistar Hanover, Crl:WI(Han) (from (b) (4))
#/Animals/Group: 10/sex. An additional 6 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).
Age: 8 weeks old at initiation of dosing
Weight: Males: 183-243 gm, Females: 147-190 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 number identification	Dose level SPP100 (mg/kg/day)	Dose level Valsartan (mg/kg/day)	Animal number			
			Main study		Recovery study	
1/ Vehicle control	0	0	1001-1010	1501-1510	1011-1016	1511-1516
2/ SPV100[a]	50	50	2001-2010	2501-2510	-	-
3/ SPV100[a]	150	150	3001-3010	3501-3510	-	-
4/ SPV100[a]	300	300	4001-4010	4501-4510	4011-4016	4511-4516
5/ SPP100	300	0	5001-5010	5501-5504, 5506, 5508-5512	-	-
6/ Valsartan	0	300	6001-6010	6501-6510	-	-

a SPV100 is a combination of SPP100 and Valsartan

The doses of aliskiren hemifumarate (SPP100B) are expressed in terms of the base.

Dosing

Doses: Aliskiren hemifumarate and valsartan were administered (at a dose ratio of 1:1) at three dose levels: 50:50, 150:150 or 300:300 mg (aliskiren:VAL)/kg/day. Two additional groups of rats received either aliskiren hemifumarate or valsartan at 300 mg/kg/day (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 dose-related decreases in body weight and food consumption ($p > 0.05$) were noted in animals receiving 100:100 mg or more (aliskiren:valsartan)/kg/day. Also noted in these two groups were mild dose-related decreases in reticulocyte, leukocyte and lymphocyte counts. Notable histopathological changes in animals receiving 300:300 mg (aliskiren:valsartan)/kg/day were a decrease in extramedullary hemopoiesis in the spleen and increased thymic lymphocytolysis or cortical atrophy.

Route, Mode and Duration of Administration: Orally by gavage (20 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.

Hematology[1] and Clinical Biochemistry[2]: Blood samples were collected at the end of the treatment (from the abdominal aorta) and recovery periods (from the jugular vein) from all surviving animals under anesthesia. The animals were fasted overnight.

[1] erythrocytes, hematocrit, hemoglobin, red cell volume distribution width, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration blood cell morphology, reticulocytes, white blood cell count, white blood cell differential, mean platelet volume

[2] 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

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.
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 the animals that were found dead or euthanized prior to scheduled necropsy, and all gross lesions, tissues showing treatment-related findings and target organs (kidney, liver, bone marrow, spleen, thymus, stomach, large and small intestine and urinary bladder) from all animals in the remaining groups.

TABLE 3.1.1.2
TISSUES SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

W	P	Adrenals		P	Pancreas
	P	Aorta (thoracic)	W	P	Parathyroid
	P	Bone marrow (in bone)	W	P	Pituitary
W	P	Brain	W	P	Prostate
	P	Cecum		P	Rectum
	P	Colon		P	Salivary gland
	P	Duodenum		P	Sciatic nerve
	P	Epididymides		P	Seminal vesicles
	P	Esophagus		P	Skeletal muscle
	P	Eyes		P	Skin
	P	Harderian glands		P	Spinal cord
W	P	Heart	W	P	Spleen
	P	Ileum		P	Sternum
	P	Jejunum		P	Stomach
W	P	Kidneys	W	P	Testes
	P	Lacrimal glands	W	P	Thymus
	P	Larynx	W	P	Thyroid
W	P	Liver		P	Tongue
W	P	Lungs		P	Trachea
	P	Lymph node – mandibular		P	Ureters
	P	Lymph node – mesenteric		P	Urinary bladder
	P	Mammary gland	W	P	Uterus
	P	Optic nerves		P	Vagina
W	P	Ovaries		P	Macroscopic lesions
	P	Oviducts			Animal identification

w: Organ weighed; P: processed

Toxicokinetics: Blood samples for determination of levels of aliskiren and valsartan 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. Mean concentrations of all samples collected in weeks 1 and 13 were within the expected range (86% to 113% of target) with the exception of the high combination dose in week 13 (valsartan 81% of expected). Additionally, the concentrations in a few samples collected in week 6 varied from 84% to 116%.

Mortality: Four animals died during the study. According to the sponsor none of these deaths were attributed to treatment with drug substance. One female (#2506) receiving 50:50 mg (aliskiren:valsartan)/kg/day was found dead on day 33. Microscopic examination revealed severe pyelonephritis as the cause of death, which was considered secondary to the presence of bladder calculi. The remaining deaths were in the group receiving 300 mg aliskiren/kg/day. A female (#5512) was found dead on day 85 with hemorrhage in the ventral cervical area and the thorax and the death was considered accidental. A male (#5008) was euthanized on day 44 after it displayed decreased activity, sluggish breathing with abnormal sounds, dehydration and was cold to touch. A female (#5503) that was breathing with abnormal sounds on the previous day was found dead on day 30. A cause of death could not be established for this animal.

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

Body Weights and Food Consumption: There were no significant treatment-related changes in either body weight or food consumption for the duration of the study.

Ophthalmoscopy: No remarkable ocular changes.

Hematology: Minimal decreases (9% to 12%, $p < 0.05$) in red cell parameters (RBC, hemoglobin and hematocrit) relative to control were noted in animals receiving 300 mg/kg/day valsartan alone. No differences were seen at the end of the recovery period.

Clinical Chemistry: At the end of treatment period, mild to moderate, non-dose-dependent decreases in mean ALT (12 to 32%) and AP (16 to 34%) relative to control were noted in males in all treated groups ($p < 0.05$ for the high dose combination, aliskiren hemifumarate, and valsartan groups) and in females treated with aliskiren hemifumarate or valsartan alone ($p < 0.05$). In addition, nondose-dependent decreases in creatine kinase (20 to 36%) relative to control were noted in females in all dose groups ($p < 0.05$ for the high dose combination, aliskiren hemifumarate, and valsartan groups) and in males receiving aliskiren hemifumarate or valsartan alone ($p > 0.05$). None of these changes correlated with histopathological findings and thus their significance remains uncertain. These differences were no longer seen at the end of recovery.

Urinalysis: A mean increase (12 to 50%) in urine volume relative to control was noted at the end of the treatment period for males in all dose groups and for females in the high dose combination and aliskiren groups. The increases were statistically significant for both males (147%) and females (70%) of the aliskiren treatment group. They were observed with minimal concurrent decreases in urine specific gravity. There were no differences in urine volume at the end of the recovery period, indicating reversibility of changes.

Organ Weights: Statistically significantly lower than control mean heart weights (both absolute and relative) were noted in males (14 and 18%) at 300:300 mg and females (8 and 14%) at 150:150 or more mg (aliskiren:valsartan)/kg/day and in both sexes given valsartan alone. This weight difference was no longer present at the end of the recovery period.

Gross Pathology: No treatment-related findings

Histopathology: Microscopic findings considered related to treatment were noted in the non-glandular stomach. Vacuolation of the squamous epithelium at the limiting ridge was present in 4/10 males and 4/10 females treated with the high dose combination and 2/10 males treated with valsartan alone. In the kidney, an increase in the incidence of tubular basophilia was noted in rats administered 300 mg valsartan/kg/day (9/20 animals). The incidence in control, low, mid and high dose combination and aliskiren groups was 1/20, 3/20, 3/20, 2/20 and 1/20, respectively. In the recovery group animals, vacuolation of the squamous mucosa of the stomach was noted in 1/6 males treated with the high dose combination.

Toxicokinetics: For aliskiren or valsartan, due to variability, no tendency could be drawn with regard to dose proportionality of exposure for either day 1 or week 13 for both males and females. A higher exposure (AUC_{0-24h}) to aliskiren was noted, either in combination with valsartan (1.6- to 2.3 fold) or alone (1.9- to 3.3- fold), in week 13 than on day 1. Another significant finding was that exposure to aliskiren in week 13 was lower by 75% and 82%, respectively, in females and males, in the presence of valsartan than in the absence of valsartan (Table 3.1.1.3). In contrast, no effect of aliskiren on valsartan exposure was noted (Table 3.1.1.4). No accumulation of valsartan was detected between day 1 and week 13. Apparent peak plasma concentrations of aliskiren or valsartan were reached between 0.5 and 1 hr post dose for all groups except for the group receiving aliskiren alone, where concentrations peaked 3 hr post dose on day 1. No gender differences were noted.

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

Parameter (units)	Group 2 (SPP100+VAL489) (50 + 50) mg/kg/day		Group 3 (SPP100+VAL489) (150 + 150) mg/kg/day		Group 4 (SPP100+VAL489) (300 + 300) mg/kg/day		Group 5 (SPP100+VAL489) (300 + 0) mg/kg/day		Group 6 (SPP100+VAL489) (0 + 300) mg/kg/day	
	Males (n=10)	Females (n=10)	Males (n=10)	Females (n=10)	Males (n=10)	Females (n=10)	Females (n=10)	Males (n=10)	Males (n=10)	Females (n=10)
	Day 1									
t_{max} (h)	3	1	0.5	0.5	1	1	3	3	0	0
C_{max} (ng/mL)	10.4	83.0	665 9.88(*)	32.1	19.3	24.7	161	79.0	0	0
C_{max}/Dose (ng/mL/mg/kg/day)	0.208	1.66	4.43 0.0659(*)	0.214	0.0643	0.0823	0.537	0.263	0	0
$AUC_{(0-24h)}$ (ng.h/mL)	40.3	116	367 39.1(*)	64.3	116	238	793	451	0	0
$AUC_{(0-24h)}$/Dose (ng.h/mL/mg/kg/day)	0.807	2.32	2.44 0.261(*)	0.429	0.386	0.792	2.64	1.50	0	0
	Week 13									
t_{max} (h)	0.5	1	0.5	1	0.5	1	1	1	0	0
C_{max} (ng/mL)	5.79	5.75	21.7	17.7	41.9	51.6	375	203	0	0
C_{max}/Dose (ng/mL/mg/kg/day)	0.116	0.115	0.145	0.118	0.14	0.172	1.25	0.677	0	0
$AUC_{(0-24h)}$ (ng.h/mL)	50.1	47.6	190	123	265	371	1510	1500	0	0
$AUC_{(0-24h)}$/Dose (ng.h/mL/mg/kg/day)	1.00	0.953	1.27	0.820	0.882	1.24	5.03	4.99	0	0

(*) TK value when sample 0001_03004 on day 1 0.5h for SPP100 is deactivated, and also not taken account into TK parameters calculation.

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

Parameter (units)	Group 2 (SPP100+VAL489) (50 + 50) mg/kg/day		Group 3 (SPP100+VAL489) (150 + 150) mg/kg/day		Group 4 (SPP100+VAL489) (300 + 300) mg/kg/day		Group 5 (SPP100+VAL489) (300 + 0) mg/kg/day		Group 6 (SPP100+VAL489) (0 + 300) mg/kg/day	
	Males (n=10)	Females (n=10)	Males (n=10)	Females (n=10)	Males (n=10)	Females (n=10)	Males (n=10)	Females (n=10)	Males (n=10)	Females (n=10)
	Day 1									
t_{max} (h)	0.5	0.5	1	0.5	1	1	0	0	1	0.5
C_{max} (ng/mL)	6250	3950	21200	8800	10600	24600	0.00	0.00	20400	12400
C_{max}/Dose (ng/mL/mg/kg/day)	125	79.0	141	58.7	35.3	82.0	0.00	0.00	68.0	41.3
$AUC_{(0\text{-}24h)}$ (ng.h/mL)	16600	11600	83400	44200	70700	146000	0.00	0.00	121000	145000
$AUC_{(0\text{-}24h)}$/Dose (ng.h/mL/mg/kg/day)	331	233	556	295	236	485	0.00	0.00	405	485
	Week 13									
t_{max} (h)	0.5	0.5	0.5	1	1	0.5	0	0	0.5	0.5
C_{max} (ng/mL)	5070	5190	14300	8370	8900	10000	0.00	0.00	10300	15900
C_{max}/Dose (ng/mL/mg/kg/day)	101	104	95.3	55.8	29.7	33.3	0.00	0.00	34.3	53.0
$AUC_{(0\text{-}24h)}$ (ng.h/mL)	17500	12700	66700	39200	65800	94700	0.00	0.00	96900	165000
$AUC_{(0\text{-}24h)}$/Dose (ng.h/mL/mg/kg/day)	351	254	445	261	219	316	0.00	0.00	323	549

SPP100: aliskiren (the doses of aliskiren hemifumarate are expressed in terms of the base).
VAL: valsartan

3.1.2. 13 Week Oral Gavage Impurity (b) (4) Qualification Study in Rats

Key Study Findings: Daily oral administration of aliskiren hemifumarate (containing (b) (4) impurity) to rats for 13 weeks resulted in 17 deaths, 7 at 200 and 10 at 600 mg/kg/day. Clinical signs of respiratory disturbances and histopathological findings in the respiratory tract suggest aspiration of test substance into the system. Deaths were attributed to pulmonary congestion and edema followed by congestive heart failure. A statistically significant decrease in mean body weight gain relative to control was noted for surviving males receiving 600 mg/kg/day. A no observed adverse effect level for this study is 60 mg/kg/day.

Study No.: 966132
Location of Report: EDR
Conducting Laboratory and Location: Novartis Pharma AG, Preclinical Safety, Sections of Toxicology and Pathology, Basel, Switzerland.
Dates of Study: The animals were initially dosed on January 7, 1997 and necropsied between April 8 and May 6, 1997.
GLP Compliance: Yes
QA'd Report: yes
Drug, Lot #: Aliskiren hemifumarate, lot #817196. This batch contains (b) (4), one of the degradation products (considered as impurity) at a concentration of (b) (4)%.
Formulation: Aliskiren hemifumarate was dissolved in distilled water and refrigerated. It was prepared approximately once in three weeks. Samples of the formulations from all weeks were analyzed for concentration.
Animals

Species/Strain: Rats, Tif:RAIf (SPF)
#/Animals/Group: See Table 3.1.2.1.
Age: 7 to 9 weeks old at initiation of dosing
Weight: Males: 190-304 gm, Females: 158-229 gm, at initiation of dosing
Husbandry: Animals of the same sex and same dosing group were housed 5 per cage. Food and water were available *ad libitum*.

Dosing

Doses: Aliskiren hemifumarate was administered at three dose levels: 60, 200 or 600 mg/kg/day (Table 3.1.2.1). Doses were selected on the basis of a 2 week dose range-finding oral toxicity study in the same rat strain in which 1 of 12 males (on study day 12) and 1 of 12 females (study day 15) receiving 600 mg/kg/day died. Necropsy was not conducted. Also noted in this high dose group was a moderate increase in the activities of the enzymes lactate dehydrogenase and creatinine kinase.
Route, Mode and Duration of Administration: Orally by gavage, 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.

TABLE 3.1.2.1
STUDY DESIGN

	Group 1	Group 2	Group 3	Group 4
	Control Article	CGP 60536 B	CGP 60536 B	CGP 60536 B
Dose (mg/kg)	0	60	200	600
Volume (mL/kg)	10	10	10	10
No. of animals (main study)	10 m + 10 f	10 m + 10 f	11 m + 12 f	10 m + 12 f
Recovery*	5 m + 5 f		4 m + 3 f	5 m + 3 f
Satellite**	3 m + 3 f	6 m + 6 f	6 m + 6 f	6 m + 6 f
Duration of treatment	91 / 92 days			

*Recovery groups were allowed a period of one month without treatment
** Satellite groups were dosed and sacrificed after the last blood sampling
CGP 60536B: Aliskiren hemifumarate

Observations and Measurements

Clinical Signs: All animals were observed daily for clinical signs and mortality.
Body Weight: Daily during the dosing period, 3 times per week during recovery period.
Food Consumption: Twice per week
Ophthalmology: Conducted once pretest for all dose groups and in week 13 for control and high dose groups only
Urinalysis: Urine was collected over a 3 hr period in weeks 4, 8, 12 and 17 (high dose and control groups only). The following parameters were assessed: color, volume, specific gravity, pH, protein, bilirubin, blood, leukocytes, nitrite, glucose, ketone bodies and urobilinogen.
Hematology[1] and Clinical Biochemistry[2]:
Blood samples were collected in weeks 5, 8/9, 13 and 18 from orbital plexus under light isoflurane anesthesia. The animals were not fasted overnight.
Pathology: A complete necropsy was conducted on all (main study and recovery phase) animals, including those found dead, with a detailed internal examination. Representative samples of the protocol tissues (Table 3.1.2.2) 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 groups, and from the animals in other groups that

[1] erythrocytes, hematocrit, hemoglobin, red cell volume distribution width, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocytes, white blood cell count, white blood cell differential, thrombocytes, partial thromboplastin time, prothrombin time, thrombin time, fibrinogen
[2] ALT, AST, AP, cholinesterase, bilirubin, total protein, glucose, urea, creatinine, sodium, potassium, chloride, calcium, phosphate, triglycerides, cholesterol, magnesium

were found dead or were euthanized prior to scheduled necropsy. Organ weights were determined for scheduled sacrifice animals only.

TABLE 3.1.2.2
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

Adrenal glands*	Kidneys*	Seminal vesicles
Aorta	Knee joint	Skin/mammary area
Bone marrow: sternum	Lacrimal gland, extraorbital	Spinal cord
Bone marrow: femur	Liver*	Spleen*
Brain*	Lung*	Stomach
Cecum	Lymph node (axillary, mesenteric)	Testes*
Colon	Ovaries*	Thigh muscle
Duodenum	Pancreas	Thymus*
Epididymides	Parathyroid	Thyroid
Esophagus	Pituitary*	Tongue
Eyes with optic nerves	Prostate*	Trachea
Harderian gland	Rectum	Urinary bladder
Heart*	Salivary gland	Uterus
Ileum	Sciatic nerve	Vagina
Jejunum		Gross lesions

*: Organ weighed

Toxicokinetics: Blood samples for determination of levels of aliskiren were collected from the sublingual vein under anesthesia on day 1 from satellite animals (which were sacrificed thereafter) and on the last day of treatment (males) or one day before the last day of treatment (females) from selected main study and recovery animals. The time points and allocation of animals to each period is given in the following Table.

Dose (mg/kg)/ subgroup	No. of animals	Time of blood collection	
		Day 1 (satellite animals)	One day during the last treatment week*
0/-	3 m + 3 f	2 hours postdose	2 hours postdose
60/a	3 m + 3 f	0.25, 1 and 4 hours postdose	0.25, 1 and 4 hours postdose
60/b	3 m + 3 f	0.5, 2 and 8 hours postdose	0.5, 2 and 8 hours postdose
200/a	3 m + 3 f	0.25, 1 and 4 hours postdose	0.25, 1 and 4 hours postdose
200/b	3 m + 3 f	0.5, 2 and 8 hours postdose	0.5, 2 and 8 hours postdose
600/a	3 m + 3 f	0.25, 1 and 4 hours postdose	0.25, 1 and 4 hours postdose
600/b	3 m + 3 f	0.5, 2 and 8 hours postdose	0.5, 2 and 8 hours postdose

Results

Analysis of Formulations: The dosing formulations were stable. Mean concentrations of all samples were within the expected range (93% to 110% of target).

Mortality: Oral gavage administration of aliskiren hemifumarate resulted in deaths or moribund sacrifices of 2 males and 8 females at 600 mg/kg/day, and 3 males and 4 females at 200 mg/kg/day (Table 3.1.2.3). Necropsy findings in all 17 animals showed foamy bronchial outflow, discoloration of the lungs, foamy contents in the trachea and a deformed trachea. Microscopical examination revealed pulmonary edema in 4 and 8 animals, respectively, at 200 and 600 mg/kg/day, and fibrinous necrotizing tracheitis in 6 animals at 600 mg/kg/day (see Table 3.1.2.5). According to the sponsor, deaths could be attributed to acute bronchopneumonia and accidental instillation or aspiration of the formulation into the respiratory tract. Concomitant congestion of heart, liver and kidneys in most of these animals suggest heart failure as an additional cause of death.

TABLE 3.1.2.3
FOUND DEAD OR EUTHANIZED *IN EXTREMIS*

Dose, mg/kg/day	# of deaths	Study day and cause of death
200	3 M	#1093 spontaneous death on day 7 #1085 spontaneous death on day 62 #1092 spontaneous death on recovery day 4
	4 F	#1119 euthanized *in extremis* on day 26 #1118 spontaneous death on day 52 #1117 spontaneous death on day 86 #1114 euthanized *in extremis* on recovery day 1
600	2 M	#1136 spontaneous death on day 72 #1137 spontaneous death on day 81
	8 F	#1159 euthanized *in extremis* on day 36 #1160 euthanized *in extremis* on day 37 #1158 euthanized *in extremis* on day 55 #1162 euthanized *in extremis* on day 61 #1166 spontaneous death on day 61 #1169 spontaneous death on day 67 #1165 spontaneous death on day 76 #1157 spontaneous death on day 83

Clinical Signs: Respiratory noises and salivation occurred predominantly in animals, which had to be killed prematurely. Respiratory rales were still present in high dose animals at the end of the recovery period.
Body Weights: Minimal reduction in body weight gain relative to control was noted for males at 200 ($p > 0.05$) and 600 (11%, $p < 0.05$) mg/kg/day throughout treatment and for the first 2 weeks during the recovery period in a dose dependent manner.
Food Consumption: There were no significant treatment-related changes
Ophthalmoscopy: No remarkable ocular changes.
Urinalysis: No relevant findings
Hematology: Minimal decreases ($p < 0.05$) in red cell parameters (RBC, hemoglobin and hematocrit) relative to control were noted in females receiving 600 mg/kg/day. No differences were seen in this group at the end of the recovery period.

Clinical Chemistry: No significant differences between drug treated and control groups.
Organ Weights: Statistically significant ($p < 0.05$) decreases in mean liver weights (both absolute and relative) relative to control were noted for males at 600 mg/kg/day. Absolute and relative thymus weights were significantly ($p < 0.05$) lower than control for males at 200 or more mg/kg/day and for females at 600 mg/kg/day. No histopathologic correlates for these organ weights were evident. This weight difference was no longer present at the end of the recovery period.
Gross Pathology: No treatment-related findings were evident in animals surviving to scheduled sacrifice. In animals that were killed or died before scheduled sacrifice, findings noted in the lungs (discoloration) and trachea (foamy contents and deformation) correlated with the signs of respiratory distress (Table 3.1.2.4).

TABLE 3.1.2.4
SUMMARY OF RELEVANT MACROSCOPIC FINDINGS IN UNSCHEDULED DEATHS

Main + recovery study	Group/Sex Dose (mg/kg) No. of deaths	03 M 200 3*	03 F 200 4	04 M 600 2	04 F 600 8
Bronchial outflow, foamy		1	2	1	5
Discoloration of lungs		1*	2	2	2
Tracheal contents: foamy				1	1
Deformed trachea					1

* = Including the rat which died early in the recovery period

Histopathology: Microscopical examination of 17 animals that were found dead or killed before scheduled sacrifice revealed findings in lungs, trachea, heart, liver, kidneys and thymus. Pulmonary edema (accompanied by congestion) was noted in 12 animals at 200 or more mg/kg/day and fibrinous necrotizing tracheitis in 6 animals at 600 mg/kg/day. Also noted in these animals were inflammatory changes in and around the trachea. Additional findings included congestion of the heart, liver and kidneys. Based on these findings, the sponsor asserts that aspiration of the formulation into the respiratory tract during gavage administration, followed by irritation of the mucosa and development of tracheal necrosis, suggests a relationship between the dose and the degree of tracheopulmonary irritation (Table 3.1.2.5). Concomitant congestion of heart, liver and kidneys in most of these animals suggests heart failure as an additional cause of death. There were no relevant microscopic findings in the animals that survived until the end of the treatment period.

TABLE 3.1.2.5
SUMMARY OF RELEVANT MICROSCOPIC FINDINGS IN UNSCHEDULED DEATHS

Main + recovery study Organ/finding	Group/Sex Dose (mg/kg) No. of deaths	03 M 200 3*	03 F 200 4	04 M 600 2	04 F 600 8
Lungs	No. examined	3*	4	2	8
Congestion		3*	2	2	4
	Av. grading	3.3	3.0	4.0	3.3
Alveolar edema		3*	1	1	7
	Av. grading	2.7	3.0	3.0	2.4
Acute bronchopneumonia		1			2
	Av. grading	3.0			1.5
Aspiration pneumonia			1		
	Av. grading		4.0		
Trachea	No. examined	3*	4	2	8
Fibrinous necrotizing tracheitis				1	5
Peritracheitis	Av. grading			4.0	3.8
			1		1
	Av. grading		2.0		1.0
Heart	No. examined	3*	4	2	8
Congestion		2	3	2	3
	Av. grading	3.0	2.0	3.5	3.3
Dilatation		1		1	2
	Av. grading	1.0		2.0	1.5
Liver	No. examined	3*	4	2	8
Congestion		3*	2	1	4
	Av. grading	2.7	2.0	3.0	1.5
Necrosis/ Single cell necr.		2			2
	Av. grading	1.5			1.0
Microvacuolation		1			3
	Av. grading	3.0			1.3
Kidneys	No. examined	3*	4	2	8
Congestion		3*	4	2	3
	Av. grading	2.7	1.8	1.5	1.3
Thymus	No. examined	3*	4	2	8
Atrophy			2		3
	Av. grading		3.5		1.7

* = Including the rat which died early in the recovery period

Grade 1: minimal/very few/very small
Grade 2: slight/few/small
Grade 3: moderate/moderate number /moderate size
Grade 4: marked/many/large
Grade 5: massive/extensive number/extensive size

Toxicokinetics: Aliskiren hemifumarate is rapidly absorbed, reaching peak plasma concentrations 0.25 to 2 hr post-dose. After single or repetitive doses, systemic exposure (AUC_{0-8h}) to aliskiren in males and females increased with increasing dose level but not proportionately (Table 3.1.2.6). Since inter-animal plasma level variability was high (mean coefficient of variation, 38% to 66%), any gender difference would be difficult to detect. Based on AUC_{0-8h}, a higher exposure to aliskiren was noted on day 91 than on day 1 for both males (1.18 to 5.58 times higher) and females (0.40 to 1.66 times higher) depending on the dose. This suggests a slight accumulation of test substance, which is higher in males than in females. Elimination of aliskiren from plasma was rapid in the first phase (until 2-4 hr postdose) and slower in a second phase. However, a large variation in $t_{1/2}$ (1.29 to 20.6 hr) was noted.

TABLE 3.1.2.6

TOXICOKINETIC PARAMETERS OF ALISKIREN (CGP 60536) IN RAT PLASMA

Dose	PK	Male		Female	
(mg/kg)	parameter	Day 1	Day 91	Day 1	Day 91
60	C_{max}	310	494	283	350
	$C_{maxspec}$	5.71	9.10	5.21	6.45
	t_{max}	0.25	0.25	0.5	1
	$AUC_{(0-8h)}$	217	1210	614	709
	AUC_{spec}	4.0	22.3	11.3	13.1
	t½	1.82	2.02	na	1.29
200	C_{max}	315	1610	329	1220
	$C_{maxspec}$	1.74	8.90	1.82	6.74
	t_{max}	2	0.25	0.25	0.25
	$AUC_{(0-8h)}$	1020	2800	1420	2360
	AUC_{spec}	5.63	15.5	7.84	13.0
	t½	1.39	na	1.55	2.03
600	C_{max}	5090	1800	25700	2120
	$C_{maxspec}$	9.37	3.31	47.3	3.90
	t_{max}	0.5	0.25	0.5	0.5
	$AUC_{(0-8h)}$	4350	5150	14500	5780
	AUC_{spec}	8.01	9.48	26.7	10.6
	t½	4.37	8.59	3.23	20.6

C_{max} : maximum concentration (ng/mL) ; $C_{maxspec}$: maximum concentration corrected to a dose of 1 mg/kg active substance (ng/mL per mg/kg) ; t_{max} : sampling time (h) corresponding to C_{max} ; $AUC_{(0-8h)}$: area under the concentration curve calculated over the time interval 0-8 h (ng·h/mL) ; AUC_{spec} : $AUC_{(0-8h)}$ corrected to a dose of 1 mg/kg active substance (ng·h/mL per mg/kg) ; t½ : apparent terminal elimination half-life (h). na : not available.

$C_{maxspec}$ and AUC_{spec} were calculated by dividing C_{max} and $AUC_{(0-8h)}$ by the dose expressed in mg of free base of CGP 60536 (i.e. 54.3, 181 and 543 mg/kg of CGP 60536 free base for 60, 200 and 600 mg/kg of CGP 60536B, respectively).

3.1.3. 4 Week Oral Gavage Impurity (b) (4) Qualification Study in Rats

The objective of the study was to investigate the potential toxicity of aliskiren hemifumarate impurities during daily oral gavage to the Wistar rat for 4 weeks.

Key Study Findings: Aliskiren hemifumarate pure and aliskiren hemifumarate spiked with impurities caused an equal degree (minimal to slight) of mucosal hyperplasia in the cecum. The toxic potential of aliskiren hemifumarate with impurities (b) (4) and (b) (4) is considered comparable to that of aliskiren hemifumarate without those impurities.

Study No.: 802895, Novartis ref #0770449
Location of Report: EDR
Conducting Laboratory and Location: (b) (4)
Dates of Study: The animals were initially dosed on September 20, 1997 and necropsied October 18/19, 1997.
GLP Compliance: Yes
QA'd Report: Yes
Drug: Aliskiren hemifumarate, batch #CO132, purity 99.2%. TOX2/Aliskiren hemifumarate (batch #07/1, purity 98.3 %) contains two impurities: (b) (4)%) and (b) (4) %), Total (b) (4)%.
Formulation: Both aliskiren hemifumarate and TOX2/Aliskiren hemifumarate were dissolved in purified water and refrigerated protected from light. Solutions were prepared once a week. Samples of the formulations prepared in weeks 1 and 4 were analyzed for stability (for 24 hr at room temperature or up to 8 days when refrigerated) and concentration.
Animals
Species/Strain: Rats, IGS Wistar Hanover, Crl:WI(Han) (from (b) (4))
#/Animals/Group: Each treated and control group consisted of 10 rats/sex (Table 3.1.3.1).
Age: 8 weeks at initiation of dosing
Weight: Males: 194-240 gm, Females: 143-179 gm, at initiation of dosing
Husbandry: Animals of the same sex and same dosing group were housed 2 per cage. Food and water were available *ad libitum* except for study defined fasting procedures
Dosing
Doses: Aliskiren hemifumarate spiked with two impurities (b) (4)%) and (b) (4) %), Total (b) (4)%) was administered at two dose levels: 50 or 250 mg/kg/day. An additional group of rats received pure aliskiren hemifumarate at 250 mg/kg/day (Table 3.1.3.1). Doses are expressed as free base equivalents. Doses were selected on the basis of a 26 week oral toxicity study (#1940/18, reviewed under NDA 21,985) in the same rat strain in which a significant decrement in group mean body weight gain relative to control was noted for animals receiving aliskiren at 150 or 250 mg/kg/day. Histopathologic findings comprised minor inflammatory and degenerative changes of the respiratory epithelium of the tracheal upper respiratory tract and hyperplasia in the cecum at 250 mg/kg/day.
Route, Mode and Duration of Administration: Orally by gavage (5 ml/kg), once daily, for 28 days. Control animals received the vehicle.

TABLE 3.1.3.1
STUDY DESIGN

Group number identification	Dose level (mg/kg/day)	Animal number	
		Main study	
		Males	Females
1/ Vehicle control	0	1001-1010	1501-1510
2/ TOX2/SPP100	50	2001-2010	2501-2510
3/ TOX2/SPP100	250	3001-3010	3501-3510
4/ SPP100	250	4001-4010	4501-4510

SPP100: Aliskiren hemifumarate
TOX2/SPP100: Aliskiren hemifumarate spiked with 2 impurities, (b) (4)%) and (b) (4)%).

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 period.
Ophthalmology: Conducted once pretest and in week 4.
Urinalysis: Overnight urine samples were collected from individual animals at the end of the treatment 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, glucose, ketones and urobilinogen.
Hematology[1] and Clinical Biochemistry[2]: Blood samples were collected at the end of the treatment (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 3.1.3.2) were collected from all study animals and processed for microscopic examination which was performed on the tissues from all animals in the control and two high dose groups, from the animals that were found dead or euthanized prior to scheduled necropsy, and all gross lesions in the remaining group (50 mg/kg/day).
Toxicokinetics: Blood samples for determination of levels of aliskiren were collected by jugular vein puncture on day 28 at 0.5, 1, 3, 7 and 24 hr post dose (n=2/sex/group/time point).

[1] erythrocytes, hematocrit, hemoglobin, red cell volume distribution width, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, blood cell morphology, reticulocytes, white blood cell count, white blood cell differential, thrombocytes, activated partial thromboplastin time, prothrombin time, fibrinogen

[2] 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

TABLE 3.1.3.2
TISSUES SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

W	P	Adrenals	W	P	Oviducts
	P	Aorta (thoracic)		P	Pancreas
	P	Bone and marrow (sternum)**	W	P	Parathyroid
W	P	Brain	W	P	Pituitary
	P	Cecum	W	P	Prostate
	P	Colon		P	Rectum
	P	Duodenum			
	P	Epididymides*		P	Salivary gland (mandibular)
	P	Esophagus		P	Sciatic nerve
				P	Seminal vesicles
	P	Eyes*		P	Skeletal muscle
	P	Femorotibial joint**		P	Skin (inguinal)
	P	Harderian glands		P	Spinal cord (cervical, thoracic, lumbar)
W	P	Heart	W	P	Spleen
	P	Ileum		P	Stomach
	P	Jejunum	W	P	Testes*
W	P	Kidneys	W	P	Thymus
	P	Lacrimal glands	W	P	Thyroid lobes
	P	Larynx		P	Tongue
W	P	Liver			
	P	Lung++		P	Trachea
	P	Lymph node - tracheobronchial		P	Ureter (bilateral)
	P	Lymph node - mandibular		P	Urinary bladder
	P	Lymph node - mesenteric	W	P	Uterus (horns, body and cervix)
	P	Mammary gland (inguinal)		P	Vagina
	P	Optic nerves*		P	Macroscopic lesions
W	P	Ovaries			Animal identification

* Fixed in Davidson's (eyes and optic nerves) or modified Davidson's (testes and epididymides) fluid.

** Bone decalcified prior to sectioning.

++ Infused with neutral buffered 10% formalin.

For all animals, 3 femoral bone marrow smears were prepared and stained for possible examination.

W: Organ weight; P: processed

Results

Analysis of Formulations: The dosing formulations were stable. Mean concentrations of all samples were within the expected range (96% to 109% of target).
Mortality: Oral gavage administration of aliskiren hemifumarate at 250 mg/kg/day resulted in the death of a female (#4503) on study day 6. There were no clinical signs prior to death. Histological examination revealed marked inflammation of the larynx and slight inflammation of the trachea with large amounts of fibrin in the lumen. The sponsor contends that the death is likely related to the dosing procedure.
Clinical Signs: Respiratory noises (labored breathing) were noted for a few animals in the high dose groups. This is a drug-related phenomenon as its aspires into the lungs.
Body Weights and Food Consumption: There were no significant treatment-related changes in either body weight or food consumption for the duration of the study.
Ophthalmoscopy: No remarkable ocular changes.
Urinalysis: No treatment-related effects
Hematology: No significant changes.
Organ Weights: There were no changes relative to control group.
Gross Pathology: No treatment-related findings
Histopathology: Main microscopic finding considered related to treatment was minimal to slight mucosal hyperplasia in the cecum. The incidences for control, 50 (spiked), 250 (spiked), and 250 (reference) mg/kg/day were, respectively, 3/10, 0/10, 7/10, 4/10 for males, and 2/10, 4/10, 5/10, 5/10 for females.
Toxicokinetics: Apparent peak plasma concentrations of aliskiren were reached 1 hr post dose for all groups and for both genders. In the low dose group, concentration of aliskiren above the limit of quantitation was measured in one female sampled at 1 hr post-dose. Due to high inter-animal variability, significant differences in exposure between reference batch and spiked batch could not be documented. No gender differences were noted (Table 3.1.3.3).

TABLE 3.1.3.3
TOXICOKINETIC PARAMETERS OF ALISKIREN IN RAT PLASMA

	Dose group			
	3- high dose		4- high dose	
	250 mg/kg/day (TOX2/SPP100)		250 mg/kg/day (reference batch)	
Time (h)	Male	Female	Male	Female
t_{max}	1.00	1.00	1.00	1.00
C_{max}	114	509	152	123
C_{max}/dose	0.456	2.04	0.608	0.492
$AUC_{(0-24h)}$	653	1390	958	1210
$AUC_{(0-24h)}$/dose	2.61	5.55	3.83	4.85

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 and $AUC_{(0-24h)}$ in (ng·hours/mL)/(mg/kg/day).

3.2. Genetic Toxicology

3.2.1. Ames Assay. In Vitro Bacterial Test of Aliskiren Hemifumarate with Impurities

The objective of the study was to test the mutagenic effect of aliskiren hemifumarate and (b) (4)% of related impurities ((b) (4) and (b) (4)).

Key Findings: Aliskiren hemifumarate with total of (b) (4)% of related impurities (b) (4) and (b) (4) was reproducibly negative in all tester strains both with and without metabolic activation.

Study No: 0770448
Location of Report: EDR
Conducting Laboratory and Location: Novartis Crop Protection AG, Toxicology/Genetic Toxicology, CH-4002 Basel, Switzerland
Dates of Study: Initiated on October 10 and terminated on November 08, 1997.
GLP Compliance: Yes
QA'd Report: Yes
Drug: TOX2/Aliskiren hemifumarate (batch #07/1, purity 98.3 %) contained aliskiren hemifumarate and two impurities: (b) (4)%) and (b) (4)%), Total (b) (4)% .

Methods

Five *Salmonella typhimurium* strains (TA97a, TA98, TA100, TA102, TA1535) were used. Test substance was dissolved in DMSO (concentrations expressed in terms of base). Since this study was done to confirm the results of a previous study with another batch of the same test substance (study #966158, see review of NDA #21,985), only one experiment was done. Aliskiren hemifumarate was tested at doses of 312.5, 525, 1250, 2500 and 5000 µg/plate with and without metabolic activation. Concentrations are expressed as free base equivalents. The experiment was conducted using the plate incorporation method without preincubation.

Basis of dose selection: The concentrations were chosen on the basis of the results of study #966158 (see review of NDA #21,985).

Metabolic activation system: S9 homogenate (liver microsomal enzymes) was prepared from the livers of male Aroclor-induced rats.

Controls

Negative control: DMSO

Positive controls: Each tester strain was treated with an appropriate positive control substance (Table 3.2.1.1).

Criteria for a valid study: The assay is considered acceptable if the solvent control data for all tester strains are within the laboratory's historical control range for spontaneous mutant frequency and the positive controls induce increases in the mutation frequency which are significant.

Criteria for a positive result: For test substance to be considered positive, it had to produce in at least one concentration, a response equal to 2 or more times the corresponding negative control count for strains TA97a, TA98, TA100, TA1535; 1.5 times the corresponding negative control count for strain TA102. The results have a

greater significance if a concentration-related increase in the number of revertant colonies is observed.

TABLE 3.2.1.1
BACTERIAL REVERSE MUTATION ASSAY. POSITIVE CONTROLS

Strain	Direct method		Metabolic activation method	
	Substance	Conc. µg/plate	Substance	Conc. µg/plate
TA97a	9-Aminoacridine	100	2-aminoanthracene	10
TA98	2-Nitrofluorene	2.0	2-aminoanthracene	3
			Benzo(a)pyrene	3
TA100	Sodium azide	3.0	2-aminoanthracene	3.0
TA102	Mitomycin-C	0.5	2-aminoanthracene	10.0
TA1535	Sodium azide	3.0	2-aminoanthracene	3

Results

No precipitation of test substance was observed in this study. Bacteriotoxicity of the test substance was noted at 5000 µg/plate for strains TA100 (with and without metabolic activation) and TA102 (with metabolic activation). Treatment with TOX2/Aliskiren hemifumarate did not increase the revertant numbers of any of the bacterial tester strains used (Table 3.2.1.2). The positive control compounds induced reverse mutations in each strain, with revertant colony counts ranging from 4 to 100 times corresponding negative control.

TABLE 3.2.1.2
SUMMARY OF BACTERIAL REVERSE MUTATION ASSAY (±S9 MIX)

Strain:		TA1535		TA97a		TA98		TA100		TA102	
S9:		-	+	-	+	-	+	-	+	-	+
Concentration (µg/ plate):	0	28	19	232	257	29	36	157	150	430	619*
	312.5	24	15	250	248	28	38	153	148	487	595
	625	17	12	240	271	24	32	142	161	474	577
	1250	24	13	241	267	23	39	150	151	447	552
	2500	22	19	223	286	28	43	130	144	366	386
	5000	21	16	229	252	27	52	88t	90t	281	321t

t: toxic, * values above historical negative control range

In conclusion, the results demonstrate that aliskiren hemifumarate spiked with impurities (b) (4) and (b) (4) is not mutagenic.

3.2.2. Chromosome Aberration Test of Aliskiren Hemifumarate with Impurities in Cultured Human Peripheral Blood Lymphocytes

The objective of the study was to evaluate the clastogenic potential of aliskiren hemifumarate with a total of (b) (4)% of related impurities (b) (4) by its effects on chromosomes of cultured human peripheral-blood lymphocytes.

Key Findings: The test substance did not show any clastogenic potential in the chromosomal aberration test with human peripheral-blood lymphocytes.

Study No: 0770447
Location of Report: EDR
Conducting Laboratory and Location: Novartis Crop Protection AG, Toxicology/Genetic Toxicology, CH-4002 Basel, Switzerland
Dates of Study: Initiated on January 8 and terminated on April 16, 2008.
GLP Compliance: Yes
QA'd Report: Yes
Drug: TOX2/Aliskiren hemifumarate (batch #07/1, purity 98.3 %) contained aliskiren hemifumarate and two impurities: (b) (4)%) and (b) (4)%), Total (b) (4)%.

Methods

The clastogenic potential of aliskiren was evaluated in cultured human peripheral-blood lymphocytes prepared from the pooled blood of healthy volunteers with and without metabolic activation. The metabolic activation system was S9, prepared from the liver of a rat given Aroclor 1254. S9 mix was made prior to the start of an experiment. TOX2/Aliskiren hemifumarate was dissolved in the culture medium. All doses are expressed in term of free base. Tests conducted without the S9 mixture are considered to have been conducted by the "direct method." Cells were exposed to a medium containing the test substance for 20 hours with the direct method, and for 3 hours with the metabolic activation method, followed by continued culture for an additional 17 hours with a fresh medium excluding the test substance and S9 mixture. Two hours prior to harvesting, the cultures were treated with colcemide (0.2 μg/ml) to arrest cells in metaphase. Whenever possible, 200 well spread metaphases from two vehicle control and two treated cultures (100 metaphases per replicate culture) were scored. At least 50 metaphases were scored in the positive control cultures (25 per replicate culture). Cyclophosphamide (+S9) and ethyl methanesulfonate (-S9) were used as positive control cultures. Only one study was conducted.

TABLE 3.2.2.1
EXPERIMENTAL DESIGN

Metabolic activation, S9 mix	-	-	+
Treatment with aliskiren (h)	20	3	3
Recovery after treatment (h)	0	17	17
Drug conc. Used (µg/ml)	100 to 1000	1300 to 2300	1000 to 2300
Concentration (µg/ml) selected for chromosome analysis based on cell growth and mitotic index	129.2 to 359.4	1203.3 to 2096.7	1300 to 1475.5
Positive control, (µg/ml)	EMS, 5 mM	EMS, 12.5 mM	CP 55 µM

The concentration of test substance that suppresses mitotic activity (cytotoxicity measured as mitotic index which is defined as percentage of cells in mitosis) between 35.1 and 45.3% relative to the control group was selected as the highest for the analysis of chromosome aberrations. The slides were examined for the following structural aberrations.

1. Cells with structural aberrations including gaps
2. Cells with structural aberrations excluding gaps
3. Polyploidy, hyperdiploidy or endoreduplicated cells

Statistical analysis was not performed since frequencies of cells with structural aberrations excluding gaps were within the historical control range. The test substance is considered to be positive if a) statistically significant increases in the frequency of metaphases with aberrant chromosomes are observed at one or more concentrations, b) the increases exceed the historical negative control range, and c) the increases are reproducible between replicate cultures and between tests.

Results

TOX2/Aliskiren hemifumarate produced a concentration-dependent decrease in the mitotic index. The incidence rates of cells possessing chromosomal aberrations, including or excluding gaps, with or without metabolic activation (Tables 3.2.2.2 to 3.2.2.4), were within the historical negative control range. The frequencies of cells with numerical aberrations were within historical control range for all treated cultures.

Chromosomal aberrations detected in the negative concurrent control ranged from 1.5 to 2.0%. In contrast, the incidence of chromosomal aberration in cultures treated with the positive controls, EMS and cyclophosphamide, ranged between 27 and 44%.

It is concluded that TOX2/Aliskiren hemifumarate does not have any clastogenic potential under the conditions of this chromosomal aberration test.

TABLE 3.2.2.2
CHROMOSOME ABERRATION ANALYSIS AFTER CONTINUOUS TREATMENT FOR 20 HR WITH TOX2/ALISKIREN HEMIFUMARATE IN THE ABSENCE OF RAT LIVER S9 MIX

Treatment : (20h-S9); Experiment A	% Mitotic Index (mean) *	Rel. Mitotic Index (mean) **	% Ab. cells excl. gaps	% cells with exchanges	% Numerical aberrant cells
RPMI1640	6.7	100.0	2.0	0.0	0.0
1000.0 µg/ml	ND	ND	ND	ND	ND
774.3 µg/ml	ND	ND	ND	ND	ND
599.5 µg/ml	ND	ND	ND	ND	ND
464.2 µg/ml	0.8	11.2	ND	ND	ND
359.4 µg/ml	2.4	35.1	1.5	0.0	1.0
278.3 µg/ml	6.2	91.8	ND	ND	ND
215.4 µg/ml	3.8	56.7	1.5	0.0	2.4
166.8 µg/ml	4.7	69.4	3.0	0.0	0.5
129.2 µg/ml	5.4	80.6	2.5	0.0	2.9
100.0 µg/ml	5.9	87.3	ND	ND	ND
EMS 5.0 mM	2.0	29.9	42.0	0.0	3.8

ND not determined/ not displayed

* Mitotic indices as % of mitotic cells within the total population of mitotic and non-mitotic cells.

** Mitotic indices as % of the controls.

% Cells Exch. % cells with exchanges

% Ab. Cells % aberrant cells (exclusive gaps)

TABLE 3.2.2.3
CHROMOSOME ABERRATION ANALYSIS AFTER CONTINUOUS TREATMENT FOR 3 HR WITH TOX2/ALISKIREN HEMIFUMARATE AND RECOVERY FOR 17 HR IN THE ABSENCE OF RAT LIVER S9 MIX

Treatment : (3h-S9); Experiment B	% Mitotic Index (mean) *	Rel. Mitotic Index (mean) **	% Ab. cells excl. gaps	% cells with exchanges	% Numerical aberrant cells
RPMI1640	5.3	100.0	2.0	0.0	0.5
2300.0 µg/ml	ND	ND	ND	ND	ND
2096.7 µg/ml	2.4	45.3	2.5	0.0	2.4
1911.4 µg/ml	3.1	57.5	ND	ND	ND
1742.4 µg/ml	2.7	50.9	ND	ND	ND
1588.4 µg/ml	2.8	52.8	ND	ND	ND
1448.0 µg/ml	3.3	61.3	1.0	0.0	2.9
1320.0 µg/ml	3.4	64.2	ND	ND	ND
1203.3 µg/ml	4.7	88.7	0.5	0.0	1.0
1097.0 µg/ml	3.9	72.6	ND	ND	ND
1000.0 µg/ml	5.8	108.5	ND	ND	ND
EMS 12.5 mM	2.3	43.4	44.0	10.0	2.0

ND not determined/ not displayed

* Mitotic indices as % of mitotic cells within the total population of mitotic and non-mitotic cells.

** Mitotic indices as % of the controls.

% Cells Exch. % cells with exchanges

% Ab. Cells % aberrant cells (exclusive gaps)

TABLE 3.2.2.4
CHROMOSOME ABERRATION ANALYSIS AFTER CONTINUOUS TREATMENT FOR 3 HR WITH TOX2/ALISKIREN HEMIFUMARATE AND RECOVERY FOR 17 HR IN THE PRESENCE OF RAT LIVER S9 MIX

Treatment : (3h+S9); Experiment A	% Mitotic Index (mean) *	Rel. Mitotic Index (mean) **	% Ab. cells excl. gaps	% cells with exchanges	% Numerical aberrant cells
RPMI1640/S9-Mix	5.4	100.0	1.5	0.0	1.0
2300.0 µg/ml	ND	ND	ND	ND	ND
2158.7 µg/ml	ND	ND	ND	ND	ND
2026.1 µg/ml	1.2	21.3	ND	ND	ND
1901.7 µg/ml	1.9	34.3	ND	ND	ND
1784.8 µg/ml	1.9	34.3	ND	ND	ND
1675.2 µg/ml	1.4	25.9	ND	ND	ND
1572.3 µg/ml	2.7	50.0	ND	ND	ND
1475.7 µg/ml	2.2	39.8	1.0	0.0	2.0
1385.1 µg/ml	3.2	58.3	1.5	0.0	2.9
1300.0 µg/ml	3.1	56.5	2.0	0.0	2.9
CP 55.0 µM	1.9	35.2	27.0	0.0	5.7

ND not determined/ not displayed

* Mitotic indices as % of mitotic cells within the total population of mitotic and non-mitotic cells.

** Mitotic indices as % of the controls.

% Cells Exch. % cells with exchanges

% Ab. Cells % aberrant cells (exclusive gaps)

4.0. OVERALL SUMMARY AND EVALUATION

Valturna® is a fixed dose combination of aliskiren hemifumarate and valsartan proposed for the treatment of essential hypertension. Aliskiren hemifumarate is a renin inhibitor, recently approved (March 2007) for the treatment of hypertension (Novartis Pharmaceuticals NDA 21,985). Valsartan, an AT-1 receptor antagonist, was approved for the treatment of hypertension in 1996. Both affect the renin angiotensin system by suppressing either the formation or action of the end product, angiotensin II. There are subtle differences in their mechanism of action. Since both aliskiren and valsartan increase total renin concentration, co-administration increases total renin concentration above levels observed with either drug administered alone, consistent with synergistic RAS blockade. On the other hand, valsartan enhances circulating levels of renin activity (PRA), while aliskiren inhibits PRA and subsequent increases in angiotensin I and angiotensin II. Hence, co-administration of aliskiren prevents the reactive rise in PRA observed with valsartan. Because of their different modes of action, the combination of these drugs is expected to provide better blood pressure control than the component monotherapies.

No preclinical pharmacodynamic or pharmacokinetic studies were performed with aliskiren hemifumarate and valsartan combinations.

A 13 week oral toxicity study in Wistar Hanover rats was performed with the combination. The animals were treated with either drug alone or both drugs in combination at a dose ratio of 1:1. The oral gavage administration of 300 mg/kg/day aliskiren in combination with 300 mg/kg/day valsartan induced minimal or slight vacuolation of the squamous epithelium at the limiting ridge of the non-glandular stomach in 4/10 rats of each sex. It was also noted in 2/10 males treated with valsartan alone. A trend to reversibility was seen in recovery group animals. Animals receiving valsartan alone at 300 mg/kg/day exhibited an increased incidence of renal tubular basophilia and minimal but statistically significant decreases in erythrocyte parameters. Based on the histopathological changes, the no observed adverse effect level for this study was 150:150 mg/kg/day.

Two significant observations were made in the toxicokinetics study. a) A higher exposure to aliskiren was noted in week 13 than on day 1 with accumulation of aliskiren similar whether given alone or in combination with valsartan. b) Exposure to aliskiren was at least 4 times higher in absence of valsartan than in combination with valsartan. In contrast, there was no effect of aliskiren on valsartan exposure.

The plasma concentrations of aliskiren at the highest dose used in the 13 week toxicity study were below those anticipated clinically (0.2 to 0.6 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 valsartan in the same study (2 to 3 times human exposure, Table 4.2).

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

Species	Study number/ Rev section	Dose (aliskiren: valsartan) mg/kg/day	Gender	AUC_{0-24h} (ng·h/ml)	C_{max} (ng/ml)	Exposure multiples based on	
						AUC_{0-24h}	C_{max}
13-wk rat	0680120 3.1.1	150:150[a]	male	190	21.7	0.3	0.1
			female	123	17.7	0.2	0.1
		300:300[b]	male	265	41.9	0.4	0.2
			female	371	51.6	0.6	0.3

Aliskiren exposure multiples are based on the human AUC_{0-24h} = 658 ng·h/ml and C_{max} = 184 ng/ml after a single oral dose of 300:320 mg (aliskiren: valsartan) to male and female healthy subjects (Study #CSPV100A2111)

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

Species	Study number/ Rev section	Dose (aliskiren:HCTZ) mg/kg/day	Gender	AUC_{0-24h} (ng·h/ml)	C_{max} (ng/ml)	Exposure multiples based on	
						AUC_{0-24h}	C_{max}
13-wk rat	0680120 3.1.1	150:150[a]	male	66700	14300	2.2	3.3
			female	39200	8370	1.3	1.9
		300:300[b]	male	65800	8900	2.2	2.0
			female	94700	1000	3.2	2.3

Valsartan exposure multiples are based on the human AUC_{0-24h} = 30019 ng·h/ml and C_{max} = 4391 ng/ml after a single oral dose of 300:320 mg (aliskiren: valsartan) to male and female healthy subjects (Study # CSPV100A2111)
a: NOAEL
b: Minimal adverse effects (histopathological changes in non-glandular stomach)

Three aliskiren hemifumarate degradation products (impurities) have been identified by the sponsor. The specification limits proposed by the sponsor for impurities (b) (4) and (b) (4) are, respectively, (b) (4)%, (b) (4)% and (b) (4)%, all above the threshold for qualification. To qualify (b) (4) at the proposed specification (b) (4)%), a 13 week oral gavage study in Tif:RAIf rats was performed at doses of 60, 200 or 600 mg aliskiren/kg/day using a batch of aliskiren hemifumarate that contained (b) (4) at a concentration of (b) (4)% . The toxicological profile of aliskiren in this study was not different from that observed with aliskiren free of impurities. Total daily intake of (b) (4) (impurity at the level of (b) (4)%) achieved during this study was up to 2.7-fold higher than anticipated in humans at the highest therapeutic dose of aliskiren hemifumarate. Additionally, this batch of aliskiren hemifumarate was negative in an Ames test and an *in vitro* chromosome aberration test.

Aliskiren hemifumarate impurities (b) (4) and (b) (4) were tested for toxicity using a batch of aliskiren hemifumarate spiked with both of these materials. The toxicological profile of the spiked batch of aliskiren hemifumarate was comparable to that of aliskiren hemifumarate without the impurities when administered to Wistar Hanover rats for 4 weeks at doses up to 250 mg aliskiren/kg/day. No evidence of genotoxicity was noted for this batch in an Ames test and an *in vitro* chromosome aberration study. Total daily intake of these impurities during the 4 week study was up to 8.7-fold higher than anticipated in humans at the highest therapeutic dose of aliskiren hemifumarate.

Evaluation

The combined administration of aliskiren hemifumarate and valsartan did not augment any existing toxicities of the individual agents in the 13 week toxicology study. We note, however, that the highest dose used in the toxicology study, 300:300 mg (aliskiren: valsartan)/kg/day, was not high enough to demonstrate toxic effects that had been seen in other rat studies in which aliskiren hemifumarate increased the incidence of mucosal epithelial hyperplasia/hypertrophy in the small and large intestine, 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). Systemic exposure to aliskiren in the combination toxicity study was markedly reduced (mean AUC value - males and females combined - more than 75% lower) when aliskiren hemifumarate was given in combination with valsartan. Although a similar result has been observed in humans (clinical study #2216), the reduction was much less (about 26%) and exposure to aliskiren at the highest dose in the combination toxicology study is lower than the anticipated clinical exposure. This may not be a concern for humans, based on the apparent efficacy and tolerance when the combination was administered in clinical trials. There was no noteworthy effect of aliskiren on valsartan exposure in either animal or human studies.

The toxicity of aliskiren hemifumarate with impurities (b) (4), (b) (4) and (b) (4) is comparable to that of aliskiren hemifumarate without these impurities when administered to rats for a minimum duration of 4 weeks. Also, the batches containing these impurities were negative in Ames and chromosome aberration tests. Impurities (b) (4) and (b) (4) were tested at levels (b) (4)% and (b) (4)%, respectively) above the sponsor's proposed limits ((b) (4)% and (b) (4)%). Though the third impurity, (b) (4), was tested at a concentration of (b) (4)%, well below the current specification of (b) (4)%, total daily intake for (b) (4) achieved at the highest dose level in the 13 week toxicity study (2.52 mg/m^2) was 2.7-fold higher than anticipated in humans (0.925 mg/m^2 or 1.5 mg/day for a 60 kg individual with an impurity level of (b) (4)%). In the 4 week oral toxicity study in rats, total daily intake for (b) (4) and (b) (4) (combined impurities (b) (4)%) achieved at the highest dose level (21 mg/m^2) was 8.7-fold higher than anticipated in humans (2.4 mg/m^2 or 3.9 mg/day for a 60 kg individual with combined impurities at the current specification of (b) (4)%). This suggests that animals were adequately exposed to all three impurities and, thus, the proposed specifications for these impurities in the drug product are supported.

Recommendations for Labeling: None

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/s/

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