PRODUCT MONOGRAPH

[Pr]SANDOZ ALISKIREN

aliskiren (as aliskiren fumarate)

Tablets, 150 and 300 mg

Renin inhibitor

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	tablet 150 mg, 300 mg	Colloidal silicon dioxide, crospovidone, hypromellose, iron oxide colorants, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide.

INDICATIONS AND CLINICAL USE

Sandoz Aliskiren (aliskiren) is indicated for the treatment of mild to moderate essential hypertension. It may be used alone or concomitantly with thiazide diuretics or dihydropyridine calcium channel blockers.

Geriatrics (> 65 years of age):
Of the total number of patients receiving aliskiren in clinical studies, 1275 (19 %) were ≥65 years and 231 (3.4%) were ≥75 years. No differences were observed in safety and efficacy of aliskiren in older patients compared to those under age 65.

Pediatrics (<18 years of age):
Safety and efficacy in children and adolescents have not been established. Therefore, Sandoz Aliskiren is not indicated in this patient population.

CONTRAINDICATIONS

Sandoz Aliskiren (aliskiren) is contraindicated in:

- Patients who are hypersensitive to any component of this product (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- Patients with a history of angioedema with aliskiren or other drugs, including agents acting on the renin-angiotensin system (RAS) (i.e. angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB)) (see WARNINGS AND PRECAUTIONS, Immune, Anaphylactic reactions and angioedema).
- Patients with hereditary or idiopathic angioedema.
- Patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR <60 mL/min/1.73 m^2) who are using ARBs or ACE inhibitors (see WARNINGS AND

PRECAUTIONS, Cardiovascular, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal, and DRUG INTERACTIONS, Drug-Drug Interactions, Dual Blockade of the Renin-Angiotensin System (RAS) with ARBs, ACE inhibitors or aliskiren).

- Pregnant women (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women)
- Nursing women (see WARNINGS AND PRECAUTIONS, Special Populations, Nursing Women)
- Pediatric patients less than 2 years of age (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics and TOXICOLOGY, Juvenile animal studies).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, Sandoz Aliskiren should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS: Special Populations: Pregnant Women).

Information to be Provided to the Patient

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the RAS, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible

General

Concomitant use with potent P glycoprotein inhibitors

The concomitant use of aliskiren with potent P glycoprotein inhibitors, such as cyclosporine or itraconazole, is not recommended (see Drug Interactions, Drug-Drug Interactions).

Cardiovascular

Risk of symptomatic hypotension

Symptomatic hypotension was rarely seen (0.1%) in patients with uncomplicated hypertension treated with aliskiren alone. Hypotension was also infrequent during combination therapy with other antihypertensive agents (<1%). Aliskiren-induced hypotension is more likely to occur in patients with an activated RAS, such as volume- or salt-depleted patients (possibly as a result of treatment with a diuretic), or in patients on dialysis or with fluid loss through diarrhea or vomiting, or with the combined use of aliskiren with other agents acting on the RAS, such as angiotensin receptor antagonists (ARBs) or angiotensin converting enzyme (ACE) inhibitors (see DRUG INTERACTIONS, Drug-Drug Interactions). Volume- or salt-depletion should be corrected prior to administration of Sandoz Aliskiren, or the treatment should start under close medical supervision.

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline (see DOSAGE AND ADMINISTRATION). A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized. However, lower doses of Sandoz Aliskiren and/or reduced concomitant diuretic therapy should be considered when symptoms re-occur.

Dual Blockade of the Renin-Angiotensin System (RAS)
Hypotension, syncope, stroke, hyperkalemia, and deterioration of renal function (including acute renal failure) have been reported when co-administrating aliskiren with an ARB or an ACE inhibitor in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR < 60 mL/min/1.73m^2). Therefore, the use of Sandoz Aliskiren in combination with ARBs or ACE inhibitors is contraindicated in these patients (see CONTRAINDICATIONS).

Further, co-administration of aliskiren with other agents blocking the RAS, such as ARBs or ACE inhibitors, is generally not recommended in other patients, since the dual use of agents acting on the RAS is associated with an increased incidence of hypotension, hyperkalemia, and deterioration of renal function compared to monotherapy.

Endocrine and Metabolism
Serum electrolyte changes
As for other agents that act on the RAS, aliskiren may increase serum potassium, creatinine and blood urea nitrogen (BUN). Increases in serum potassium may be exacerbated by the concomitant use of NSAIDs, including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) (see DRUG INTERACTIONS, Drug-Drug Interactions). Patients with diabetes mellitus are at an increased risk of hyperkalemia during aliskiren therapy.

Consistent with standard medical practice, close monitoring of serum electrolytes to detect possible electrolyte (potassium) imbalances is advised at initiation of therapy with Sandoz Aliskiren and followed by periodic monitoring thereafter. Treatment adjustment or discontinuation should be considered if benefit/risk becomes adverse.

Renal
Patients with pre-existing renal impairment or other conditions predisposing to renal dysfunction
As a consequence of inhibiting the RAS, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the RAS, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

Severe renal impairment: Use of aliskiren should be avoided in patients with severe renal impairment (GFR <30 mL/min/1.73m^2). In clinical studies, aliskiren has not been studied in hypertensive patients with severe renal dysfunction (creatinine ≥150 mcmol/L for women and

≥177 mcmol/L for men and/or estimated GFR <30 mL/min/1.73m^2), a history of dialysis, nephrotic syndrome, or renovascular hypertension. Other drugs blocking the RAS can potentially increase serum creatinine and BUN.

Use of Sandoz Aliskiren concomitantly with another agent acting on the RAS, such as an ARB or an ACE inhibitor, is contraindicated in patients with moderate to severe renal impairment (GFR <60 mL/min/1.73 m^2) (see CONTRAINDICATIONS).

Worsening of renal function may occur in patients receiving aliskiren and NSAIDs concomitantly, or in those with pre-existing renal disease, diabetes mellitus or with other conditions pre-disposing to renal dysfunction such as hypovolemia, heart failure or liver disease (see DRUG INTERACTIONS, Non-steroidal anti-inflammatory drugs (NSAIDs)).

Gastrointestinal

In the event of severe and persistent diarrhea, Sandoz Aliskiren therapy should be stopped (see CLINICAL TRIALS ADVERSE DRUG REACTIONS).

Immune

Anaphylactic reactions and angioedema:

Allergic reactions such as anaphylactic reactions and angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have been reported during treatment with aliskiren (see ADVERSE REACTIONS). Anaphylactic reactions and angioedema may occur at any time during treatment and may be life threatening. Special caution is necessary in patients with a predisposition for hypersensitivity. Patients should be informed to report to the physician any signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of face, extremities, eyes, lips or tongue).

If an anaphylactic reaction or angioedema occurs, Sandoz Aliskiren should be discontinued immediately, and the patient should be treated appropriately in accordance with accepted medical care, and carefully observed until complete and sustained resolution of signs and symptoms has occurred. Angioedema associated with laryngeal involvement may be fatal. Where there is involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3-0.5 ml of subcutaneous epinephrine solution 1:1000) should be administered promptly.

In patients who experience angioedema, future administration of Sandoz Aliskiren is contraindicated (see CONTRAINDICATIONS).

Skin

Severe cutaneous adverse reactions, including Stevens Johnson syndrome and toxic epidermal necrolysis, have been reported with aliskiren (see Post-Market Adverse Drugs Reactions).

Special Populations

Pregnant Women: Drugs that act directly on the RAS, such as Sandoz Aliskiren, can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, Sandoz Aliskiren should be discontinued as soon as possible. Sandoz Aliskiren is

contraindicated in pregnant women (see CONTRAINDICATIONS).

The use of drugs that act directly on the RAS during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function. In this setting, oligohydramnios has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to a renin inhibitor during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of Sandoz Aliskiren as soon as possible (see CONTRAINDICATIONS).

There is no clinical experience with the use of aliskiren in pregnant women. Infants with histories of *in utero* exposure to a renin inhibitor should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Aliskiren is not removed by hemodialysis.

Animal data: Reproductive toxicity studies did not reveal any evidence of embryofetal toxicity or teratogenicity at oral doses ≤600 mg/kg/day in rats or ≤100 mg/kg/day in rabbits. Aliskiren was present in the placenta, amniotic fluid and fetuses of pregnant rabbits. In rats, there were no adverse effects on fertility, early embryonic development or reproductive performance of the F1 generation.

Nursing Women: It is not known whether aliskiren is excreted in human milk. Aliskiren was excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother (see CONTRAINDICATIONS).

Pediatrics (< 18years of age): The safety and effectiveness of aliskiren in children and adolescents have not been established. Therefore, Sandoz Aliskiren is not indicated in this patient population. Aliskiren is a *P-glycoprotein (*Pgp) substrate, and there is a potential for aliskiren overexposure in children with an immature Pgp drug transporter system. The age at which the transporter system is mature cannot be determined (see ACTION AND CLINICAL PHARMACOLOGY and TOXICOLOGY). Therefore, Sandoz Aliskiren is contraindicated in children less than 2 years of age-and should not be used in children 2 to less than 6 years of age.

Limited safety data are available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children 6 to 17 years of age (see ACTION AND CLINICAL PHARMACOLOGY). Use of Sandoz Aliskiren in this age group is not indicated.

Geriatrics (> 65 years of age): Of the total number of patients receiving aliskiren in clinical

studies, 1275 (19 %) were ≥65 years and 231 (3.4%) were ≥75 years. No clinically significant differences were observed in safety and efficacy of aliskiren in older patients compared to those under age 65.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Aliskiren has been evaluated for safety in >7,440 patients, including ≥2,580 treated for >6 months, and ≥1,730 for >1 year. The incidence of adverse events (AEs) showed no association with gender, age, body mass index, race, or ethnicity. Treatment with aliskiren ≤300 mg was well tolerated with an overall incidence of AEs similar to placebo. AEs were generally mild and transient in nature and only infrequently required discontinuation of therapy. In placebo-controlled clinical trials, discontinuation of therapy due to a clinical AE occurred in 2.2% of patients treated with aliskiren versus 3.5% of patients given placebo. In long-term active controlled clinical trials, discontinuation of therapy due to an AE occurred in 5.4% of aliskiren-treated patients versus 4.7% of ramipril-treated patients and 7.3% of hydrochlorothiazide-treated patients.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The following AEs occurred in the short-term, placebo controlled clinical trials in patients treated with aliskiren at a rate of ≥ 1% over that of placebo-treated patients (see Table 1).

Table 1. Number (%) of patients with frequent AEs (≥1% over placebo in any group) by preferred term – Placebo controlled, short-term studies (Pooled safety population)

	Placebo N= 781 n (%)	Ali 75mg N=478 n (%)	Ali 150mg N=774 n (%)	Ali 300mg N=768 n (%)	Ali 600mg N=296 n (%)	Ali /HCTZ N=1464 n (%)	HCTZ N=555 n (%)
Any Adverse Event	314 (40.2)	193 (40.4)	290 (37.5)	309 (40.2)	130 (43.9)	591 (40.4)	226 (40.7)
Preferred term:							
Nasopharyngitis	45 (5.8)	34 (7.1)	33 (4.3)	29 (3.8)	5 (1.7)	56 (3.8)	21 (3.8)
Diarrhea	9 (1.2)	6 (1.3)	9 (1.2)	18 (2.3)	28 (9.5)	24 (1.6)	11 (2.0)
Edema peripheral	5 (0.6)	5 (1.0)	6 (0.8)	7 (0.9)	6 (2.0)	13 (0.9)	6 (1.1)
Constipation	5 (0.6)	5 (1.0)	1 (0.1)	5 (0.7)	6 (2.0)	12 (0.8)	3 (0.5)
Influenza	5 (0.6)	1 (0.2)	9 (1.2)	5 (0.7)	2 (0.7)	33 (2.3)	6 (1.1)
Asthenia	1 (0.1)	6 (1.3)	4 (0.5)	4 (0.5)	0 (0.0)	19 (1.3)	6(1.1)
Rash	0 (0.0)	0 (0.0)	2 (0.3)	3 (0.4)	3 (1.0)	7 (0.5)	1 (0.2)
Rhinitis	1 (0.1)	1 (0.2)	3 (0.4)	2 (0.3)	0 (0.0)	7 (0.5)	5 (1.1)

Ali = aliskiren; HCTZ = hydrochlorothiazide

Note that 600 mg is double the highest recommended dose. At 600 mgOD, diarrhea was consistently seen across trials.

The following AEs of special interest occurred in two long-term double-blind studies (Table 2).

Table 2 Number (%) of patients with adverse events of special interest during the double-blind active controlled periods of two long-term studies.

	Aliskiren regimen[#]	HCTZ regimen[#]	Aliskiren Regimen[&]	Ramipril Regimen[&]
	N=566	N=558	N=419	N=422
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any Adverse Event	369 (65.2)	343 (61.5)	257 (61.3)	255 (60.4)
Headache	38 (6.7)	53 (9.5)	47 (11.2)	35 (8.3)
Nasopharyngitis	25 (4.4)	30 (5.4)	25 (6.0)	26 (6.2)
Bronchitis	16 (2.8)	16 (2.9)	13 (3.1)	4 (0.9)
Cough	16 (2.8)	22 (3.9)	17 (4.1)	40 (9.5)
Back pain	27 (4.8)	25 (4.5)	15 (3.6)	13 (3.1)
Diarrhoea	16 (2.8)	16 (2.9)	16 (3.8)	7 (1.7)
Edema peripheral	30 (5.3)	31 (5.6)	16 (3.8)	13 (3.1)

[#] In this 12-month study, the treatment regimen was aliskiren or hydrochlorothiazide (HCTZ) with forced titration and optional add-on of amlodipine.

[&] In this 6-month study, the treatment regimen was aliskiren or ramipril with optional titration and optional add-on of HCTZ.

Aliskiren use in clinical trials was associated with a slightly increased incidence of dry cough, but less so than with ACE inhibitor use. In controlled, short-term clinical trials, the incidence of cough was similar in patients treated with placebo (0.6%) and aliskiren (1.1%).

In a short-term active controlled trial, peripheral edema occurred in 3.4% of patients treated with amlodipine 5 mg, 11.2% of patients treated with amlodipine 10 mg, and 2.1% of patients treated with the combination of amlodipine 5 mg and aliskiren 150 mg. In other controlled short-term clinical trials, the incidence of edema was similar in placebo (0.6%) and aliskiren-treated patients (0.8-1.0%) except at a dose of 600 mg (2.0%).

Uncommon cases of hypersensitivity were reported in clinical trials**.**

Cases of dizziness (common), hypotension (uncommon), hyperkalemia (common), renal impairment (uncommon), and renal failure (rare), were reported in clinical trials with aliskiren.

Other AEs that occurred in short-term, controlled clinical trials in >0.5% of patients treated with aliskiren are listed below. It cannot be determined whether these events were causally related to aliskiren.

Digestive: abdominal pain, dyspepsia, nausea

Musculoskeletal: arthralgia, muscle spasms, neck pain, pain in extremity, shoulder pain

Neurologic and Psychiatric: insomnia, vertigo

Respiratory: bronchitis, epistaxis, pharyngolaryngeal pain

Urinary: urinary tract infection

Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% in placebo patients. In women and the elderly (age ≥ 65 years), increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroups at 150 mg comparable to those seen at 300 mg for men or younger patients (all rates about 2.0%-2.3%). Other GI symptoms included abdominal pain, dyspepsia, and gastroesophageal reflux, although increased rates for abdominal pain and dyspepsia were distinguished from placebo only at 600 mg daily. Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation.

Rare cases of colonic cancer (0.05%) were reported in clinical trials with aliskiren. The incidence is consistent with the expected prevalence rates of 0.1-0.3% in this patient population.

Angioedema
Angioedema, including edema of the larynx, has occurred during treatment with aliskiren (see WARNINGS AND PRECAUTIONS, Immune, Angioedema). In short-term controlled clinical trials, angioedema occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or HCTZ.

Abnormal Hematologic and Clinical Chemistry Findings
In short-term, controlled clinical trials, clinically relevant changes in standard laboratory parameters were rarely associated with the administration of aliskiren. In multiple dose studies in hypertensive patients, aliskiren had no clinically important effects on total cholesterol, HDL, fasting triglycerides, fasting glucose, or uric acid.

In a 1-year open label safety study of the aliskiren/valsartan combination, elevations of serum triglycerides >3.4 mmol/L were observed in 7% of patients who had triglyceride values of ≤3.4 mmol/L prior to treatment. It could not be determined whether this would have been different from placebo, as the study had no control arm. The use of aliskiren with another RAS blocking agent, such as the ARB valsartan, is generally not recommended (see WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS)).

No special monitoring is necessary in patients receiving Sandoz Aliskiren.

Blood Urea Nitrogen, Creatinine
Minor increases in blood urea nitrogen (BUN) were observed in <7% of patients with essential hypertension treated with aliskiren alone vs. 6% on placebo. Aliskiren alone increased creatinine slightly (by ~1mcmol/L), but this effect increased (to 2.4mcmol/L) with co-administration of HCTZ.

In an active controlled, double-blind 1-year clinical trial, 13.4% of aliskiren-treated patients compared to 15.8% of HCTZ-treated patients experienced >50% increases in BUN. In another

active controlled, double-blind trial, >50% increases in BUN occurred in 15.5% of aliskiren-treated patients and 16.0% of ramipril-treated patients. Increases in serum creatinine (>50%) were less frequent, occurring in 2.7% of aliskiren-treated patients in the 1-year study compared to 1.1% of patients treated with HCTZ, and 1.7% of aliskiren-treated patients and 1.4% of ramipril-treated patients in the other trial.

Hemoglobin and Hematocrit
Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.8 g/L and 0.16 volume percent, respectively) were observed with aliskiren monotherapy. These decreases led to slight increases in the rate of anemia with aliskiren: 0.1% for any aliskiren use, 0.3% for aliskiren 600 mg OD, vs. 0% for placebo. No patients discontinued therapy due to anemia. This effect is also seen with other agents acting on the RAS, such as ACE inhibitors and ARBs, and may be mediated by reduction of angiotensin II which stimulates erythropoietin production via the AT_1 receptor.

Serum Potassium
In short-term placebo controlled clinical trials, increases in serum potassium were minor and infrequent in patients with essential hypertension treated with aliskiren alone (1.2% of patients had serum potassium levels > 5.5 mmol/L compared to 1.1% with placebo). In combination with the ARB valsartan, transient increases in potassium (>5.5 mmol/L) not reported as AEs occurred in 3.4% of patients compared to 2.1% for placebo. Significant potassium elevations (>6.0 mmol/L) occurred in 0.3% and 1.0% of patients in the aliskiren/valsartan and placebo groups, respectively. The use of aliskiren with another RAS blocking agent, such as the ARB valsartan, is generally not recommended (see WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS)).

However, when used in combination with an ACE inhibitor in a diabetic population, increases in serum potassium were more frequent (5.5%). The use of aliskiren with an ACE inhibitor is contraindicated in patients with diabetes (see CONTRAINDICATIONS).

Monitoring of electrolytes and renal function is indicated when using Sandoz Aliskiren (see WARNINGS AND PRECAUTIONS).

In an active controlled, double-blind, 1-year clinical trial in patients with essential hypertension, increases in serum potassium (> 5.5 mmol/L) occurred in 36/550 (6.5%) of patients on aliskiren compared to 20/535 (3.7%) on HCTZ and decreases in serum potassium (< 3.5 mmol/L) occurred in 5/550 (0.9%) patients on aliskiren compared to 96/535 (17.9%) on HCTZ. In a 1 year trial of aliskiren and valsartan alone and in combination with HCTZ, elevated serum potassium (>5.5 mmol/L) occurred in 4.1% and 2.0% of patients, respectively. In another active controlled, double-blind trial, increases in serum potassium (> 5.5 mmol/L) occurred in 8/412 (1.9%) of aliskiren-treated patients compared to 4/417 (1.0%) on ramipril and decreases in potassium (< 3.5 mmol/L) occurred in 22/412 (5.3%) on aliskiren compared to 19/417 (4.6%) on ramipril.

Creatine Kinase
In the short-term, placebo-controlled clinical trials, increases in creatine kinase (CK) of >300% were found in 22/2233 (~1%) patients on aliskiren monotherapy vs. in 4/746 (0.5%) of patients on placebo. The effect, suggesting to be dose-related, seemed more common in men, and at ages <65 years. No cases were associated with renal dysfunction.

In an active controlled, double-blind, 1-year clinical trial, 21/543 patients (3.9%) on an aliskiren regimen and 9/535 patients (1.7%) on an HCTZ regimen had > 300% increases in CK. This increase was seen more often in men than in women. In another long term study, almost no elevations in CKs were seen in patients (0.5%) on an aliskiren regimen vs. in 1.3% of the patients on a ramipril regimen

Post-Market Adverse Drug Reactions
Other adverse reactions reported in post-marketing use include: peripheral edema, vomiting, increase in blood creatinine, hepatic enzyme increased, renal impairment including rare combined cases of renal failure and acute renal failure, hyponatraemia, and liver disorder (isolated cases of liver disorder with clinical symptoms and laboratory evidence of more marked hepatic dysfunction). Cases of hypersensitivity have been reported, many of them being serious.

Cases of anaphylactic reactions and urticaria in patients treated with aliskiren have been reported.

Angioedema (involving swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, tongue and/or pharynx) have been reported in patients treated with aliskiren (cases of fatal outcome have been reported, however a causal relationship has not been clearly established).

Severe cutaneous adverse reactions, including Stevens Johnson syndrome and toxic epidermal necrolysis, have been reported (see WARNINGS AND PRECAUTIONS, Skin). Cases of urticaria, pruritus and erythema have also been reported.

DRUG INTERACTIONS

Overview
Aliskiren has low potential for drug interactions. Aliskiren is mainly excreted as unchanged drug within the feces and is minimally metabolized in man. *In-vitro* studies have shown that aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and CYP3A) or induce CYP3A4. As CYP3A4 is the major enzyme responsible for the metabolism of aliskiren, complete inhibition may be expected to result in increased plasma levels of aliskiren (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). *In vitro* studies indicate that MDR1 (Pgp) is the major efflux transporter involved in absorption and disposition of aliskiren. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter.

Drug-Drug Interactions

Table 3 - Established or Potential Drug-Drug Interactions for Aliskiren

Proper Name	Ref.	Effect	Clinical comment
Furosemide	CT	Oral co-administration of aliskiren and furosemide had no effect on the pharmacokinetics of aliskiren but reduced exposure to furosemide. When aliskiren (300 mg/day) was co-administered with oral furosemide (20 mg/day) in healthy subjects, the AUC and Cmax of furosemide were reduced by 28% and 49%, respectively.	In patients treated with both aliskiren and oral furosemide, it is recommended that the effects of furosemide be monitored when initiating or adjusting the dose of furosemide or aliskiren.
Non-steroidal anti-inflammatory drugs (NSAIDs)	CT	In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs with agents acting on the RAS, such as aliskiren, may result in deterioration of renal function, including possible acute renal failure, which is usually reversible. Concomitant administration of NSAIDs may attenuate the antihypertensive effect of agents acting on the RAS, including aliskiren.	Monitor renal function when initiating or modifying treatment in patients on aliskiren who are taking NSAIDs concomitantly.
Pgp substrates or weak inhibitors	CT	No relevant interactions with atenolol, digoxin, amlodipine, and cimetidine have been observed. When administered with atorvastatin (80 mg), steady-state aliskiren (300 mg) AUC and Cmax increased by 50%.	No dose adjustment for aliskiren is necessary.
Moderate Pgp inhibitors	CT	Co-administration of ketoconazole (200 mg) with aliskiren (300 mg) resulted in an 80% increase in plasma levels of aliskiren (AUC and Cmax). Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. In healthy volunteers, co-administration	The change in plasma levels of aliskiren in the presence of ketoconazole or verapamil is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren at doses ≤600 mg, or twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. As a result

Proper Name	Ref.	Effect	Clinical comment
		of a single oral dose of 300 mg aliskiren with 240 mg verapamil increased AUC and Cmax of aliskiren by ~2-fold.	no dose adjustment for aliskiren is necessary.
Potent Pgp inhibitors	CT	A single dose drug interaction study in healthy subjects has shown that cyclosporine A (200 and 600 mg) increases Cmax of aliskiren 75 mg by approximately 2.5-fold and the AUC by approximately 5-fold. In a randomized study, itraconazole (100 mg bid) was administered for 5 days in healthy subjects and a single dose of aliskiren (150 mg) was administered on Day 3. Itraconazole was shown to increase the AUC0-∞ and Cmax of aliskiren by 6.5-fold and 5.8-fold, respectively.	The concomitant use of these potent PgP inhibitors, such as cyclosporine A and itraconazole, with aliskiren is not recommended (see Warnings and Precautions, Concomitant use of potent P glycoprotein inhibitors).
Potassium and potassium sparing diuretics	CT	Based on experience with the use of other drugs that affect the RAS, concomitant use of aliskiren with the following medicines may lead to increases in serum potassium: potassium-sparing diuretics, potassium supplements, or salt substitutes containing potassium.	If co-medication is considered necessary, caution is advisable. Consistent with standard medical practice, close monitoring of serum electrolytes to detect possible electrolyte (potassium) imbalances is advised at initiation of therapy with Sandoz Aliskiren and periodic monitoring thereafter. Treatment adjustment or discontinuation should be considered if benefit/risk becomes adverse.
Dual Blockade of the renin-angiotensin-system (RAS) with ARBs, ACE inhibitors or aliskiren-containing drugs	CT	The concomitant use of aliskiren with other agents acting on the RAS such as ACE inhibitors or ARBs is associated with an increased risk of hypotension, hyperkalemia, and deterioration of renal function (including acute renal failure) compared to monotherapy. Therefore, dual RAS blockade is generally not recommended.	See WARNINGS and PRECAUTIONS, Cardiovascular, Dual Blockade of the Renin-Angiotensin System (RAS).

CT = Clinical Trial

Effects of other drugs on aliskiren

Co-administration of aliskiren with amlodipine, digoxin, furosemide, hydrochlorothiazide, metformin, ramipril and valsartan did not result in clinically significant changes in aliskiren exposure.

Effects of aliskiren on other drugs
Co-administration of aliskiren did not affect the steady-state pharmacokinetics of amlodipine, digoxin, hydrochlorothiazide, metformin, ramipril, ramiprilat or valsartan.

Drug-Food Interactions
When taken with food, mean AUC and C_{max} of aliskiren were decreased by 71% and 85%, respectively (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption). There was a delay in median t_{max} by 1 h.

Drug-Herb Interactions
The interaction of aliskiren with herbal medications or supplements has not been studied.

Drug-Lifestyle Interactions
There are no physical restrictions for patients who receive aliskiren.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
The usual recommended starting dose of Sandoz Aliskiren is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 300 mg. The antihypertensive effect is substantially present (85%-90%) within 2 weeks after initiating therapy with 150 mg per day with the maximum effect reached after 4 weeks.

Sandoz Aliskiren may be administered alone or concomitantly with thiazide diuretics or dihydropyridine calcium channel blockers. Co-administration of 150 mg aliskiren and 5 mg amlodipine has been shown to be safe and effective; higher doses and other calcium channel blockers have not been tested.

The use of Sandoz Aliskiren in combination with ACE inhibitors or ARBs is contraindicated in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR <60 mL/min/1.73m^2) (see CONTRAINDICATIONS). Combination use in other patients is generally not recommended (see WARNINGS AND PRECAUTIONS, Cardiovascular, Dual Blockade of the Renin-Angiotensin System (RAS)).

Sandoz Aliskiren may be administered with or without food, although a high fat meal decreases drug absorption significantly (see DRUG INTERACTIONS, Drug-Food Interactions and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption). Patients should establish a convenient daily schedule of drug intake and maintain a steady temporal relationship with food intake.

No initial dosage adjustment is required for elderly patients, for patients with mild to moderate renal impairment, or for patients with mild to severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics (≥65 years), Renal Insufficiency and Hepatic Insufficiency). Sandoz Aliskiren should be avoided in patients with severe renal impairment (GFR <30 mL/min/1.73m^2) (see WARNINGS AND

PRECAUTIONS, Renal and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Missed Dose

If one or several doses of Sandoz Aliskiren are missed, patients should be advised to take the dose as soon as they remember. If it is almost time for the next dose, patients should skip the missed dose and go back to their regular schedule. Patients should not increase the dose of Sandoz Aliskiren to compensate for the missed dose(s).

OVERDOSAGE

Limited data are available related to overdosage in humans. The most likely manifestation of overdosage would be hypotension. If symptomatic hypotension should occur, supportive treatment should be initiated.

In a study conducted in patients with end stage renal disease receiving hemodialysis, dialysis clearance of aliskiren was low (<2% of oral clearance). Therefore dialysis is not adequate to treat aliskiren over-exposure.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Aliskiren has a novel mechanism of action from that of ACE inhibitors, ARBs, aldosterone blockers, beta blockers, alpha blockers, diuretics and calcium channel blockers.

Aliskiren is an orally active, nonpeptide, highly specific and potent direct renin inhibitor. Aliskiren targets the RAS at its point of activation by binding to the renin enzyme. Renin is secreted by the kidney in response to decreases in blood volume and renal perfusion. This response initiates a cycle that includes the RAS and a homeostatic feedback loop. Renin cleaves angiotensinogen to form the inactive decapeptide angiotensin I (Ang I). Ang I is converted to the active octapeptide angiotensin II (Ang II) by ACE and non-ACE pathways. Ang II is a powerful vasoconstrictor and leads to the release of catecholamines from the adrenal medulla and prejunctional nerve endings. It also promotes aldosterone secretion and sodium reabsorption. Together, these effects increase blood pressure. Chronic increases in Ang II result in the expression of markers and mediators of inflammation and fibrosis that are associated with end organ damage.

Aliskiren is a direct renin inhibitor that inhibits the production of Ang I, Ang II by acting at the point of activation of the renin cycle, inhibiting the conversion of angiotensinogen to Ang I and Ang II. This action suppresses the entire system, resulting in a reduction in plasma renin activity (PRA), Ang I, Ang II and aldosterone.

All agents that inhibit the RAS suppress the negative feedback loop and lead to a compensatory rise in plasma renin concentration. When this rise occurs, it is accompanied by increased levels of PRA. However, treatment with aliskiren neutralizes the feedback loop effects. As a result, despite an elevation of the plasma renin concentration, PRA, Ang I and Ang II are all reduced, whether aliskiren is used as monotherapy or in combination with other antihypertensive agents.

Pharmacodynamics

Treatment with aliskiren decreases PRA and increases plasma renin concentration (PRC) in hypertensive patients. In clinical trials, PRA reductions ranged from approximately 50%-80% and occurred with aliskiren monotherapy or when aliskiren was combined with other antihypertensive drugs. There was no rebound increase in PRA or blood pressure either acutely or over a 4-week period after aliskiren discontinuation. There was a weak correlation between the magnitudes of PRC elevation and blood pressure reduction.

Antihypertensive effect

In hypertensive patients, once-daily administration of aliskiren at doses of 150 mg and 300 mg provided dose-dependent reductions in both systolic (SBP) and diastolic blood pressure (DBP) that were maintained over the entire 24-hour dose interval (maintaining benefit in the early morning) with a mean trough to peak ratio for diastolic response of ≤98% for the 300 mg dose.

Cardiac electrophysiology

The potential of aliskiren to affect cardiac conduction and repolarisation was studied in a randomized, double-blind, placebo and active-controlled (moxifloxacin), repeat dosing, parallel group study, conducted for 7 days in 283 subjects. Twelve lead Holter ECGs were monitored over the entire dosing interval. No effect of aliskiren on the QT interval was seen.

Pharmacokinetics

Absorption: Following oral administration, peak plasma concentrations of aliskiren are reached within 1-3 hours. Aliskiren is poorly absorbed, its approximate bioavailability is 2.6%. *In vitro* studies indicate that MDR1 (Pgp) is the major efflux transporter involved in absorption and disposition of aliskiren. Peak plasma concentrations (C_{max}) and exposure (AUC) are expected to increase 2.6-fold and 2.4-fold when doubling the dose of aliskiren. When taken with food with a high fat content, mean AUC and C_{max} of aliskiren are decreased by 71% and 85%, respectively, and t_{max} is delayed by 1 h. Steady state plasma concentrations are reached within 5-7 days after starting once daily administration, and steady state levels are approximately 2-fold greater than following a single dose.

Distribution: Aliskiren is evenly distributed systemically after oral administration. Following intravenous administration, mean volume of distribution at steady state is approximately 135 L indicating that aliskiren distributes extensively into extravascular space. Aliskiren plasma protein binding is moderate (47%-51%) and independent of concentration.

Metabolism: Aliskiren is predominantly eliminated via the feces (91% of an oral dose), mainly as unchanged drug (86% of an oral dose as adjusted for extraction efficiency). CYP3A4 of the cytochrome P450 system is the major enzyme responsible for the metabolism of aliskiren (see DRUG INTERACTIONS, Moderate Pgp inhibitors). Only 1.4% of the total dose is metabolized

by CYP3A4. Metabolism accounted for ≤20% of the absorbed dose in the systemic circulation. The amount of absorbed dose metabolized is unknown.

Excretion: Following oral administration, approximately 0.6% of the dose is recovered in urine. However, a quarter of the absorbed fraction in the systemic circulation is excreted unchanged in the urine. Following intravenous administration, the mean plasma clearance is approximately 9 L/h. The mean elimination half-life is about 40 hours (range 34-41 hours).

Special Populations and Conditions

Pediatrics (<18 years of age): In a pharmacokinetic study of aliskiren treatment in 39 pediatric hypertensive patients aged 6 to 17 years, given daily doses of 2 mg/kg or 6 mg/kg aliskiren, administered as mini-tablets (3.125 mg/mini-tablet), pharmacokinetic parameters were similar to those in adults. The results of this study did not suggest that age, body weight or gender have any significant effect on aliskiren systemic exposure.

Results from *in vitro* MDR1 (Pgp) human tissue study suggested an age and tissue dependent pattern of MDR1 maturation. A high inter-individual variability of mRNA expression levels was observed (up to 600-fold). Hepatic MDR1 mRNA expression was statistically significantly lower in samples from fetuses, neonates, and infants up to 23 months.

There is a potential for aliskiren overexposure in children with low MDR1 mRNA expression (see CONTRAINDICATIONS and TOXICOLOGY).

Geriatrics (≥65 years of age): The pharmacokinetics of aliskiren were studied in the elderly (≥ 65 years). The exposure (measured by AUC) and C_{max} of aliskiren is increased in elderly by 57% and 28%, respectively. Adjustment of the starting dose is not required in these patients (see DOSAGE AND ADMINISTRATION).

Gender: Males have slightly lower AUC (24%) than females. This difference is not clinically significant.

Race: The pharmacokinetics of aliskiren do not differ significantly among different races and ethnicities (Blacks, Caucasians, Hispanics, and Japanese).

Diabetes: The pharmacokinetics of aliskiren are similar between type 2 diabetics and healthy volunteers.

Hepatic Insufficiency: The pharmacokinetics of aliskiren are not significantly affected in patients with mild-to-severe liver disease. Consequently, adjustment of the starting dose is not required in these patients (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency: The pharmacokinetics of aliskiren have been evaluated in patients with varying degrees of renal insufficiency. Relative AUC and C_{max} of aliskiren in subjects with renal impairment ranged between 0.8- to 2-fold those observed in healthy subjects following single dose administration and at steady state. These observed changes, however, did not correlate with the severity of renal impairment. Consequently, adjustment of the starting dose is not

required in patients with mild to moderate renal impairment (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION). Use of Sandoz Aliskiren should be avoided in patients with severe renal impairment (GFR < 30 mL/min/1.73m^2).

STORAGE AND STABILITY

Do not store >30ºC. Protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Sandoz Aliskiren is available for oral administration as film-coated tablets containing 150 mg, and 300 mg of aliskiren and the following inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, iron oxide colorants, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide.

Sandoz Aliskiren is supplied as a light-pink, biconvex round tablet containing 150 mg of aliskiren, and as a light-red biconvex ovaloid tablet containing 300 mg of aliskiren. Tablets are imprinted with NVR on one side and IL, IU, on the other side of the 150 mg and 300 mg tablets, respectively.

All strengths are packaged in PA/AL/PVC blister packages (4 strips of 7 tablets) or PCTFE/PVC blister packages (2 strips of 14 tablets).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

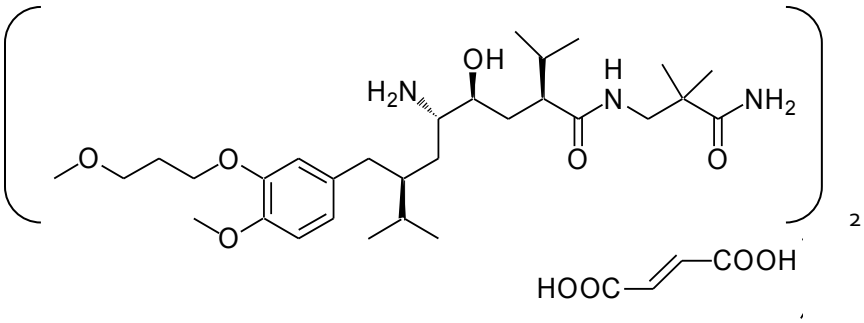
Common name: Aliskiren fumarate

Chemical name Bis (2S, 4S, 5S, 7S) – 5 amino-*N*-(3-amino-2,2-dimethyl-3-oxopropyl)-4-hydroxy-7-[4-methoxy-3-(3-methoxypropoxy) benzyl]-8-methyl-2-(1-methylethyl)nonanamide] (2*E*)-but-2-enedionate

Molecular formula: $(C_{30}H_{53}N_3O_6)_2 \bullet C_4H_4O_4$

Molecular mass: 1219.6

Structural formula:



Physicochemical properties: Aliskiren is a white to slightly yellowish crystalline powder. It is soluble in phosphate buffer, n-Octanol, and highly soluble in water.

CLINICAL TRIALS

Study demographics and trial design: Aliskiren Monotherapy

The antihypertensive effects of aliskiren have been demonstrated in 5 randomized, double-blind, placebo-controlled 8-week clinical trials in patients with mild-to-moderate hypertension. The placebo response and placebo-subtracted changes from baseline in seated trough cuff blood pressure (BP) are shown in Table 4.

Table 4: Reductions in Seated Trough Cuff Blood Pressure in the Placebo-Controlled Studies

Study	Placebo	Aliskiren daily dose, mg			
		75	150	300	600
	Mean change	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted
1201	2.9/3.3	5.7/4[a]	5.9/4.5[a]	11.2/7.5[a]	--
2201	5.3/6.3	--	6.1/2.9[a]	10.5/5.4[a]	10.4/5.2[a]
2203	10/8.6	2.2/1.7	2.1/1.7	5.1/3.7[a]	--
2204	7.5/6.9	1.9/1.8	4.8/2 [a]	8.3/3.3[a]	--
2308	3.8/4.9	--	9.3/5.4[a]	10.9/6.2[a]	12.1/7.6[a]

[a] $p<0.05$ vs. placebo by ANCOVA with Dunnett's procedure for multiple comparisons.

The studies included approximately 2316 patients given doses of 75-600 mg of aliskiren and 781 patients given placebo. As shown in Table 3, there is some increase in response with administered dose in all studies, with reasonable effects seen at 150-300 mg, and no clear further increase at 600 mg. A substantial proportion (85%-90%) of the BP lowering effect was observed within 2 weeks of treatment. Studies with ambulatory BP monitoring showed reasonable control throughout the interdosing interval; the ratios of mean daytime to mean nighttime ambulatory BP ranged from 0.6 to 0.9.

Patients in the placebo-controlled trials continued open-label aliskiren for ≤1 year. A persistent BP lowering effect was demonstrated by a randomized withdrawal study (patients randomized to continued drug or placebo), which showed a statistically significant difference between patients kept on aliskiren and those randomized to placebo. With cessation of treatment, BP gradually returned toward baseline levels over a period of several weeks. There was no evidence of rebound hypertension after abrupt cessation of therapy.

Aliskiren lowered BP in all demographic subgroups, although Black patients tended to have smaller reductions than Caucasians and Asians, as has been seen with ACE inhibitors and ARBs.

Aliskiren in Combination with Other Antihypertensives

Diuretics

Aliskiren 75, 150, and 300 mg and hydrochlorothiazide (HCTZ) 6.25, 12.5, and 25 mg were studied alone and in combination in an 8-week, 2,776-patient, randomized, double-blind, placebo-controlled, parallel-group, 15-arm factorial study. BP reductions with the combinations were greater than the reductions with the monotherapies as shown in Table 5.

Table 5: Placebo-Subtracted Reductions in Seated Trough Cuff Blood Pressure in Combination with Hydrochlorothiazide

		Hydrochlorothiazide, mg			
	Placebo	0	6.25	12.5	25
Aliskiren, mg	mean change	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted
0	7.5/6.9	--	3.5 [p] /2.1 [p]	6.4 [p] /3.2 [p]	6.8 [p] /2.4 [p]
75	--	1.9 /1.8 [p]	6.8 [pha] /3.8 [pha]	8.2 [pa] /4.2 [pa]	9.8 [pha] /4.5 [pha]
150	--	4.8 [p] /2 [p]	7.8 [pha] /3.4 [p]	10.1 [pha] /5 [pha]	12 [pha] /5.7 [pha]
300	--	8.3 [p] /3.3 [p]	--	12.3 [pha] /7 [pha]	13.7 [pha] /7.3 [pha]

p = statistically significant vs. placebo ($p < 0.05$)
h = statistically significant vs. component monotherapy HCTZ dose ($p < 0.05$)
a = statistically significant vs. component monotherapy aliskiren dose ($p < 0.05$)

Amlodipine
Aliskiren provided additional BP reduction when co-administered with amlodipine 5 mg in 1 study, but the combination was not statistically significantly better than amlodipine 10 mg (see Table 6).

Table 6: Reductions in Seated Trough Cuff Blood Pressure in Combination with amlodipine

	Amlodipine 5 mg N=177	Amlodipine 10 mg N=177	Aliskiren 150 mg + Amlodipine 5 mg N=187
SBP/DBP mm Hg	5.0/4.8	9.6/8.0	11[a]/8.5[a]

[a]$p < 0.0001$ vs Amlodipine 5 mg
SBP: Systolic blood pressure; DBP: Diastolic blood pressure

DETAILED PHARMACOLOGY

Effects of aliskiren in double transgenic rats (dTGR) expressing human renin and angiotensinogen

Double transgenic rats exhibit fulminant hypertension and end-organ damage as a result of an over-stimulated RAS. Because these animals express human genes for renin and angiotensinogen, they are well suited to test human renin inhibitors for organ protective effects. Accordingly, aliskiren was tested in dTGR for its ability to inhibit renal and cardiac damage that ensues in this model.

Antihypertensive effects of aliskiren in dTGR

The dose-response profile for the antihypertensive effects of aliskiren was defined in dTGR. Two methods of continuous, direct BP monitoring in conscious, unrestrained animals were utilized: (i) radiotelemetry, and (ii) chronic catheterization of the femoral artery and vein. In the latter model, the femoral vein was also chronically catheterized for infusion of test agents and withdrawal of blood. Aliskiren induces a dose-dependent reduction in mean arterial pressure (MAP) following single IV and PO doses administration. Responses to aliskiren under various dosing regimen were compared to those for the ARB valsartan and/or the ACE inhibitor enalapril(at) in dTGRs. Aliskiren administered IV was approximately equipotent with IV

valsartan and enalapril, whereas with po administration, aliskiren was less potent due to the lower oral bioavailability of aliskiren compared to the two other agents.

Effect on albuminuria
The 24-hour mean urinary albumin excretion (UAE) before randomization averaged 2.0 ± 0.2 mg/day in all dTGR groups. This level of UAE reflects a significant elevation ($p<0.05$) compared to historical values seen in normal Sprague-Dawley control rats (0.2 ± 0.05 mg/day). At 7 weeks of age, UAE in vehicle-treated dTGR was increased to 36.4 ± 4.6 mg/day. In contrast, in the 0.3 and 3 mg/kg/day aliskiren treated groups, albuminuria decreased at 9 weeks ($p<0.05$) to 1.6 ± 0.6 mg/day or 0.4 ± 0.2 mg/day, respectively.

Effect on left ventricular hypertrophy
In the dTGR model, cardiac hypertrophy and left ventricular wall thickness were significantly ($p< 0.05$) reduced in the aliskiren-treated groups (0.3 and 3mg/kg/day) and in the valsartan 10mg/kg/day group compared to the low dose valsartan group (1mg/kg/day). Tissue Doppler measurements showed improved early and late diastolic inflow quotient (Ea/Aa) in both aliskiren groups and in the 10 mg/kg/day valsartan group, demonstrating improved diastolic filling.

Effect on renal fibrosis
The effect of aliskiren on the renal fibrosis observed in dTGR was assessed by immunostaining for collagen IV in kidney sections. Semi-quantitative evaluation showed that both aliskiren doses (0.3 and 3mg/kg/day) and valsartan 10 mg/kg/day suppressed collagen IV immunostaining of Bowman's capsule and tubular basement membranes relative to that observed in the valsartan 1 mg/kg/day group.

Renal inflammation, evidenced by the infiltration of macrophages and T-cells, is typically present in the kidneys of dTGR. Aliskiren 0.3 and 3mg/kg/day and valsartan 10mg/kg/d completely prevented the renal accumulation of these inflammatory markers, presumably by inhibiting the formation of Ang II at the local (tissue) level.

In a separate study, 4 weeks old dTGR were treated with aliskiren (3 mg/kg/day, subcutaneous osmotic mini-pumps) or losartan (10 mg/kg/day in the diet) for 3 weeks. During the progression of hypertension, untreated dTGR exhibited increases in serum and renal inflammatory markers: serum C-reactive protein, renal TNF-α, and various components of complement, including the membrane attack complex C5b-9. Aliskiren as well as losartan suppressed the expression of these markers of inflammation, as assessed by immunostaining.

TOXICOLOGY

Acute Toxicity
No adverse findings were noted at doses of 1000 or 2000 mg/kg. It was concluded that the acute oral toxicity (LD_{50}) of aliskiren in rats is >2000 mg/kg.

Sub-chronic and Chronic Toxicity
Exposure to aliskiren at the no-observed-adverse-effect levels (NOAEL**) in the repeat dose toxicity studies** was generally similar to or less than that in humans at 300 mg. The doses in rodents were limited by local respiratory irritation following aspiration of the dosing solutions. In marmosets, altered kidney function and early deaths as a result of marked hypotension were the main dose-limiting effects during the chronic toxicity studies but these were attributable to the expected pharmacology of aliskiren. These limitations prevented the animal toxicology studies from obtaining high multiples of human exposure. Nevertheless, no target organ toxicities relevant for human use were observed during the chronic toxicity studies at doses ≤600 mg/kg/day in rats or ≤50 mg/kg/day in marmosets which correspond to systemic exposures based on mean AUC of approximately 3- and 46-fold higher, respectively than those observed in humans at the dose of 300 mg.

Carcinogenesis
Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic mouse study. No carcinogenic potential was detected. Inflammatory and proliferative changes were observed in the lower gastro-intestinal tract at doses of 750 or 1500 mg/kg/day in both species. These findings were attributed to the known irritation potential of aliskiren. One colonic adenoma and one cecal adenocarcinoma also recorded in rats at the dose of 1500 mg/kg/day were not statistically significant. Safety margins based on local, intra-intestinal exposure obtained in humans at the dose of 300 mg during a study in healthy volunteers were 9- to 11-fold based on fecal concentrations, and 6-fold based on rectal mucosa concentrations compared to exposures at a dose of 250 mg/kg/day in the rat carcinogenicity study. On a systemic exposure ($AUC_{0\text{-}24hr}$) basis, 1500 mg/kg/day in the rat study resulted in plasma levels 4- to 5-fold higher than those following the maximum recommended human dose of 300 mg OD.

Mutagenesis
Aliskiren fumarate was devoid of any mutagenic potential in the *in vitro* (bacterial and mammalian cells) and *in vivo* (rats) mutagenicity studies.

Reproduction and Teratology
Reproductive toxicity studies did not reveal any evidence of embryofetal toxicity or teratogenicity at doses ≤600 mg/kg/day in rats or ≤100 mg/kg/day in rabbits. These doses result in plasma levels 3- and 5-fold higher than those following the maximum recommended dose in humans (300 mg).

Fertility, pre-natal development and post-natal development were unaffected in rats at doses ≤250 mg/kg/day, resulting in plasma levels comparable to those following the maximum recommended dose in humans.

Juvenile animal studies
Toxicity studies in rats indicated that excessive aliskiren exposure (>400 fold higher in 8-day-old rats compared with adult rats) and toxicity were caused by low intestinal MDR1 mRNA expression in juvenile rats. This suggests that in pediatric patients with low MDR1 expression, there is a potential for aliskiren overexposure and associated toxicity (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Pediatric).

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PART III: CONSUMER INFORMATION

[Pr]Sandoz Aliskiren
aliskiren (as aliskiren fumarate), Tablets

Read this carefully before you start taking Sandoz Aliskiren and each time you get a refill. This leaflet is a summary and will not tell you everything about Sandoz Aliskiren. Talk to your doctor, nurse, or pharmacist about your medical condition and treatment and ask if there is any new information about Sandoz Aliskiren.

ABOUT THIS MEDICATION

What the medication is used for:
Sandoz Aliskiren is a medication that helps to control high blood pressure (hypertension).

High blood pressure increases the workload of the heart and arteries. If this condition continues for a long time, damage to the blood vessels of the brain, heart, and kidneys can occur, and may eventually result in a stroke, heart failure or kidney failure. High blood pressure also increases the risk of heart attacks. Reducing your blood pressure decreases your risk of developing these illnesses.

This medicine does not cure your disease. It helps to control it. Therefore, it is important to continue taking Sandoz Aliskiren regularly even if you feel fine.

What it does:
Sandoz Aliskiren belongs to a new class of medicines called "direct renin inhibitors". They prevent the body from producing angiotensin II, a substance that causes blood vessels to tighten, thus increasing blood pressure. As a result, blood vessels relax and blood pressure is lowered. It can be used alone or in combination with selected other agents to get a better reduction in blood pressure.

When it should not be used:
Do not take Sandoz Aliskiren if you:
- Are allergic to aliskiren or to any non-medicinal ingredient in the formulation (see What the nonmedicinal ingredients are:).
- Have experienced a severe allergic reaction called angioedema with swelling of the face, lips, tongue, or throat, or sudden difficulty breathing or swallowing while taking aliskiren or any other medication, including medications for blood pressure, or without a known cause. Be sure to tell your doctor, nurse, or pharmacist that this has happened to you.
- Have been diagnosed with hereditary angioedema: an increased risk of getting an allergic reaction that is passed down through families. This can be triggered by different factors, such as surgery, flu, or dental procedures.
- Have diabetes or kidney disease and are already taking a blood pressure-lowering medicine which is an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).
- Are pregnant or plan to become pregnant
- Are breastfeeding

Sandoz Aliskiren is only for use in adults. It must not be used in patients less than 2 years of age and should not be used in patients 2 to less than 6 years of age. Sandoz Aliskiren is not recommended for use in patients 6 to less than 18 years of age.

What the medicinal ingredient is:
aliskiren.

What the nonmedicinal ingredients are:
Colloidal silicon dioxide, crospovidone, hypromellose, iron oxide colorants, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide.

What dosage forms it comes in:
Tablets; 150 (light-pink) and 300 mg (light-red).

WARNINGS AND PRECAUTIONS

Serious Warning and Precaution - Pregnancy
Sandoz Aliskiren should not be used during pregnancy. If you discover that you are pregnant while taking Sandoz Aliskiren, stop the medication and contact your doctor, nurse, or pharmacist as soon as possible.

BEFORE you use Sandoz Aliskiren talk to your doctor, nurse, or pharmacist if you:
- Have or have had an impaired kidney function
- Are taking non-steroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling.
- Are taking a blood pressure-lowering medicine which is an angiotensin receptor blocker (ARB) or an angiotensin converting enzyme (ACE) inhibitor.
- Have severe and persistent diarrhea
- Are on a low salt diet
- Are taking cyclosporine, used in transplantation to prevent organ rejection or for other conditions, e.g. rheumatoid arthritis or atopic dermatitis
- Are taking itraconazole, used to treat fungal infections

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with Sandoz Aliskiren:
- Cyclosporine, used in transplantation to prevent graft rejection or for other conditions, e.g. rheumatoid arthritis or atopic dermatitis (red, flaky, itchy skin)
- Itraconazole, or ketoconazole, used to treat fungal infections
- Potassium-sparing diuretics (a specific kind of "water pill"), potassium supplements, or salt substitutes containing potassium.
- Other blood pressure lowering medications, such as furosemide, verapamil, angiotensin receptor blockers (ARBs), such as irbesartan or angiotensin converting enzyme

(ACE) inhibitors.
- Non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase-2 (Cox-2) inhibitors, used to reduce pain and swelling. Examples include ibuprofen, naproxen, and celecoxib.

PROPER USE OF THIS MEDICATION

Take Sandoz Aliskiren exactly as prescribed. You can take Sandoz Aliskiren with or without food, but it should be taken the same way each day. It is recommended to take your dose at about the same time every day. Swallow Sandoz Aliskiren tablets whole with a small amount of water. Do not chew or crush the tablets.

Usual adult dose:
The usual starting dose is one 150 mg tablet once a day. In some cases, your doctor may prescribe a higher dose of one 300 mg tablet once a day or an additional blood pressure-lowering medicine.
Do not exceed the maximum dose of 300 mg once a day.

Overdose:

If you think you have taken too much Sandoz Aliskiren, contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of this medicine, take it as soon as you remember. However, if it is almost time for the next dose, skip the missed dose and go back to your regular dosing schedule. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:
- nasopharyngitis (common cold, viral infectious disease of the upper respiratory tract which affects primarily the nose, the throat and sinus), influenza, cough
- diarrhea, constipation, nausea, vomiting
- edema (accumulation of fluid in tissues that can cause swelling of hands, ankles or feet)
- headache, dizziness, fatigue
- back pain
- itching, skin reddening
- weakness
- low sodium levels in blood

If any of these affects you severely, tell your doctor, nurse, or pharmacist.

Sandoz Aliskiren can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	**Increased levels of potassium in the blood:** irregular heartbeats, muscle weakness and generally feeling unwell		✓	
Uncommon	Severe diarrhea			✓
	Allergic reaction: rash, itching, hives, swelling of the face, lips, tongue or throat, difficulty breathing or swallowing, dizziness, vomiting, abdominal pain.			✓
	Reduced kidney function: decreased urination, nausea, vomiting, swelling of extremities, fatigue		✓	
	Low blood pressure: dizziness, fainting, lightheadedness May occur when you go from lying or sitting to standing up.	✓		
	Kidney failure or acute kidney failure: Severely decreased or lack of urination			✓
Unknown	Angioedema: (symptoms like difficulty breathing or swallowing, tightness of the chest, hives, general rash, swelling, itching, dizziness, vomiting, abdominal pain)			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
	Liver disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
	Toxic epidermal necrolysis: severe skin peeling especially in mouth and eyes			✓
	Stevens Johnson syndrome: blistering of the mucous membranes of the skin including mouth, lips, eyes or mouth eyelids, and genitals			✓

This is not a complete list of side effects. For any unexpected effects while taking Sandoz Aliskiren, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

- Do not store above 30°C.
- Do not use after the expiry date shown on the box.
- Store in the original package in order to protect from moisture.
- Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Please consult your doctor or pharmacist with any questions or concerns you may have regarding your individual condition.

This document, plus the full Product Monograph prepared for health professionals, can be obtained by contacting the sponsor, Sandoz Canada Inc., at: 1-800-361-3062
or
by written request at:
145, Jules-Léger
Boucherville, (QC), Canada
J4B 7K8

or by e-mail at : medinfo@sandoz.com

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