

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200045Orig1s000

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: 200045
Supporting document/s: None
Applicant's letter date: February 25, 2010
CDER stamp date: February 26, 2010
Product: [REDACTED] ^(b)₍₄₎ Tablets
Drug substance: Aliskiren hemifumarate, amlodipine besylate and hydrochlorothiazide
Indication: Hypertension
Applicant: Novartis Pharmaceuticals Corporation
Review Division: Cardiovascular and Renal Products
Reviewer: G. Jagadeesh, Ph.D.
Supervisor/Team Leader: Thomas Papoian, Ph.D.
Division Director: Norman Stockbridge, M.D., Ph.D.
Project Manager: Lori Wachter
Date of review submission to DARRTS: July 28, 2010

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1 Executive Summary

Background

The widely recognized ALLHAT (antihypertensive and lipid-lowering treatment to prevent heart attack trial) study suggested that the majority (63%) of patients required more than 2 antihypertensive agents and a minor set (27%) needed more than 3 drugs to combat high blood pressure. Simultaneous blockade of two or more related or complementary 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 possibly 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, amlodipine besylate and hydrochlorothiazide (SAH100, ^(b)) in the treatment of essential hypertension. Aliskiren is a direct renin inhibitor that inhibits ⁽⁴⁾ 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. Hydrochlorothiazide is a thiazide diuretic. It affects the renal tubular mechanism of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. All three 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 for better 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 February, 2010) that deal with nonclinical studies covered by this review are considered satisfactory with the following exceptions.

5.1 Fetal/Neonatal Morbidity and Mortality

Based on the format followed for NDA 022545(aliskiren and amlodipine), the sponsor's text is replaced with the following text.

The use of drugs that act directly on the renin-angiotensin-aldosterone system during (b) (4) pregnancy can cause fetal and neonatal morbidity and death. No animal studies were conducted with (b) (4); however, decreased fetal birth weight was observed in animal studies with aliskiren and intrauterine deaths were observed in animal studies with amlodipine. (b) (4) can cause fetal harm when administered to a pregnant woman. When pregnancy is detected, discontinue (b) (4) as soon as possible. If (b) (4) is used during pregnancy, or if a patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus [*see Use in Specific Populations (8.1)*].

8.1 Pregnancy

Based on the format followed for NDA 022545(aliskiren and amlodipine), the sponsor's text is edited for consistency. The first paragraph is replaced with the following text. As suggested in NDA 022545, the animal reprotox study data is moved from section 13 and placed here. In addition, the text does not include rodent-to-human mg/m² dosage multiples for HCTZ.

The use of drugs that act directly on the renin-angiotensin-aldosterone system during the second and third trimesters of pregnancy can cause fetal and neonatal morbidity and death. No animal studies were conducted with (b) (4); however, decreased fetal birth weight was observed in animal studies with aliskiren and intrauterine deaths were observed in animal studies with amlodipine. (b) (4) can cause fetal harm when administered to a pregnant woman. When pregnancy is detected, discontinue (b) (4) as soon as possible. If (b) (4) is used during pregnancy, or if a patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus.

Animal Data

(b) (4)

Aliskiren

In developmental toxicity studies, pregnant rats and rabbits received oral aliskiren hemifumarate during organogenesis at doses up to 20 and 7 times the maximum recommended human dose (MRHD) based on body surface area (mg/m²), in rats and rabbits, respectively. (Actual animal doses were up 600 mg /kg/day in rats and up to 100 mg/kg/day in rabbits.) No teratogenicity was observed; however, fetal birth weight was decreased in rabbits at doses 3.2 times the MRHD based on body surface area (mg/m²). Aliskiren was present in placentas, amniotic fluid and fetuses of pregnant rabbits.

Amlodipine

In developmental toxicity studies pregnancy rats and rabbits received oral amlodipine maleate during organogenesis at doses approximately 10 and 20 times the maximum recommended human dose (MRHD) based on body surface area (mg/m^2), in rats and rabbits, respectively. (Actual animal doses were up to 10 $\text{mg}/\text{kg}/\text{day}$.) No evidence of teratogenicity or other embryofetal toxicity was observed. However, litter size was decreased approximately 50% and the number of intrauterine deaths was increased approximately 5-fold for rats receiving amlodipine maleate at doses approximately 10 times the MRHD based on body surface area (mg/m^2) for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

Hydrochlorothiazide

[REDACTED] (b) (4)

10. OVERDOSAGE

The sponsor text does not include rodent-to-human mg/m^2 dosage multiples for HCTZ. In addition, the sponsor's text is edited for format and consistency. The following statement incorporates our recommended changes (underlined).

Amlodipine

Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/ kg and 100 mg amlodipine/ kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/ kg [REDACTED] (b) (4) caused a marked peripheral vasodilation and hypotension.

Hydrochlorothiazide

The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD_{50} of hydrochlorothiazide is greater than 10 g/kg in both mice and rats. These doses are 1946 and 3892 times, respectively, the MRHD of 25 mg/day , when based on a mg/m^2 basis of a 60 kg individual.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The sponsor text does not include rodent-to-human mg/m² dosage multiples for HCTZ. In addition, the sponsor's text is edited for format and consistency. The sponsor text is reproduced below with our recommended changes (underlined).

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). These doses in mice and rats are about 117 and 39 times, respectively, the MRHD of 25 mg/day, when based on a mg/m² basis of a 60 kg individual. The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic in vitro in the Ames mutagenicity assay of *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538, in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in vivo in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. (b) (4) positive test results were obtained in the in vitro CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mcg/ml, and in the *Aspergillus Nidulans* nondisjunction assay at an unspecified concentration.

13.2 Animal Toxicology and/or Pharmacology

The sponsor has not conducted nonclinical studies with the combination. The reprotox text originally placed in section 13.2 by the sponsor is moved to section 8.1.

No nonclinical studies have been conducted for (b) (4) as these studies have been previously conducted for each individual component.

For animal reproductive and developmental toxicology findings, see Use in Specific Populations (8.1).

1.2 Brief Discussion of Nonclinical Findings

The sponsor has not performed pharmacology, ADME or toxicology studies for the combination product. Nonclinical studies of the individual active components of the combination product are summarized in the pharmacology and toxicology reviews of related NDAs listed in sections 2.3 and 3.1 below.

2 Drug Information

2.1 **Drug Product:** (b) (4) Tablets (SAH100)

2.2 Drug Substances

Generic name: Aliskiren hemifumarate

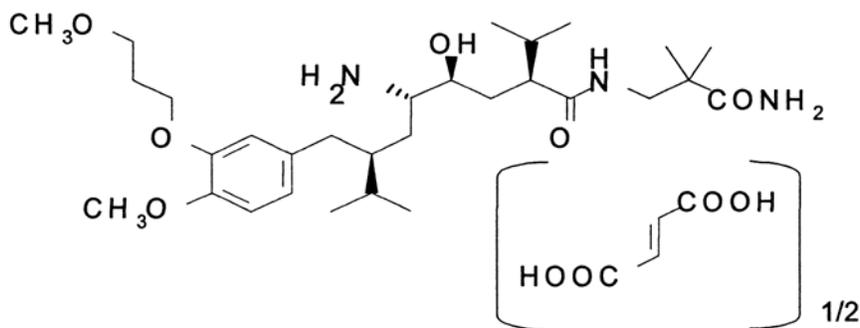
Code names: SPP 100 (base); SPP 100A (HCl), SPP 100B (hemifumarate)

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

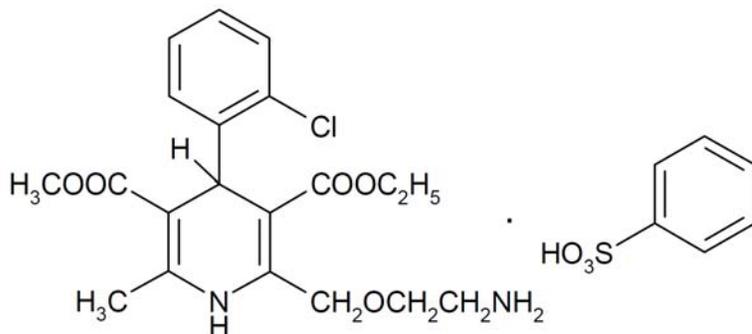
Chemical name: (RS)-2-[(2'-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid 3-ethyl ester, 5-methyl ester, benzene sulfonate.

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)



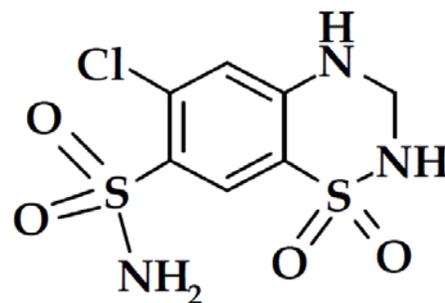
Generic name: **Hydrochlorothiazide (HCTZ)**

Chemical name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Chemistry: Hydrochlorothiazide is a white, or practically white, crystalline powder which is slightly soluble in water and freely soluble in sodium hydroxide solution.

CAS registry number: 58-93-5

Molecular formula/molecular weight: C₇H₈ClN₃O₄S₂ / 297.74



2.3 Related Applications: Clinical trials supporting the current NDA were conducted under Novartis Pharmaceuticals Corporations IND 62,976 (aliskiren monotherapy) and IND 101,386 (aliskiren/amlodipine/ hydrochlorothiazide). 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: 022107 (aliskiren and HCTZ), 022217 (aliskiren and valsartan), 022545 (aliskiren and amlodipine).

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

2.5 Intended Clinical Population: Hypertensive subjects

2.6 Clinical Formulation and Dosing Regimen: The tablets are formulated in five strengths of aliskiren hemifumarate:amlodipine besylate:hydrochlorothiazide, respectively: 150:5:12.5 mg, 300:5:12.5 mg, 300:10:12.5 mg, 300:5:25 mg, and 300:10:25 mg. Table 1 lists proposed final commercial formulations.

Table 1. The composition of drug product

Ingredient	Amount (mg) per tablet					Function	Reference to standards
	150/5/12.5 mg	300/5/12.5 mg	300/10/12.5 mg	300/5/25 mg	300/10/25 mg		
(b) (4)						(b) (4)	
Aliskiren hemifumarate						Active substance	Novartis monograph
Amlodipine besylate						Active substance	Novartis monograph
Hydrochlorothiazide						Active substance	Novartis monograph
Microcrystalline cellulose/ Cellulose microcrystalline						(b) (4)	NF / Ph. Eur.
Croscopovidone							NF / Ph. Eur.
Povidone							USP / Ph. Eur.
(b) (4)							Novartis monograph
Colloidal silicon dioxide / Silica, colloidal anhydrous							NF / Ph. Eur.
Magnesium stearate ⁶							NF / Ph. Eur.
(b) (4)							Novartis monograph
							Novartis monograph
							Novartis monograph
							Novartis monograph
							USP/ Ph. Eur.

¹ Corresponds to e.g. 150 mg aliskiren base

² Corresponds to e.g. 300 mg aliskiren base

³ Corresponds to e.g. 5 mg amlodipine base

⁴ Corresponds to e.g. 10 mg amlodipine base

(b) (4)

3 Studies Submitted

No nonclinical studies submitted with this NDA.

3.1 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[®])
- NDA 22,545 for aliskiren and amlodipine (Tekamlo[®]).

4 Pharmacology, Pharmacokinetics/ADME/Toxicokinetics, General Toxicology

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

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/s/

GOWRA G JAGADEESH
10/27/2010



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Review Division: Cardiovascular and Renal Products
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1 Executive Summary

Background

The widely recognized ALLHAT (antihypertensive and lipid-lowering treatment to prevent heart attack trial) study suggested that the majority (63%) of patients required more than 2 antihypertensive agents and a minor set (27%) needed more than 3 drugs to combat high blood pressure. Simultaneous blockade of two or more related or complementary 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 possibly 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.

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Approvable

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None

1.1.3 Labeling

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Based on the format followed for NDA 022545(aliskiren and amlodipine), the sponsor's text is edited for consistency. The first paragraph is replaced with the following text. As suggested in NDA 022545, the animal reprotox study data is moved from section 13 and placed here. In addition, the text does not include rodent-to-human mg/m² dosage multiples for HCTZ.

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Animal Data

(b) (4)

Aliskiren

In developmental toxicity studies, pregnant rats and rabbits received oral aliskiren hemifumarate during organogenesis at doses up to 20 and 7 times the maximum recommended human dose (MRHD) based on body surface area (mg/m²), in rats and rabbits, respectively. (Actual animal doses were up 600 mg /kg/day in rats and up to 100 mg/kg/day in rabbits.) No teratogenicity was observed; however, fetal birth weight was decreased in rabbits at doses 3.2 times the MRHD based on body surface area (mg/m²). Aliskiren was present in placentas, amniotic fluid and fetuses of pregnant rabbits.

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In developmental toxicity studies pregnancy rats and rabbits received oral amlodipine maleate during organogenesis at doses approximately 10 and 20 times the maximum recommended human dose (MRHD) based on body surface area (mg/m^2), in rats and rabbits, respectively. (Actual animal doses were up to 10 $\text{mg}/\text{kg}/\text{day}$.) No evidence of teratogenicity or other embryofetal toxicity was observed. However, litter size was decreased approximately 50% and the number of intrauterine deaths was increased approximately 5-fold for rats receiving amlodipine maleate at doses approximately 10 times the MRHD based on body surface area (mg/m^2) for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

Hydrochlorothiazide

[REDACTED] (b) (4)

10. OVERDOSAGE

The sponsor text does not include rodent-to-human mg/m^2 dosage multiples for HCTZ. In addition, the sponsor's text is edited for format and consistency. The following statement incorporates our recommended changes (underlined).

Amlodipine

Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/ kg and 100 mg amlodipine/ kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/ kg [REDACTED] (b) (4) caused a marked peripheral vasodilation and hypotension.

Hydrochlorothiazide

The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD_{50} of hydrochlorothiazide is greater than 10 g/kg in both mice and rats. These doses are 1946 and 3892 times, respectively, the MRHD of 25 mg/day , when based on a mg/m^2 basis of a 60 kg individual.

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13.2 Animal Toxicology and/or Pharmacology

The sponsor has not conducted nonclinical studies with the combination. The reprotox text originally placed in section 13.2 by the sponsor is moved to section 8.1.

No nonclinical studies have been conducted for (b) (4) as these studies have been previously conducted for each individual component.

For animal reproductive and developmental toxicology findings, see Use in Specific Populations (8.1).

1.2 Brief Discussion of Nonclinical Findings

The sponsor has not performed pharmacology, ADME or toxicology studies for the combination product. Nonclinical studies of the individual active components of the combination product are summarized in the pharmacology and toxicology reviews of related NDAs listed in sections 2.3 and 3.1 below.

2 Drug Information

2.1 **Drug Product:** (b) (4) Tablets (SAH100)

2.2 Drug Substances

Generic name: Aliskiren hemifumarate

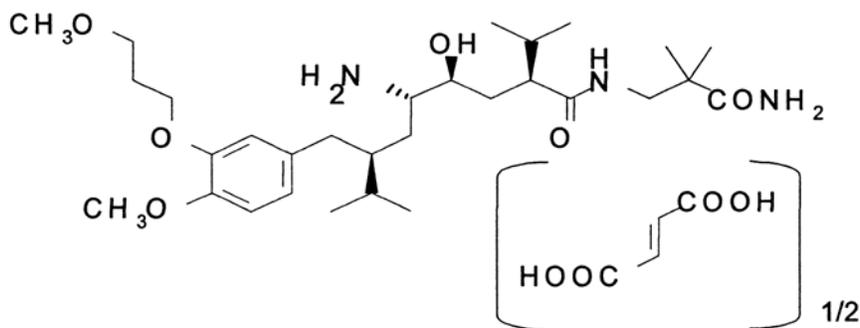
Code names: SPP 100 (base); SPP 100A (HCl), SPP 100B (hemifumarate)

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

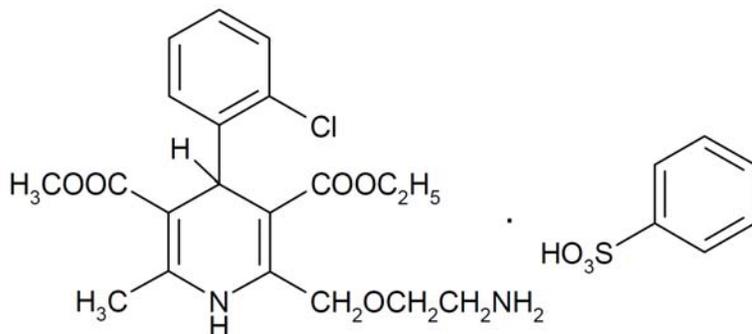
Chemical name: (RS)-2-[(2'-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid 3-ethyl ester, 5-methyl ester, benzene sulfonate.

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)



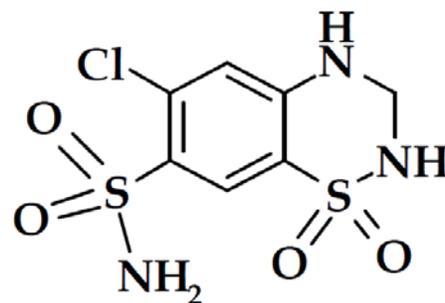
Generic name: **Hydrochlorothiazide (HCTZ)**

Chemical name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Chemistry: Hydrochlorothiazide is a white, or practically white, crystalline powder which is slightly soluble in water and freely soluble in sodium hydroxide solution.

CAS registry number: 58-93-5

Molecular formula/molecular weight: C₇H₈ClN₃O₄S₂ / 297.74



2.3 Related Applications: Clinical trials supporting the current NDA were conducted under Novartis Pharmaceuticals Corporations IND 62,976 (aliskiren monotherapy) and IND 101,386 (aliskiren/amlodipine/ hydrochlorothiazide). 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: 022107 (aliskiren and HCTZ), 022217 (aliskiren and valsartan), 022545 (aliskiren and amlodipine).

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

2.5 Intended Clinical Population: Hypertensive subjects

2.6 Clinical Formulation and Dosing Regimen: The tablets are formulated in five strengths of aliskiren hemifumarate:amlodipine besylate:hydrochlorothiazide, respectively: 150:5:12.5 mg, 300:5:12.5 mg, 300:10:12.5 mg, 300:5:25 mg, and 300:10:25 mg. Table 1 lists proposed final commercial formulations.

Table 1. The composition of drug product

Ingredient	Amount (mg) per tablet					Function	Reference to standards
	150/5/12.5 mg	300/5/12.5 mg	300/10/12.5 mg	300/5/25 mg	300/10/25 mg		
(b) (4)					(b) (4)		
Aliskiren hemifumarate						Active substance	Novartis monograph
Amlodipine besylate						Active substance	Novartis monograph
Hydrochlorothiazide						Active substance	Novartis monograph
Microcrystalline cellulose/ Cellulose microcrystalline						(b) (4)	NF / Ph. Eur.
Crospovidone							NF / Ph. Eur.
Povidone							USP / Ph. Eur.
(b) (4)							Novartis monograph
Colloidal silicon dioxide / Silica, colloidal anhydrous							NF / Ph. Eur.
Magnesium stearate ⁶							NF / Ph. Eur.
(b) (4)							Novartis monograph
							Novartis monograph
							Novartis monograph
							Novartis monograph
							USP/ Ph. Eur.

¹ Corresponds to e.g. 150 mg aliskiren base
² Corresponds to e.g. 300 mg aliskiren base
³ Corresponds to e.g. 5 mg amlodipine base
⁴ Corresponds to e.g. 10 mg amlodipine base

(b) (4)

3 Studies Submitted

No nonclinical studies submitted with this NDA.

3.1 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[®])
- NDA 22,545 for aliskiren and amlodipine (Tekamlo[®]).

4 Pharmacology, Pharmacokinetics/ADME/Toxicokinetics, General Toxicology

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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200045

ORIG-1

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 (b) (4)

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/s/

GOWRA G JAGADEESH
07/28/2010

THOMAS PAPOIAN
07/28/2010

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 200045

Applicant: Novartis

Stamp Date:

Drug Name: (b) (4)

NDA/BLA Type: NDA

2/26/2010

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		No new studies were performed with the combination.
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		No new studies were performed with the combination.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	Not applicable		We did not request any new studies with the combination.

**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?			None
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 April 8, 2010

_____ Reviewing Pharmacologist	_____ Date
Signed: Patricia P. Harlow, Ph.D.	April 8, 2010
_____ Team Leader/Supervisor	_____ Date

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200045

ORIG-1

NOVARTIS
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 (b) (4)

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/s/

GOWRA G JAGADEESH
04/09/2010

PATRICIA P HARLOW
04/09/2010