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PHARMACOLOGY REVIEW(S)



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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND
EVALUATION**

Application number: 022,545
Supporting document/s: None
Applicant's letter date: October 28, 2009
CDER stamp date: October 29, 2009
Product: Tekamlo[®] Tablets
Drug substance: Aliskiren hemifumarate and amlodipine besylate
Indication: Hypertension
Applicant: Novartis Pharmaceuticals Corporation
Review Division: Cardiovascular and Renal Products
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TABLE OF CONTENTS

1 EXECUTIVE SUMMARY	4
BACKGROUND.....	4
1.1 RECOMMENDATIONS.....	4
1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS	6
2 DRUG INFORMATION.....	8
3 STUDIES SUBMITTED	10
4 PHARMACOLOGY.....	10
5 PHARMACOKINETICS/ADME/TOXICOKINETICS.....	10
6 GENERAL TOXICOLOGY.....	11
6.1 SINGLE-DOSE TOXICITY	11
6.2 REPEAT-DOSE TOXICITY.....	11
6.2.1 THIRTEEN WEEK ORAL GAVAGE STUDY IN WISTAR RATS	11
6.2.2 FOUR WEEK ORAL GAVAGE IMPURITY TOXICITY STUDY IN WISTAR RATS	18
7 GENETIC TOXICOLOGY	23
8. INTEGRATED SUMMARY AND SAFETY EVALUATION.....	30

Table of Tables

Table 1. The composition of drug product.....	9
Table 2. Study design.....	12
Table 3. Tissues sampled for histopathological examination.....	14
Table 4. Summary of animals found dead (FD) or sacrificed early (ES).....	15
Table 5. Mean toxicokinetics parameters for aliskiren in rat plasma.....	16
Table 6. Mean toxicokinetics parameters for amlodipine in rat plasma.....	17
Table 7. Study design.....	19
Table 8. Tissues sampled for histopathological examination.....	20
Table 9. Summary of mean body weight gain in 4 week toxicity study.....	21
Table 10. Mean absolute and relative (to body and brain) organ weights after 4 weeks of dosing in rats.....	21
Table 11. Mean toxicokinetics parameters for aliskiren in rat plasma.....	22
Table 12. Bacterial reverse mutation assay. Positive controls.....	24
Table 13. Summary of bacterial reverse mutation assay (\pm S9 mix).....	25
Table 14. Chromosome aberration analysis after treatment for 3 hr with TOX1/SPA100 and recovery for 17 hr in the presence of rat liver S9 mix.....	29
Table 15. Chromosome aberration analysis after treatment for 3 hr with TOX1/SPA100 and recovery for 17 hr in the absence of rat liver S9 mix.....	29
Table 16. Human SPA100 exposure multiples in 3 month toxicity study in rats.....	32
Table 17. Human SPA100 (aliskiren:amlodipine) exposure multiples in toxicity study in rats for drug substance impurities.....	33

1 Executive Summary

Background

The renin angiotensin aldosterone system is an important regulator of blood pressure, plasma volume and sodium homeostasis. Calcium channels in vascular smooth muscle cells are a key regulator of contraction and blockade of these channels prevent vasoconstriction and decrease blood pressure. Simultaneous blockade of these two pathways is expected to be an effective means of treating high blood pressure. This increases the chances of achieving a greater reduction in blood pressure in a short period and at lower doses of the individual components. In addition, combining agents may improve patient compliance and enhance tolerability by reducing the incidence of certain side effects that are more prevalent when the drugs are used alone.

The current NDA, a 505(b)(2) application, describes the efficacy and safety of the fixed-dose combination of aliskiren hemifumarate and amlodipine besylate (SPA100, Tekamlo[®]) in the treatment of essential hypertension. Aliskiren is a direct renin inhibitor that inhibits the renin angiotensin aldosterone system at the point of activation. Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group. It inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle, which results in peripheral arterial vasodilatation, reduction in peripheral vascular resistance and reduction in blood pressure. Both these drugs have been extensively studied and are widely used as monotherapies for the treatment of hypertension. Since these drugs have different modes of action, their combination should allow more control of blood pressure than either of the respective monotherapy components.

1.1 Recommendations

1.1.1 Approvability

Approvable

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

Those sections of the proposed labeling (EDR version revised October, 2009) that deal with nonclinical studies covered by this review are considered satisfactory with the following exceptions.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The sponsor has not conducted carcinogenesis, mutagenesis, and impairment of fertility studies with the combination. In addition, the sponsor's text is edited for format and consistency. The sponsor text is reproduced below with our recommended changes (underlined).

Studies with aliskiren hemifumarate and amlodipine besylate.

No carcinogenicity, mutagenicity or fertility studies have been conducted with the combination of aliskiren hemifumarate and amlodipine besylate. However, these studies have been conducted for aliskiren hemifumarate and amlodipine besylate alone.

Studies with aliskiren hemifumarate.

Carcinogenic potential was..... mg/m² basis

Studies with amlodipine besylate.

Rats and mice..... mg/m² basis).

13.2 Animal Toxicology and/or Pharmacology

The sponsor has not conducted reproductive toxicology studies with the combination. In addition, the sponsor's text is edited for format and consistency. The sponsor text is reproduced below with our recommended changes (underlined).

Preclinical safety studies have demonstrated that the combination of aliskiren hemifumarate and amlodipine besylate was well tolerated in rats. The findings from the 2- and 13-week oral toxicity studies in rats were consistent with those of aliskiren hemifumarate and amlodipine besylate when both drugs were administered alone. There were no new toxicities or increased severity of the toxicities which were associated with either component.

Reproductive Toxicology Studies

Studies with aliskiren hemifumarate and amlodipine besylate.

(b) (4)

Studies with aliskiren hemifumarate.

Reproductive toxicity studies ofpregnant rabbits.

Studies with amlodipine besylate.

No evidence of teratogenicity..... risk to the fetus.

1.2 Brief Discussion of Nonclinical Findings

The sponsor has not performed pharmacology or ADME studies for the combination product. To support the chronic administration of the aliskiren hemifumarate and amlodipine besylate (SPA100) to adult hypertensive patients, a 13 week repeat dose toxicity study was performed in Wistar-Hanover rats. In this study, aliskiren hemifumarate and amlodipine besylate were administered orally, by gavage, separately and together at a dose ratio of 30:1 [30:1, 90:3 or 300:10 (aliskiren:amlodipine) mg/kg/day] for 13 weeks followed by a 4 week post dosing period to assess the reversibility of any effects observed. (All doses and dose ratios in this review are presented in terms of the aliskiren and amlodipine bases.)

Daily administration of aliskiren hemifumarate and amlodipine besylate (300:10 mg/kg/day) or aliskiren hemifumarate alone (300 mg/kg/day) for 13 weeks resulted in 8 mortalities. Of these, 3 mortalities (2 males in the high dose combination and one male in the aliskiren groups) were attributed to drug treatment. Though a cause of death was not established, clinical signs (noted prior to death or moribund sacrifice) such as labored/congested breathing and gasping, panting, abnormal breathing sounds point toward aliskiren. Aliskiren is a local irritant and can cause necrosis of the respiratory epithelium as a result of aspiration of the dosing solution into the respiratory tract (NDA 21985, aliskiren).

The target organ of toxicity in both sexes was adrenals. Pale discoloration or foci of the adrenals correlating with hypertrophy/vacuolation of the zona glomerulosa was noted in animals treated with the combination at 90:3 or more mg/kg/day and in animals receiving amlodipine alone (10 mg/kg/day). This effect in adrenals was reversible following the 4-week recovery period. Similar findings in adrenals have been reported in toxicology studies with amlodipine (see NDAs (b) (4)). Based on the histopathological finding, the no observed adverse effect level for this study was 30:1 (aliskiren:amlodipine) mg/kg/day. The combination did not identify any new toxicity.

Toxicokinetics demonstrated accumulation of amlodipine (but not aliskiren) by a factor of two after multiple daily dosing compared to single dose. There was no significant effect in animals on the exposure (AUC) of either drug components after single or multiple dosing of the combination drug SPA100. On the other hand, clinical studies demonstrated an 18% and a 29% increase in aliskiren steady-state C_{max} and AUC, respectively, when co-administered with amlodipine. According to the sponsor, these changes were not clinically significant.

The plasma concentrations of aliskiren measured at the highest combination dose used in the current study were below those anticipated clinically (0.4 to 0.6 times based on AUC values), indicating the absence of a safety margin for humans. On the other hand, rats were substantially exposed to amlodipine in the same study (about 8 times human exposure). Exposures to aliskiren and amlodipine at the NOAEL (the dose not causing hypertrophy/vacuolation of the zona glomerulosa) was, respectively, 40 and 3 (based on mean AUC values for both sexes) times lower than the expected exposure at the maximum recommended human dose [300:10 mg (aliskiren:amlodipine)/day]. The absence of safety margin for aliskiren hemifumarate may not be a concern since no toxicity was noted for aliskiren hemifumarate alone at the highest dose used in the present study and the combination has demonstrated good clinical tolerance. Furthermore,

the individual drugs of the combination, drugs which are currently approved for use in this patient population, have often been used concomitantly.

A note on impurities: Toxicity studies on impurities or degradation products were performed. The toxicity of aliskiren and amlodipine with the impurities is comparable to that of aliskiren and amlodipine without them in repeat dose toxicity studies. Sponsor proposed specifications for the final product to include limits for four aliskiren hemifumarate degradation products: (b) (4) for (b) (4) for (b) (4) and (b) (4) for (b) (4). Total daily intake for impurities (b) (4), and (b) (4) achieved at the highest aliskiren dose level (250 mg/kg/day) was, on body surface area basis, (b) (4) (combined impurities of (b) (4) and (b) (4) fold of that expected in humans at a maximal clinical dose of 300 mg/day for aliskiren at the specification limits for impurities. The amlodipine impurity (b) (4) was qualified at the level of (b) (4). The total daily intake for (b) (4) of impurity (b) (4) achieved at the highest dose level (10 mg/kg/day) was 10-fold higher than anticipated in humans. This suggests that animals were adequately exposed to impurities and, thus, the proposed specifications for these impurities in the drug product are supported. Furthermore, the batches containing these impurities (except for (b) (4), which was not tested) were tested negative in Ames and chromosome aberration tests.

2 Drug Information

2.1 Drug Product: Tekamlo® Tablets (SPA100)

2.2 Drug Substances

Generic name: Aliskiren hemifumarate

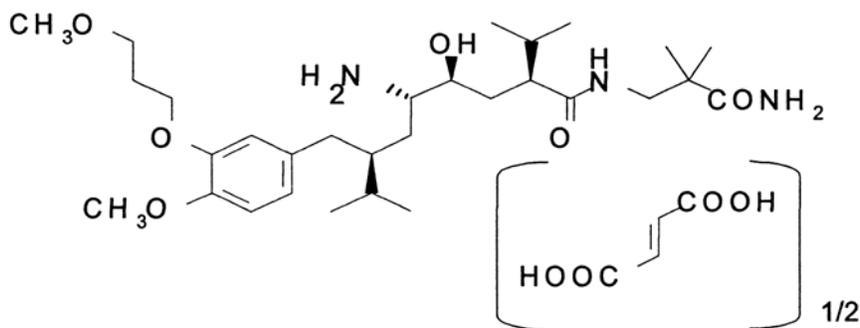
Code names: SPP 100 (base); SPP 100A (HCl), SPP 100B (hemifumarate)

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: C₃₀H₅₃N₃O₆ · 0.5 C₄H₄O₄ / 551.8 (free base), 609.8 (hemifumarate)



Generic name: Amlodipine besylate

Code name: LBT873-DMA.002

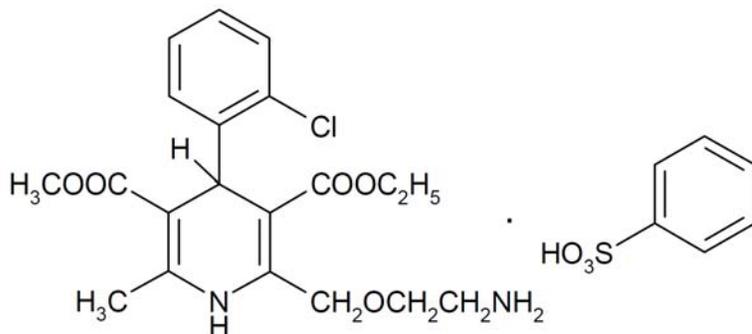
Chemical name: (RS)-2-[(2'-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid 3-ethyl ester, 5-methyl ester, benzene sulfonate.

Chemistry: Amlodipine is a racemic mixture (R and S isomers). It is a white to pale yellow crystalline powder slightly soluble in water and sparingly soluble in ethanol.

CAS registry number: 1114790-99-6 (besylate salt form)

88150-42-9 (free base form)

Molecular formula/molecular weight: C₂₀H₂₅ClN₂O₅ · C₆H₅SO₃H / 567.06 (besylate)



2.3 Related Applications: Clinical trials supporting the current NDA were conducted under Novartis Pharmaceuticals Corporations IND 101,386. Novartis Pharmaceuticals Corporation’s NDA 21,985 for aliskiren (Tekturna®) was approved for the treatment of hypertension in March 2007. Pfizer’s NDA 19,787 for racemic amlodipine besylate (Norvasc®) was approved for the treatment of hypertension, chronic stable angina and vasospastic angina in 1992. Other related NDAs are: 22,107 (aliskiren and HCTZ), 22,217 (aliskiren and valsartan).

2.4 Drug Class: Aliskiren hemifumarate is a renin inhibitor and amlodipine besylate is a dihydropyridine calcium channel blocker

2.5 Intended Clinical Population: Hypertensive subjects

2.6 Clinical Formulation and Dosing Regimen: The tablets are formulated in four strengths of aliskiren hemifumarate:amlodipine besylate, respectively: 150:5 mg, 150:10 mg, 300:5 mg and 300:10 mg. Table 1 lists proposed final commercial formulations.

Table 1. The composition of drug product

Ingredients	Amount (mg) per tablet				Function	Reference to standards
	150/5 mg	150/10 mg	300/5 mg	300/10 mg		
(b) (4)						
Aliskiren hemifumarate	165.75 ¹	165.75 ¹	331.50 ²	331.50 ²	Active substance	Novartis monograph
Amlodipine besylate	6.94 ³	13.87 ⁴	6.94 ³	13.87 ⁴	Active substance	Novartis monograph
Microcrystalline cellulose/ Cellulose, microcrystalline						(b) (4) NF / Ph. Eur.
Crospovidone						NF / Ph. Eur.
Povidone						USP / Ph. Eur.
Magnesium stearate						NF / Ph. Eur.
Colloidal silicon dioxide/ (b) (4) colloidal (b) (4)						NF / Ph. Eur.
(b) (4)						Novartis monograph
(b) (4)						
(b) (4)		Novartis monograph				
		Novartis monograph				
		Novartis monograph				
		USP / Ph. Eur.				
Total coated tablet weight	509.50	509.50	1013.00	1013.00		

¹Corresponds to 150 mg SPP100 base

²Corresponds to 300 mg SPP100 base

³Corresponds to 5 mg amlodipine base

⁴Corresponds to 10 mg amlodipine base

(b) (4)

2.7 Impurities

Aliskiren hemifumarate		Amlodipine besylate	
Impurity	Proposed limit, %	Impurity	Proposed limit, %
(b) (4)			

3 Studies Submitted

1. Repeat dose toxicity study for 2 weeks (non-GLP study): Study #0670746
2. Repeat-dose toxicity study for 13 weeks (GLP study): Study #803592
3. *In vitro* reverse mutation assay in bacterial cells: Study #0870368
4. *In vitro* chromosome aberration assays in mammalian cells: Study #0870367
5. Distribution of SPP100 after single oral administration of SPP100 hemifumarate to rats with or without co-administration of cyclosporine A: Study #700870
6. Relative oral bioavailability of SPP100 after single oral administration of SPP100 hemifumarate to rats with co-administration of cyclosporine A: Study #DMPK R0600548

3.1 Studies Reviewed

1. Repeat-dose toxicity study for 13 weeks (GLP study): Study #803592
2. Repeat-dose toxicity study for 4 weeks (GLP study): Study #0510030 (submitted with the NDA 21,985)
3. *In vitro* reverse mutation assay in bacterial cells: Study #0870368
4. *In vitro* chromosome aberration assays in mammalian cells: Study #0870367

3.2 Study Not Reviewed

1. Repeat-dose toxicity study for 2 weeks (non-GLP study): Study #0670746
2. Distribution of SPP100 after single oral administration of SPP100 hemifumarate to rats with or without co-administration of cyclosporine A: Study #700870
3. Relative oral bioavailability of SPP100 after single oral administration of SPP100 hemifumarate to rats with co-administration of cyclosporine A: Study #DMPK R0600548

3.3 Previous Reviews Referenced

NDA 21,985 for aliskiren (Tekturna®)

NDA 22,107 for aliskiren and HCTZ (Tekturna® HCT)

NDA 22,217 for aliskiren and valsartan (Valturna®)

4 Pharmacology

No new pharmacology studies with the combination are included in this NDA.

5 Pharmacokinetics/ADME/Toxicokinetics

No new pharmacokinetics studies with the combination are included in this NDA.

6 General Toxicology

6.1 Single-Dose Toxicity

No studies conducted

6.2 Repeat-Dose Toxicity

6.2.1 Thirteen Week Oral Gavage Study in Wistar Rats

Key Study Findings

The study evaluated the oral toxicity of SPA100 (at doses of 30:1 or more mg (aliskiren:amlodipine)/kg/day) for 13 weeks and the reversibility of any findings following a 4 week recovery period. A total of 5 males and 3 females died or were euthanized moribund between study days 33 and 91. Of these, 3 mortalities (2 males in the high dose combination and one male in the aliskiren groups) were attributed to drug treatment. Abnormal breathing sounds, shallow/deep/labored breathing and salivation were noted in animals receiving the high dose combination [300:10 mg (aliskiren:amlodipine)/kg/day] or 300 mg aliskiren/kg/day alone. The high dose combination group also displayed a significant ($P < 0.05$) decrease in mean lymphocyte counts and globulin concentrations relative to control group. Both of these parameters persisted in males after the recovery period. Test substance related microscopic pathology was observed in the adrenal (hypertrophy/vacuolation of the zona glomerulosa) in animals receiving amlodipine alone (10 mg/kg/day) or aliskiren:amlodipine at 90:3 or more mg/kg/day. The NOAEL was considered to be 30:1 mg (aliskiren:amlodipine)/kg/day. Toxicokinetics analysis did not show any influence of amlodipine on aliskiren exposure and *vice versa*.

Study no.: 803592, Novartis ref #0670747

Study report location: EDR

Conducting laboratory and location: (b) (4)

Date of study initiation: October 9, 2008

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: SPA100 (batch #08/1, 98.4% pure) is a combination drug composed of Aliskiren hemifumarate (SPP100 batch #C0168, 98.6% pure) and Amlodipine besylate (batch #ACAA0464, 100% pure at a ratio of 30:1. The new drug product formulation (SPA100) (batch #08/1, 98.4% pure) contained (b) (4) of impurity (b) (4) based on amlodipine. However, it did not contain impurities for aliskiren.

Methods

Doses: Aliskiren hemifumarate and amlodipine besylate were administered (at a dose ratio of 30:1) at three dose levels: 30:1, 90:3 or 300:10 mg (aliskiren:amlodipine)/kg/day. Two additional groups of rats received either aliskiren hemifumarate or amlodipine besylate at 300 or 10 mg/kg/day, respectively (See Table 2). Control animals received the vehicle.

Frequency of dosing: Once daily, for 13 weeks.

Route of administration: Orally by gavage

Dose volume: 10 ml/kg

Formulation/Vehicle: Appropriate amounts of SPA100 or individual drugs were suspended in 0.5% (w/v) hydroxypropylcellulose aqueous solution under stirring.

Suspensions were prepared daily during weeks 1 and 2, and then weekly; during which the suspensions were 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 week 1 and 1st and 7th day of week 3 dosing were taken from the top, middle and bottom of the preparation vessels for homogeneity testing.

Species/Strain: Rats, IGS Wistar Hanover, Crl:WI(Han) (b) (4)

Number/Sex/Group: 10. 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 2).

Age: 8 weeks old at initiation of dosing

Weight: Males: 213-274 gm, Females: 134-189 gm, at initiation of dosing

Table 2. Study design

Group number identification	Dose level (Base) (mg/kg/day) (SPP100: Amlodipine)	Dose volume mL/kg	Dose conc. ^{\$} (mg/mL)	Animal number			
				Main study		Recovery study	
1/ Vehicle control	0	10	0	1001 to 1010	1501 to 1510	1011 to 1016	1511 to 1516
2/ SPA100	30:1	10	3.32:0.14	2001 to 2010	2501 to 2510	-	-
3/ SPA100	90:3	10	9.95:0.42	3001 to 3004, 3006 to 3010, 3105	3501 to 3510	-	-
4/ SPA100	300:10	10	33.15:1.39	4001 to 4008	4501 to 4510	4009 to 4016	4511 to 4516
5/ SPP100	300	10	33.15	5001 to 5010	5501 to 5510		
6/ Amlodipine	10	10	1.39	6001 to 6010	6501 to 6510		

^{\$} Dose concentrations are expressed in terms as salt and are not corrected for purity. The salt base ratio is (b) (4) for SPP100 and (b) (4) for Amlodipine

Due to increased mortalities in the high dose combination group, the number of animals for the main and the recovery studies was readjusted to 8 each.

The doses of aliskiren hemifumarate (SPP100) and amlodipine besylate are expressed in terms of the base

Unique study design: The experimental design was to evaluate the effect of amlodipine on the toxicity of aliskiren. Three study groups investigated whether or not the combination could result in toxicologically additive effects in rats. Two additional groups

that received either aliskiren or amlodipine alone allowed comparison of the toxicity of SPA100 (i.e., combination of two) to the individual components of the combination (Table 2). The study was followed by a 4 week recovery period in both sexes.

Rationale for dose selection: Doses were selected on the basis of a 2 week dose range-finding study in the same rat strain in which decreases in body weight gain and food consumption were noted in animals receiving 300:10 mg (aliskiren:amlodipine)/kg/day. The ratio of 30:1 (aliskiren:amlodipine) was selected based on the drug ratio anticipated for clinical use of the fixed dose combination.

Deviation from study protocol: None.

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. A terminal body weight was recorded during necropsy.

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, glucose and ketones.

Hematology¹ and Clinical Biochemistry²: Blood samples were collected during week 5 (all animals from the jugular vein), at the end of the treatment (main study animals from the abdominal aorta) and at the end of the recovery period (from the abdominal aorta). The animals were not fasted overnight.

Pathology: Animals were not 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) were collected from all study animals and processed for microscopic examination.

Histopathology was performed on the tissues from all animals in the control and the high dose combination groups (1 and 4), 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, adrenals, cecum, colon and mesenteric lymph node) from all animals in the remaining groups (2, 3, 5 and 6).

Toxicokinetics: Systemic exposure to the test articles was evaluated by determining plasma concentrations of aliskiren and amlodipine in 2 animals/sex/group/time point. Blood samples were collected from the jugular venipuncture of each animal including the control group on study day 1 (1st dose) and in week 11 at 0.5, 1, 3, 7 and 24 hr after dosing.

¹ erythrocytes, hematocrit, hemoglobin, red cell distribution width, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocytes, white blood cell count, white blood cell differential, platelet count, prothrombin time, activated thromboplastin time, fibrinogen.

² ALT, AST, AP, creatine kinase, total bilirubin, total protein, albumin, globulins, A/G ratio, glucose, BUN, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, magnesium, triglycerides, cholesterol.

Table 3. Tissues sampled for histopathological examination

W	P	Adrenal		P	Oviduct
	P	Aorta (thoracic)		P	Pancreas
	P	Bone marrow (in bone) ^a	W	P	Parathyroid
W	P	Brain (forebrain, midbrain, cerebellum and medulla oblongata)	W	P	Pituitary
	P	Cecum	W	P	Prostate
	P	Cervix		P	Rectum
	P	Colon		P	Salivary gland (submandibular, sublingual, parotid)
	P	Duodenum		P	Sciatic nerve
	P	Epididymis ^b		P	Seminal vesicles
	P	Esophagus		P	Skeletal muscle
	P	Eye ^e		P	Skin (inguinal)
	P	Femur (distal w/ joint) ^a		P	Spinal cord (cervical, thoracic, lumbar)
	P	Harderian glands	W	P	Spleen
W	P	Heart (including sections of aorta)		P	Sternum ^a
	P	Ileum		P	Stomach
	P	Jejunum	W	P	Testis ^b
W	P	Kidney	W	P	Thymus
	P	Lacrimal gland ^f	W	P	Thyroid ^g
	P	Larynx		P	Tongue
W	P	Liver		P	Trachea
	P	Lung ^c		P	Ureters
	P	Lymph node – mandibular		P	Urinary bladder
	P	Lymph node – mesenteric	W	P	Uterus
	P	Mammary gland ^d		P	Vagina
	P	Optic nerves ^{de}		P	Macroscopic lesions
W	P	Ovary			Animal identification

a Bone decalcified prior to sectioning.

b Fixed in modified Davidson's fluid (euthanized animals only).

c Infused with neutral buffered 10% formalin (all animals).

d Examined histopathologically only if present in routine sections of eyes (optic nerves) or of skin (mammary gland).

e Fixed in Davidson's fluid (euthanized animals only).

f Bilateral collection, unilateral histopathology.

g At least one parathyroid should be examined, one recut and/or recheck of wet tissue was performed to try to find the missing tissue.

P: processing; W: weighing

Results

Mortality: A total of 6 males and 2 females died or were euthanized moribund between study days 33 and 91 (Table 4). The deaths of a control female and a high dose combination female were attributed by the sponsor to the bleeding accident. Three animals (2 males in the high dose combination and one male in the aliskiren alone groups) died or euthanized as a result of gavage errors. The remaining deaths were in the group receiving the high dose combination (2 males) or aliskiren alone (a male). Though severe adverse clinical signs were noted in these three animals, histopathological examination did not reveal the cause of mortality/morbidity to their death.

Table 4. Summary of animals found dead (FD) or sacrificed early (ES)

Dose level mg/kg/day	Study day	Animal Number/gender	FD or ES	Cause of death or reason for sacrifice
Control	33	1510/F	FD	Bleeding accident since it occurred after blood sampling; marked thymic hemorrhage
High dose combination 300:10 (aliskiren:amlodipine)	37	4014/M	FD	Abnormal breathing sounds, deep/labored breathing, pale skin, convulsions, cold to touch; inflammation of the trachea-suggesting gavage accident
	72	4005/M	FD	No clinical signs; cause undetermined*
	75	4015/M	ES	Abnormal breathing sounds, labored breathing, red fur staining*
	87	4011/M	FD	Abnormal breathing sounds; inflammation of the trachea-suggesting gavage accident
Aliskiren alone 300	33	5508/F	FD	Bleeding accident since it occurred after blood sampling
	45	5007/M	ES	Abnormal breathing sounds, labored breathing, red fur staining, decreased activity, abdominal distension, dehydration*
	91	5003/M	ES	Abnormal breathing sounds, deep/labored breathing, panting, decreased activity, weakness; inflammation of the trachea-suggesting gavage accident

*Death remained undetermined following histopathological examination, and therefore the sponsor concludes that a relation to the test substance administration could not be excluded.

Clinical Signs: Abnormal breathing sounds, shallow/deep/labored breathing, and salivation were noted in animals receiving the high dose combination or aliskiren alone. Respiratory rales were still present in high dose combination animals during the recovery period.

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 (21% to 32%, $p < 0.05$) in mean lymphocyte counts relative to control were noted in both sexes receiving 300:10 (aliskiren:amlodipine) mg/kg/day and in males receiving amlodipine alone at week 13. The decrease was still noted in males receiving the high dose combination after the recovery period.

Clinical Chemistry: At the end of treatment period, mild to moderate non-dose-dependent decreases ($p < 0.05$) in mean globulin concentrations (6 to 12% relative to control) were noted in males in all combination dose and amlodipine alone groups. For females, decreases in mean globulin concentrations (3 to 13% relative to control) were noted in the high dose combination, and aliskiren and amlodipine alone groups. Decreases in globulin persisted in treated males (12% relative to control) after the recovery period. There were no other noteworthy findings.

Urinalysis: No noteworthy findings

Gross Pathology: The major gross finding was pale discoloration or foci of the adrenals in either sexes receiving the high dose combination or amlodipine alone. This finding was associated with histological changes (see below).

Organ Weights: No noteworthy findings.

Histopathology: Main histopathological findings considered directly related to treatment were noted in the adrenal of both sexes. Minimal hypertrophy/vacuolation of the zona glomerulosa was observed in 10/10 males and 8/10 females receiving amlodipine alone, and 4/10 males and 2/10 females receiving 90:3 and 5/8 males and 5/10 females receiving 300:10 (aliskiren:amlodipine) mg/kg/day. It was absent in control and low dose combination groups. The finding was no longer seen at the end of recovery.

Toxicokinetics: Both aliskiren and amlodipine were rapidly absorbed and T_{max} values ranged from 0.5 to 3 hr for aliskiren and 1 to 7 hr for amlodipine. Systemic exposure (C_{max} and AUC) to aliskiren (Table 5) and amlodipine (Table 6) in males and females increased with increasing dose levels but not proportionately. No gender difference in exposure to test substances was noted. Exposure to aliskiren was generally similar after single as well as after multiple dosing. On the other hand, the amlodipine exposure increased approximately by a factor of 2.2 (average values for both males and females) after multiple daily dosing compared to single dose. There was no significant effect on the exposure of either drug components after single and multiple oral dosing of the combination drug.

Table 5. Mean toxicokinetics parameters for aliskiren in rat plasma

Dose SPP100:Amlodipine (mg/kg/day)	Study Day	Gender	AUC	SE of AUC	AUC/Dose	SE of AUC / Dose	C_{max}	$C_{max}/Dose$	$T_{max}(h)$
30:1	1	Male	27.5	3.79	0.917	0.126	2.56	0.0853	1
		Female	72.2	45.4	2.41	1.51	97.5	3.25	0.5
	75	Male	47.8	21.2	1.59	0.707	4.40	0.147	1
		Female	67.4	19.4	2.25	0.647	20.8	0.693	3
90:3	1	Male	315	36.0	3.50	0.400	76.2	0.847	3
		Female	269	82.2	2.99	0.913	52.3	0.581	3
	75	Male	331	55.6	3.68	0.618	39.2	0.436	3
		Female	457	152	5.08	1.69	299	3.32	0.5
300:10	1	Male	1130	310	3.75	1.03	141	0.470	3
		Female	2060	758	6.85	2.53	1460	4.87	0.5
	75	Male	1040	*	3.48	NA	114	0.380	1
		Female	1410	112	4.71	0.373	214	0.713	3
300:0	1	Male	930	53.7	3.10	0.179	123	0.410	3
		Female	900	116	3.00	0.387	158	0.527	3
	75	Male	964	*	3.21	NA	187	0.623	1
		Female	1770	*	5.90	NA	227	0.757	0.5
0:10	1	Male	NA	NA	NA	NA	NA	NA	NA
		Female	NA	NA	NA	NA	NA	NA	NA
	75	Male	NA	NA	NA	NA	NA	NA	NA
		Female	NA	NA	NA	NA	NA	NA	NA

* The concentration results are not appropriate for Nedelman/Jia/Holder (NJH) composite PK calculation as concentration data is available only for one subject at some time point(s) or pair(s) points; therefore, the parameter SE of Composite AUC (NJH) can not be calculated.

Table 6. Mean toxicokinetics parameters for amlodipine in rat plasma

Dose SPP100:Amlodipine (mg/kg/day)	Study Day	Gender	AUC	SE of AUC	AUC/Dose	SE of AUC / Dose	Cmax	Cmax/Dose	Tmax
30:1	1	Male	72.8	2.94	72.8	2.94	5.56	5.56	3
		Female	107	4.76	107	4.76	8.25	8.25	3
	75	Male	154	7.67	154	7.67	12.3	12.3	1
		Female	167	6.25	167	6.25	15.6	15.6	3
90:3	1	Male	252	23.7	84.0	7.90	29.2	9.73	3
		Female	424	47.6	141	15.9	48.2	16.1	3
	75	Male	594	24.9	198	8.30	61.0	20.3	3
		Female	850	100	283	33.3	81.2	27.1	3
300:10	1	Male	1430	215	143	21.5	97.7	9.77	7
		Female	1410	79.8	141	7.98	95.7	9.57	3
	75	Male	3990	*	399	NA	287	28.7	7
		Female	3710	232	371	23.2	256	25.6	3
300:0	1	Male	NA	NA	NA	NA	NA	NA	NA
		Female	NA	NA	NA	NA	NA	NA	NA
	75	Male	NA	NA	NA	NA	NA	NA	NA
		Female	NA	NA	NA	NA	NA	NA	NA
0:10	1	Male	2020	138	202	13.8	202	20.2	3
		Female	1780	92.2	178	9.22	120	12.0	1
	75	Male	3650	154	365	15.4	264	26.4	3
		Female	4610	181	461	18.1	358	35.8	3

* The concentration results are not appropriate for Nedelman/Jia/Holder (NJH) composite PK calculation as concentration data is available only for one subject at some time point(s) or pair(s) points; therefore, the parameter SE of Composite AUC (NJH) can not be calculated.

Stability and Homogeneity: The formulation was stable for at least 8 days refrigerated and 6 hr at room temperature. Mean concentrations of all samples analyzed were in the range of 94% to 103% of target concentrations.

6.2.2 Four Week Oral Gavage Impurity Toxicity Study in Wistar 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 (SPP100) pure and aliskiren hemifumarate with impurities was generally well tolerated at the maximum dose tested, 250 mg/kg/day. A statistically significant decrease in body weight gain relative to control was observed for males with both test item batches. The toxic potential of aliskiren hemifumarate with impurities is considered comparable to that of aliskiren hemifumarate without those impurities.

Study no.: 0510030

Study report location: EDR

Conducting laboratory and location: Exploratory Development, Safety Profiling and Assessment, Toxicology, Novartis Pharma AG, Basel, Switzerland

Date of study initiation: May 23, 2005 (the first day of administration)

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: The levels of impurities with each tested batch are shown in the following Table.

	Aliskiren hemifumarate	
Batch no.:	SPP100 0544031 (reference)	TOX1/SPP100 05/2 (with impurities)
Drug content:	98.2%	97.0%
Content of major impurities:	(b) (4)	(b) (4)

Methods

Doses: Aliskiren hemifumarate with impurities (TOX1/SPP100 05/2) was administered at two dose levels: 50 or 250 mg/kg/day. An additional group of rats received pure aliskiren hemifumarate (batch #0544031) at 250 mg/kg/day (Table 7). Doses are expressed as free base equivalents. Control animals received the vehicle (water).

Frequency of dosing: Once daily, for 4 weeks.

Route of administration: Orally by gavage

Dose volume: 5 ml/kg

Formulation/Vehicle: Both reference drug and TOX1/SPP100 05/2 were dissolved in purified water and refrigerated protected from light. Solutions were prepared once a week for the reference drug and fresh daily for the TOX1/SPP100 05/2. 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.

Species/Strain: Rats, Wistar Hanover, Crl:WI(Han) (b) (4)

Number/Sex/Group: 10

Age: About 10 weeks old at initiation of dosing

Weight: Males: 246.9 to 314.9 gm, Females: 164.8 to 198.5 gm, at initiation of dosing

Table 7. Study design

Item	Group 1		Group 2		Group 3		Group 4	
	Vehicle control (reference item)		TOX1/SPP100 (with impurities) 05/2		TOX1/SPP100 (with impurities) 05/2		SPP100 0544031	
Batch no.	Male	Female	Male	Female	Male	Female	Male	Female
Dosage mg base/kg/day (mg salt/kg/day)	0		50 (55.25)		250 (276.25)		250 (276.25)	
Dosage volume (mL/kg)	5.0		5.0		5.0		5.0	
Number of animals	10	10	10	10	10	10	10	10
Animal nos.	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
Cage nos.	1, 2	3, 4	5, 6	7, 8	9, 10	11, 12	13, 14	15, 16

Reserve animals: males no. 81-84 (cage 17), females no. 86-89 (cage no. 18).

Unique study design: None

Rationale for dose selection: 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.

Deviation from study protocol: None.

Observations and Measurements

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

Body Weight: Recorded prior to dosing and once weekly during the dosing period.

Food Consumption: Recorded prior to dosing and once weekly during the dosing period.

Ophthalmology: Conducted once pretest and at the end of dosing period (groups 1, 3 and 4).

Urinalysis: Overnight urine samples were collected from individual animals at the end of the treatment period. The following parameters were assessed: color and appearance, urine volume, specific gravity, pH, protein, bilirubin, blood, creatinine, creatinine clearance, nitrite, urobilinogen, glucose and ketones.

Hematology³ and Clinical Biochemistry⁴: Blood samples were collected at the end of the treatment period. The animals were not fasted overnight. Additionally, bone marrow smears obtained at necropsy.

Pathology: Animals were not fasted overnight prior to terminal necropsy. A complete necropsy was conducted on all animals, including those found dead, with a detailed

³ erythrocytes, hematocrit, hemoglobin, red cell distribution width, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocytes, white blood cell count, white blood cell differential, platelet count

⁴ ALT, AST, AP, creatine kinase, total bilirubin, total protein, albumin, glucose, BUN, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, magnesium, triglycerides, cholesterol

internal examination. Representative samples of the protocol tissues (Table 8) were collected from all study animals and processed for microscopic examination which was performed on the tissues from all animals in the control and the high dose combination groups (3 and 4), from the animals that were found dead or euthanized prior to scheduled necropsy, and all gross lesions, tissues showing treatment-related findings (lungs, thymus and mesenteric lymph node) from all animals in the remaining group (2).

Toxicokinetics: Systemic exposure to the test article was evaluated by determining plasma concentrations of aliskiren in 2 animals/sex/group/time point. Blood samples were collected from each animal including the control group at the end of the study at 0.5, 1, 3, 7 and 24 hr after dosing.

Table 8. Tissues sampled for histopathological examination

W	P	adrenals ^a	W	P	pituitary
	P	aorta	W	P	prostate
W	P	brain		P	rectum
	P	cecum		P	salivary glands
	P	colon		P	seminal vesicles
	P	duodenum		P	skeletal muscle
	P	epididymides		P	skin
	P	esophagus		P	spinal cord
	P	eyes with optic nerves	W	P	spleen
	P	Harderian glands		P	sternum (with bone marrow)
W	P	heart		P	stomach
	P	ileum	W	P	testes ^a
	P	jejunum	W	P	thymus
W	P	kidneys ^a	W	P	thyroid ^a (with parathyroid)
	P	knee joint (with bone marrow)		P	tongue
	P	lacrimal glands		P	trachea
	P	larynx		P	ureters
W	P	liver		P	urinary bladder
	P	lung	W	P	uterus (with cervix)
	P	lymph node – mandibular		P	vagina
	P	lymph node – mesenteric			Additional sample(s):
	P	mammary area/gland	S		bone marrow (femur)
		nasal cavity			
W	P	ovaries ^a (with oviduct)			
	P	pancreas			
	P	peripheral nerves			

^a paired organs weighed together

Abbreviations used: W = weighed, P = processed, S = smears

Results

Mortality: A male at 50 mg/kg/day (#24) and a female at 250 mg/kg/day (#60), both receiving the impurity batch 05/2, died spontaneously on study days 32 and 7, respectively, due to gavage accidents.

Clinical Signs: No clinical signs that could be attributed to the treatment with test substance.

Body Weights: Minimal reduction in body weight gain relative to control was noted for males ($P < 0.05$) and females ($p > 0.05$) receiving 250 mg/kg/day (both batches) for the duration of the study (Table 9).

Table 9. Summary of mean body weight gain in 4 week toxicity study

Study week	Sex	Control	Aliskiren with impurities		Aliskiren pure
		0	50 mg/kg/day	250 mg/kg/day	250 mg/kg/day
2	M	5.6	6.1	4.1*	3.9**
	F	5.3	6.3	5.1	5.4
3	M	11.1	11.5	8.9*	8.5**
	F	10.7	11.3	10.3	10.4
4	M	17.2	16.2	14.2*	13.4**
	F	14.6	14.8	13.6	13.7
5	M	19.2	18.4	16.1*	15.5**
	F	14.5	15.9	13.7	13.7

Values are presented as the group mean body weight gain (%) relative to weight on study week 1

* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level relative to the control group

Food Consumption: No significant treatment-related changes

Ophthalmoscopy: No remarkable ocular changes

Hematology: Generally mild, non-dose-dependent changes in the high dose groups. The values were not statistically significantly different from the control.

Clinical Chemistry: There were no noteworthy findings.

Urinalysis: No noteworthy findings

Gross Pathology: No treatment-related findings were evident.

Organ Weights: Statistically significant ($p < 0.05$) decreases in mean heart and liver weights (both absolute and relative) relative to control were noted for males at 250 mg/kg/day with both batches. Slight decreases ($p < 0.05$) in mean absolute and relative kidney weights were observed relative to control for males at 250 mg/kg/day with the impurity batch. On the other hand, high dose males receiving the pure test substance demonstrated statistically significant ($p < 0.05$) decreases in mean thymus, pituitary, and adrenal weights (both absolute and relative) relative to control (Table 10). No histopathologic correlates for any of these organ weights were evident.

Table 10. Mean absolute and relative (to body and brain) organ weights after 4 weeks of dosing in rats

Organ	Dose (mg/kg/day)								
	0			250 (Impure batch)			250 (pure batch)		
	Abs	O/BWt	O/BrWt	Abs	O/BWt	O/BrWt	Abs	O/BWt	O/BrWt
Heart	1.15	0.33745	58.23	1.02*		51.92*	1.02**	0.307**	50.07**
Liver	12.72	3.74	645	10.98**	3.45*	556**	11.27**	3.41*	555.4**
Kidney	2.41		122.4	2.21*		111.8**	2.32		114.4*
Thymus	0.4065	0.1188	20.59				0.332*	0.1*	16.4*
Pituitary	0.00972	0.00286	0.4941				0.00804 [†]	0.00244*	0.39622 [†]
Adrenal	0.0721	0.02109	3.66				0.6114	0.01851 [†]	3.02 [†]

Abs: absolute weight of the organ in grams

O/BWt: Organ to body weight ratio in percent

O/BrWt: Organ to brain weight ratio in percent

Dunnett's or Student's test at 5 % (*) or 1 % (**) level; Wilcoxon's test (†) at 5 % level relative to control group(s).

Histopathology: Histopathological findings were noted with comparable frequency in treated (both pure and impurity batches) and in control animals. Thus, the sponsor considered them to be incidental and not related to the administration of the test item.

Toxicokinetics: Apparent peak plasma concentrations of aliskiren were reached 1 hr post dose for all groups except for females receiving 50 mg/kg/day (impurity batch). The latter dose group exhibited high inter-animal variability relative to other dose groups. Based on AUC(0-24h) and C_{max} values at a dosage of 250 mg/kg/day, no significant difference could be observed between the systemic exposure of animals treated with pure batch 0544031 and impure batch TOX1/SPP100 batch 05/2. No gender differences were noted (Table 11).

Table 11. Mean toxicokinetics parameters for aliskiren in rat plasma

Time (hours)	Dose group					
	50 mg/kg/day impure batch		250 mg/kg/day impure batch		250 mg/kg/day pure batch	
	Male	Female	Male	Female	Male	Female
t _{max}	1	24	1	1	1	1
C _{max}	173	13.7	619	976	705	845
C _{max} /dose	3.46	0.274	2.48	3.9	2.82	3.38
AUC _(0-24h)	382	177	1140	1630	1630	1810
AUC _(0-24h) /dose	7.64	3.55	4.56	6.52	6.52	7.23

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).

Analysis of Formulations: Mean concentrations of all samples were within the expected range (95.9% to 105.4% of target).

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Key Study Findings

The combination drug composed of aliskiren hemifumarate and amlodipine besylate (ratio 30:1) spiked with a total of (b) (4) of impurity (b) (4) (based on amlodipine in the combination) was reproducibly negative in all tester strains both with and without metabolic activation.

Study title: **Mutagenicity test using *Salmonella typhimurium* (Batch control with impurities)**

Study no.: 0870368
Study report location: EDR
Conducting laboratory and location: Novartis Pharma AG, Department of PCS, Section of Genetic Toxicology and Safety Pharmacology and PCS Operations, Basel, Switzerland
Date of study initiation: November 5, 2008
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: SPA100 (batch #08/1, 98.4% pure) is a combination drug composed of Aliskiren hemifumarate (SPP100, batch #C0168, 98.6% pure) and Amlodipine besylate (batch #ACAA0464, 100% pure) at a ratio of 30:1, respectively. The new drug product formulation contained (b) (4) of impurity (b) (4) based on amlodipine. It does not contain impurities for aliskiren.

Methods

Strains: *Salmonella typhimurium*: TA97a, TA98, TA100, TA102, TA1535
Concentrations in definitive study: 312.5, 625, 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 concentration selection: Based on the results of a previous study (#966158) done with aliskiren hemifumarate (batch #817196 contained (b)(4) of impurity (b)(4) alone for the NDA 21,985. Aliskiren tested negative at concentrations of up to 5000 µg/plate.

Negative control: DMSO

Positive controls: See Table 12 below.

Formulation/Vehicle: DMSO

Activation system: S9 homogenate (liver microsomal enzymes) was prepared from the livers of male Aroclor-induced rats. The final concentration was 5%.

Incubation & sampling time: For each concentration of the test item, and for each positive and negative control group, 3 plates were used. The plates were incubated in dark at 30-39° C for 3 days.

Table 12. 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
TA102	Mitomycin-C	0.5	2-aminoanthracene	10
TA1535	Sodium azide	3.0	2-aminoanthracene	3

Study Validity

The assay was considered acceptable if the solvent control data for all tester strains were within the laboratory's historical control range for spontaneous mutant frequency and the positive controls induce statistically significant increases in the mutation frequency. Criteria for a positive result: For a 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, and TA1535 or 1.5 times the corresponding negative control count for the strain TA102. The results were considered meaningful if a concentration-related increase in the number of revertant colonies is observed. Appropriate positive and negative control groups were included in the study.

Results

No precipitation of test substance was observed in this study. Bacteriotoxicity of the test substance was noted at 5000 µg/plate for strains TA1535 and TA97a (without metabolic activation). Treatment did not increase the revertant numbers of any of the bacterial tester strains used (Table 13). The positive control compounds induced reverse mutations in each strain, with revertant colony counts ranging from 4 to 100 times corresponding negative control. Negative control results fell within the historical control ranges. It is concluded that the test item TOX1/SPA100 batch 08/1 (with ^{(b) (4)} of impurity ^{(b) (4)} based on amlodipine) did not show evidence of a mutagenic potential under the conditions of the study.

Table 13. Summary of bacterial reverse mutation assay (± S9 mix)

Treatment	Strain									
	TA1535		TA97a		TA98		TA100		TA102	
	S9		S9		S9		S9		S9	
	-	+	-	+	-	+	-	+	-	+
<u>Negative control</u>	19	17	216	228	26	44	202	193	456	526
<u>Test substance</u>										
312.5 µg/ plate	24	14	213	228	20	41	184	187	508	553
625 µg/ plate	16	16	223	240	22	43	182	188	447	522
1250 µg/ plate	25	15	214	252	26	38	184	185	465	522
2500 µg/ plate	22	18	233	229	22	47	183	188	378	442
5000 µg/ plate	20t	12	205t	253	25	48	180	197	328	348
<u>Positive control</u>										
2-aminoanthracene, 3 µg/plate		330				2109		2068		
Sodium azide, 3 µg/plate	1216						951			
2-aminoanthracene, 10 µg/plate				2000						1909
9-Aminoacridine, 100 µg/plate			2061							
Benzo(a)pyrene, 3 µg/plate						172				
2-Nitrofluorene, 2 µg/plate					120					
Mitomycin-C, 0.5 µg/plate									2119	

t: toxic

7.2 *In Vitro* Chromosomal Aberration Assays in Mammalian Cells

Key Study Findings

The combination drug composed of aliskiren hemifumarate and amlodipine besylate (ratio 30:1) spiked with a total of (b) (4) of impurity (b) (4) (based on amlodipine in the combination) did not show any clastogenic potential in the chromosomal aberration test with human peripheral blood lymphocytes.

Study title: Chromosome aberration test with cultured human peripheral blood lymphocytes

Study no.:	0870367
Study report location:	EDR
Conducting laboratory and location:	Novartis Pharma AG, Preclinical Safety Department, Basel, Switzerland
Date of study initiation:	October 3, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SPA100 (batch #08/1, 98.4% pure) is a combination drug composed of Aliskiren hemifumarate (SPP100, batch #C0168, 98.6% pure) and Amlodipine besylate (batch #ACAA0464, 100% pure) at a ratio of 30:1, respectively. The new drug product formulation contained (b) (4) of impurity (b) (4) based on amlodipine. It does not contain impurities for aliskiren.

Methods

Cell line:	Cultured human peripheral blood lymphocytes prepared from the pooled blood of healthy non-smoking volunteers
Concentrations in definitive study:	-S9: 250, 390.3, 382.8, 473.6, 586.1, 725.2, 897.3, 1110.3, 1373.9, 1700 µg/ml (3 hr treatment, 17 hr recovery) +S9: 250, 390.3, 382.8, 473.6, 586.1, 725.2, 897.3, 1110.3, 1373.9, 1700 µg/ml (3 hr treatment, 17 hr recovery)

- Basis of concentration selection: Two preliminary studies were conducted with concentrations ranging from 100 to 2200 µg/ml. The first experiment was invalidated due to poor cell growth and the second experiment was invalidated due to an inappropriate range of test substance toxicity. Based on the data concerning depression of the mitotic index, the following concentrations of test substance were selected for analysis in the definitive study:
Without metabolic activation: 250.0, 382.8, 473.6 µg/ml (3 h treatment, 17 hours recovery).
With metabolic activation: 250.0, 309.3, 382.8 µg/ml (3 h treatment, 17 hours recovery).
- Negative control: Culture medium
- Positive control: Ethyl methanesulfonate (EMS), a direct acting mutagen was used at concentrations 5 and 9.7 mM. Cyclophosphamide (CP), an indirect-acting mutagen was used at a concentration of 55 µM.
- Formulation/Vehicle: Culture medium
- Activation system: S9 homogenate (liver microsomal enzymes) was prepared from the livers of male Aroclor-induced rats. The final concentration was 10%.
- Incubation & sampling time: With and without metabolic activation: 3 h treatment followed by 17 hours recovery.

Two hours prior to harvesting, the cultures were treated with colcemide (0.2 µg/ml) to arrest cells in metaphase. The cells were pelleted and then fixed. Where possible, 160 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.

The concentration of test substance that suppresses mitotic activity (cytotoxicity measured as mitotic index which is defined as percentage of cells in mitosis) between 29.8 and 90.4% 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

Study Validity

The test substance was considered to be positive if a) statistically significant increases in the frequency of metaphases with aberrant chromosomes were observed at one or more concentrations, b) the increases exceeded the historical negative control range, and c) the increases were reproducible between replicate cultures and between tests, and d) the increases were not associated with extreme toxicity. A negative response was claimed if no reproducible, statistically significant increases in the number of aberrant cells above concurrent control frequencies were observed at any concentration level. Appropriate positive and negative control groups were included in the study.

Results

The identities of the two components of TOX1/SPA100, aliskiren and amlodipine, were confirmed. The concentrations of aliskiren and amlodipine measured in the dose formulation samples were found to be within the acceptable limits of deviation of $\pm 15\%$. Both aliskiren and amlodipine were demonstrated to be stable when kept for 6 hours at room temperature and day light. The vehicle samples were free of aliskiren and amlodipine. A slight precipitation was noted at the highest tested concentration, 2200 $\mu\text{g/ml}$.

TOX1/SPA100 produced a concentration-dependent decrease in the mitotic index. The incidence rates of cells possessing structural chromosomal aberrations, including or excluding gaps, with (Table 14) or without (Table 15) metabolic activation to, were within the historical negative control range. The frequencies of cells with numerical aberrations were within the historical control range for all treated cultures. Statistical analysis was not performed.

Chromosomal aberrations detected in the negative concurrent control ranged from 1.5 to 2.0%. These results fell within the historical control ranges. In contrast, the incidence of chromosomal aberration in cultures treated with the positive controls, EMS and cyclophosphamide, ranged between 16 and 28%.

It is concluded that TOX1/SPA100 does not have any clastogenic potential under the conditions of this chromosomal aberration test.

Table 14. Chromosome aberration analysis after treatment for 3 hr with TOX1/SPA100 and recovery for 17 hr in the presence of rat liver S9 mix

Treatment : (3h+S9)	Mitotic Index (%) *	Rel. Mitotic Index (%) **	% Ab. cells excl. gaps	% cells with exchanges	% Num. Aberr. cells
RPMI1640	7.0	100.0	1.0	0.0	0.0
1700.0 µg/ml	ND	ND	ND	ND	ND
1373.9 µg/ml	ND	ND	ND	ND	ND
1110.3 µg/ml	ND	ND	ND	ND	ND
897.3 µg/ml	ND	ND	ND	ND	ND
725.2 µg/ml	ND	ND	ND	ND	ND
586.1 µg/ml	2.5	35.7	ND	ND	ND
473.6 µg/ml	4.2	60.0	ND	ND	ND
382.8 µg/ml	3.5	49.3	0.5	0.0	2.5
309.3 µg/ml	4.7	67.1	0.5	0.0	2.0
250.0 µg/ml	5.6	79.3	0.0	0.0	1.5
CP 55 µM	3.8	54.3	13.1	0.0	3.2

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.

% Ab. Cells % aberrant cells (exclusive gaps)

Table 15. Chromosome aberration analysis after treatment for 3 hr with TOX1/SPA100 and recovery for 17 hr in the absence of rat liver S9 mix

Treatment : (3h-S9)	Mitotic Index (%) *	Rel. Mitotic Index (%) **	% Ab. cells excl. gaps	% cells with exchanges	% Num. Aberr. cells
RPMI1640	5.7	100.0	0.5	0.0	0.0
1700.0 µg/ml	ND	ND	ND	ND	ND
1373.9 µg/ml	ND	ND	ND	ND	ND
1110.3 µg/ml	ND	ND	ND	ND	ND
897.3 µg/ml	ND	ND	ND	ND	ND
725.2 µg/ml	ND	ND	ND	ND	ND
586.1 µg/ml	1.7	29.8	ND	ND	ND
473.6 µg/ml	2.7	47.4	0.5	0.0	3.4
382.8 µg/ml	3.4	58.8	0.0	0.0	2.0
309.3 µg/ml	4.8	84.2	ND	ND	ND
250.0 µg/ml	5.2	90.4	0.0	0.0	1.0
EMS 9.7 mM	1.3	22.8	24.0	4.0	0.0

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.

% Ab. Cells % aberrant cells (exclusive gaps)

8. Integrated Summary and Safety Evaluation

SPA100 (Tekamlo[®]) is a fixed dose combination of aliskiren hemifumarate and amlodipine besylate for the treatment of hypertension. Aliskiren is a renin inhibitor, approved in 2007 for the treatment of hypertension (NDA 21,985, Tekturna[®], Novartis Pharmaceuticals). Racemic amlodipine is a dihydropyridine calcium channel antagonist developed by Pfizer. Amlodipine was approved in 1992 as the besylate salt for the treatment of hypertension, chronic stable angina and vasospastic angina (Norvasc[®], NDA 19,787). The combinations of aliskiren hemifumarate and HCTZ (Tekturna[®] HCT, NDA 22,107), and aliskiren hemifumarate and valsartan (Valturna[®], NDA 22,217) were approved in 2008 and 2009, respectively.

A combination of these drugs is expected to result in an additive or synergistic antihypertensive effect when compared to single drug treatment. No preclinical pharmacodynamic or special pharmacokinetic studies were performed with SPA100. Toxicity studies with durations of 2 weeks (a non-GLP study) and 13 weeks (a GLP study) in rats were conducted with SPA100 (aliskiren hemifumarate and amlodipine besylate containing (b) (4) of impurity (b) (4) based on amlodipine) to evaluate nonclinical safety profile of aliskiren and amlodipine when used in combination. In addition, two genotoxicity assays including Ames and an *in vitro* chromosome aberration assays were performed. Separately, a 4 week oral gavage study in Wistar rats was conducted with aliskiren hemifumarate impurities. Based on the proposed highest therapeutic dose strength of 300/10 mg (aliskiren/amlodipine), a ratio of approximately 30:1 was used in the toxicity study.

Wistar rats were treated orally by gavage with either drug alone (300 mg aliskiren/kg/day or 10 mg amlodipine/kg/day) or both drugs in combination at a dose ratio of 30:1 [30:1, 90:3 or 300:10 (aliskiren:amlodipine) mg/kg/day] for 13 weeks followed by a 4 week post dosing period to assess the reversibility of any effects observed. Of the 8 unscheduled deaths (between study days 33 and 91), 5 mortalities were attributed to gavage and/or bleeding accidents, the remaining 3 mortalities (2 males in the high dose combination and one male in the aliskiren groups) were caused by the test substance. Though a cause of death could not be established for these animals, test substance-related clinical signs such as labored/congested breathing and gasping, panting, abnormal breathing sounds, decreased activity, and weakness were noted prior to death or moribund sacrifice. All of these clinical signs were noted in animals receiving the high dose combination or aliskiren alone. Similar findings were noted in the previous 13 week rat study with aliskiren (NDA 21,985) and associated with local irritation of aliskiren as a result of aspiration of the dosing solution into the respiratory tract. At necropsy, pale discoloration or foci of the adrenals correlating with hypertrophy/vacuolation of the zona glomerulosa was noted in animals treated with the combination at 90:3 or more mg/kg/day and in animals receiving amlodipine alone. This finding was no longer seen at the end of recovery. Based on the histopathological finding, the no observed adverse effect level for this study was 30:1 (aliskiren: amlodipine) mg/kg/day.

Exposure to aliskiren was generally similar after single as well as after multiple dosing. On the other hand, the amlodipine exposure increased approximately by factor of 2 after multiple daily

dosing compared to single dose. There was no significant effect on the exposure of either drug component after single and multiple oral dosing of the combination drug.

Toxicity studies on impurities or degradation products were performed. Aliskiren hemifumarate impurity (b) (4) (at a concentration of (b) (4)) was tested in the 4 week oral toxicity study in Wistar rats using pure and impure batches of aliskiren hemifumarate up to a maximum dose of 250 mg/kg/day. The toxic potential of aliskiren with impurities is considered comparable to that of aliskiren without those impurities. Thus, the aliskiren impurities are qualified at the levels in the impure batch. Amlodipine impurity (b) (4) was tested in the 13 week oral toxicity study in rats (discussed above) and in two genotoxicity assays using a SPA100 drug substance batch, TOX1/SPA100. The batch contained (b) (4) of impurity (b) (4) based on amlodipine. No evidence of genotoxicity was noted for this batch in an Ames test and an *in vitro* chromosome aberration study.

Evaluation

The combined administration of aliskiren hemifumarate and amlodipine besylate did not identify any new toxicity and augment any existing toxicities of the individual agents in the 13 week toxicology study. The toxicity noted was clearly associated with either aliskiren or amlodipine as evident from the previous toxicity studies with these drugs. The target organ of toxicity in both sexes was the adrenal (hypertrophy/vacuolation of the zona glomerulosa) noted in animals treated with the combination at 90:3 or more mg/kg/day and in animals receiving amlodipine alone. This finding was related to the amlodipine administration as it was not seen in the animals receiving aliskiren alone. We note, however, that the highest dose used in the toxicology study, 300:10 mg (aliskiren:amlodipine)/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).

The plasma concentrations of aliskiren at the highest dose used in the current 13 week toxicity study were below those anticipated clinically (0.4 to 0.6 times based on AUC values; Table 16), indicating the absence of a safety margin for humans. On the other hand, rats were substantially exposed to amlodipine in the same study (about 8 times human exposure, Table 16). In the present study, the NOAEL (for hypertrophy/vacuolation of the zona glomerulosa) was considered to be 30:1 mg (aliskiren:amlodipine)/kg/day. At this dose level, exposure to aliskiren and amlodipine was, respectively, 40 and 3 (based on mean AUC values for both sexes) times lower than the expected exposure at the maximum recommended human dose [300:10 mg (aliskiren:amlodipine)/day]. This is not a major concern since no toxicity was noted for aliskiren hemifumarate at the highest dose used in the present study and apparent tolerance noted when the combination was administered in clinical trials.

Table 16. Human SPA100 exposure multiples in 3 month toxicity study in rats

Drug	Dose (aliskiren: amlodipine) (mg/kg/day)	Gender	AUC _{0-last} (ng·h/ml) ^c	C _{max} (ng/ml) ^c	Exposure multiples based on ^d	
					AUC	C _{max}
Aliskiren	30:1 ^a	male	47.8	4.4	0.02	0.13
		female	67.4	20.8	0.03	0.62
	300:10 ^b	male	1040.0	114.0	0.42	3.40
		female	1410.0	214.0	0.57	6.40
Amlodipine	30:1 ^a	male	154.0	12.3	0.33	0.83
		female	167.0	15.6	0.36	1.05
	300:10 ^b	male	3990.0	287.0	8.56	19.30
		female	3710.0	256.0	7.96	17.20

a: NOAEL: No-Observed-Adverse-Effect-Level;

b: maximum dose used in the study; c: week 13 (day 75);

d: aliskiren and amlodipine exposure multiples were based on the mean human AUC_{0-24h} = 2470, 466 ng·h/ml and C_{max} = 33.6, 14.9 ng/ml, respectively, on day 49 (Study #SPP100A2218).

In study #SPP100A2218, healthy human volunteers (male and female) received a dose of 10 mg amlodipine once daily for 14 days. After a 7 day washout period, the same subjects received a dose of 300 mg aliskiren once daily for 14 days (study days 22-35), followed by 300 mg aliskiren co-administered with a dose of 10 mg amlodipine once daily for the next 14 days (study days 36-49).

The toxicity of aliskiren with impurities (b) (4) (all 3 reported in NDA 22217, a combination of aliskiren hemifumarate and valsartan) and (b) (4) (the present NDA) 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 (b) (4) (not tested) were tested negative in Ames and chromosome aberration tests. Impurities (b) (4) and (b) (4) were tested at levels (b) (4) respectively) above the sponsor's proposed limits (b) (4). The total daily intake for (b) (4) (combined impurities (b) (4)) achieved at the highest dose level (21.3 mg/m²) was (b) (4) higher than anticipated in humans (2.4 mg/m² or 3.9 mg/day for a 60 kg individual with combined impurities at the current specification of (b) (4)). The third impurity, (b) (4), was tested at a concentration of (b) (4), well (b) (4) the total daily intake for (b) (4) achieved at the highest dose level in the 13 week toxicity study (2.52 mg/m²) was (b) (4)-fold higher than anticipated in humans (0.925 mg/m² or 1.5 mg/day for a 60 kg individual with an impurity level of (b) (4)). The sponsor notes that the impurity (b) (4) is structurally identical to identified metabolite (M9) in the main toxicology species and in humans. We agree to the sponsor's assertion that the toxicological profile of (b) (4) would have been assessed during toxicology studies for aliskiren by its formation through the identified biotransformation pathways in animals. Therefore, it is considered to be qualified by the extensive toxicology studies conducted for aliskiren hemifumarate. The fourth impurity, (b) (4), was tested at a concentration of (b) (4) well (b) (4) the current specification of (b) (4), total daily intake for (b) (4) achieved at the highest dose level in the 4 week toxicity study (3.68 mg/m²) was 5-fold higher than anticipated in humans (0.74 mg/m² or 1.2 mg/day for a 60 kg individual with an impurity level of (b) (4)) (Table 17). This suggests that animals were adequately exposed to all four aliskiren impurities and, thus, the proposed specifications for these impurities in the drug product are supported.

The drug substance batch with (b) (4) of impurity (b) (4) based on amlodipine demonstrated no new toxicity. In the 13 week toxicity study in rats, total daily intake for (b) (4) of impurity (b) (4) achieved at the highest dose level (1.02 mg/m²) was 10-fold higher than anticipated in humans (0.105 mg/m² or 0.17 mg/day for a 60 kg individual with an impurity at the current specification of (b) (4)) (Table 17). This suggests that animals were adequately exposed to amlodipine impurity and, thus, the proposed specification for this impurity in the drug product is supported.

Table 17. Human SPA100 (aliskiren:amlodipine) exposure multiples in toxicity study in rats for drug substance impurities

Aliskiren hemifumarate				Amlodipine besylate			
Impurity	Proposed limit ¹	Tested at level ²	Human multiples ³	Impurity	Proposed limit ¹	Tested at level ²	Human multiples ³
(b) (4)	(b) (4)	(b) (4)	8.9 ⁴	(b) (4)	(b) (4)	(b) (4)	10
(b) (4)	(b) (4)	(b) (4)					
(b) (4)	(b) (4)	(b) (4)	5.0				
(b) (4)	(b) (4)	(b) (4)	2.7				

1: Impurity level (in %) defined in aliskiren/amlodipine drug product specification

2. Toxicological qualification level, %

3. The total daily intake for impurity (tested at a concentration given in col 3 or 7) achieved at the highest dose level in the toxicity study to that anticipated in humans at a maximum clinical dose of 300:10 mg (aliskiren:amlodipine)/day with an impurity at the current specification (given in col 2 or 6).

3. Combined impurities as they were tested together.

Recommendations on Labeling: See page 4.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

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/s/

GOWRA G JAGADEESH
06/03/2010

PATRICIA P HARLOW
06/03/2010

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number:

Applicant: Novartis

Stamp Date:

Drug Name: Tekamlo

NDA/BLA Type: 22545

10-29-09

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	yes		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	yes		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	yes		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	yes		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	yes		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	yes		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	yes		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	yes		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	yes		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	yes		
11	Has the applicant addressed any abuse potential issues in the submission?	yes		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			No comments

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____yes_

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Signed: G. Jagadeesh Jan 7, 2010

Reviewing Pharmacologist Date

Signed: P. Harlow, Jan 8, 2010

Team Leader/Supervisor Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

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

/s/

GOWRA G JAGADEESH
01/11/2010

PATRICIA P HARLOW
01/11/2010