

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALISKIREN TABLETS safely and effectively. See full prescribing information for ALISKIREN TABLETS.

ALISKIREN tablets, for oral use
Initial U.S. Approval: 2007

<div>WARNING: FETAL TOXICITY See full prescribing information for complete boxed warning.<ul style="list-style-type: none">When pregnancy is detected, discontinue aliskiren tablets as soon as possible. (5.1, 8.1)Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1, 8.1)</div>
INDICATIONS AND USAGE
Aliskiren tablets are a renin inhibitor (RI) indicated for the treatment of hypertension in adults and in pediatric patients weighing 50 kg or greater who are at least 6 years of age, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
DOSAGE AND ADMINISTRATION
<ul style="list-style-type: none">Starting dose (adults and pediatric patients): 150 mg once daily with a routine pattern with regard to meals. If blood pressure remains uncontrolled titrate up to 300 mg daily. (2.1)Majority of effect of given dose attained in 2 weeks (2.1)
DOSAGE FORMS AND STRENGTHS
Tablets: 150 mg, 300 mg (3)
CONTRAINDICATIONS
Do not use with angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEIs) in patients with diabetes.(4)

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WARNING: FETAL TOXICITY

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FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY When pregnancy is detected, discontinue aliskiren tablets as soon as possible. (5.1, 8.1) Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1, 8.1)

1 INDICATIONS AND USAGE

1.1 Hypertension

Aliskiren tablets are indicated for the treatment of hypertension in adults and in pediatric patients weighing 50 kg or greater who are at least 6 years of age and older to lower blood pressure.

Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes. There are no controlled trials demonstrating risk reduction with aliskiren tablets.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than 1 drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program’s Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality have also been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (e.g., patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

In adult patients and in pediatric patients weighing 50 kg or greater who are at least 6 years of age, the recommended starting dose of aliskiren tablets is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 300 mg once daily. Doses above 300 mg did not give an increased blood pressure response but resulted in an increased rate of diarrhea. The antihypertensive effect of a given dosage is substantially attained (85% to 90%) by 2 weeks.

2.2 Relationship to Meals

Patients should establish a routine pattern for taking aliskiren tablets with regard to meals. High-fat meals decrease absorption substantially [*See Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

150 mg Pink colored, film-coated, biconvex round tablets debossed with “E” on one side and “590” on the other side.

300 mg Brown colored, film-coated, ovaloid shaped biconvex tablets debossed with “E” on one side and “591” on the other side.

4 CONTRAINDICATIONS

Do not use aliskiren with ARBs or ACEIs in patients with diabetes [*See Warnings and Precautions (5.2) and Clinical Studies (14.3)*].

Aliskiren tablets are contraindicated in patients with known hypersensitivity to any of the components [*See Warnings and Precautions (5.3)*].

Aliskiren tablets are contraindicated in pediatric patients less than 2 years of age because of the risk of high aliskiren exposures identified in juvenile animals due to immaturity of transporters and metabolic enzymes [*See Use in Specific Populations (8.4)*].

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue aliskiren tablets as soon as possible [*See Use in Specific Populations (8.1)*].

5.2 Renal Impairment/Hyperkalemia/Hypotension when Aliskiren Tablets are Given in Combination with ARBs or ACEIs

Aliskiren tablets are contraindicated in patients with diabetes who are receiving ARBs or ACEIs because of the increased risk of renal impairment, hyperkalemia, and hypotension. In general, avoid combined use of aliskiren with ACE inhibitors or ARBs, particularly in patients with creatinine clearance (CrCl) less than 60 mL/min [*See Contraindications (4), Drug Interactions (7) and Clinical Studies (14.3)*].

5.3 Anaphylactic Reactions and Head and Neck Angioedema

Hypersensitivity reactions such as anaphylactic reactions and angioedema of the face, extremities, lips, tongue, glottis and/or larynx have been reported in patients treated with aliskiren tablets and has necessitated hospitalization and intubation. This may occur at any time during treatment and has occurred in patients with and without a history of angioedema with ACEIs or angiotensin receptor antagonists. Anaphylactic reactions have been reported from postmarketing experience with unknown frequency. If angioedema involves the throat, tongue, glottis or larynx, or if the patient has a history of upper respiratory surgery, airway obstruction may occur and be fatal. Patients who experience these effects, even without respiratory distress, require prolonged observation and appropriate monitoring measures since treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory involvement. Prompt administration of subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and measures to ensure a patent airway may be necessary.

Discontinue aliskiren tablets immediately in patients who develop anaphylactic reactions or angioedema, and do not readminister [*See Dosage and Administration (2.1) and Contraindications (4)*].

5.4 Hypotension

Symptomatic hypotension may occur after initiation of treatment with aliskiren tablets in patients with marked volume depletion, patients with salt depletion, or with combined use of aliskiren and other agents acting on the renin-angiotensin-aldosterone system (RAAS). The volume or salt depletion should be corrected prior to administration of aliskiren tablets, or the treatment should start under close medical supervision.

A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

5.5 Impaired Renal Function

Monitor renal function periodically in patients treated with aliskiren tablets. Changes in renal function, including acute renal failure, can be caused by drugs that affect the RAAS. Patients whose renal function

Hypersensitivity to any of the components. (4)

Aliskiren tablets are contraindicated in pediatric patients less than 2 years of age. (4)

WARNINGS AND PRECAUTIONS

- Avoid concomitant use with ARBs or ACEIs particularly in patients with renal impairment [creatinine clearance (CrCl) <60 mL/min]. (5.2, 5.4)
- Anaphylactic Reactions and Head and Neck Angioedema. (5.3)
- Hypotension: Correct imbalances in volume and/or salt depleted patients. (5.4)
- Impaired Renal Function: Monitor serum creatinine periodically. (5.5)
- Hyperkalemia: Monitor potassium levels periodically. (5.6)

ADVERSE REACTIONS

Most common adverse reaction: diarrhea (incidence 2.3%) (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Cyclosporine or Itraconazole: Avoid concomitant use. (5.7, 7, 12.3)
- Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): Increased risk of renal impairment and loss of antihypertensive effect. (7)

USE IN SPECIFIC POPULATIONS

Lactation: Breastfeeding not recommended. (8.2)

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may depend in part on the activity of the RAAS (e.g., patients with renal artery stenosis, severe heart failure, post-myocardial infarction or volume depletion) or patients receiving ARB, ACEI or nonsteroidal anti-inflammatory drug (NSAID), including selective Cyclooxygenase-2 inhibitors (COX-2 inhibitors), therapy may be at particular risk for developing acute renal failure on aliskiren tablets [*See Warnings and Precautions (5.2), Drug Interactions (7), Use in Specific Populations (8.6), and Clinical Studies (14.3)*].

Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function.

5.6 Hyperkalemia

Monitor serum potassium periodically in patients receiving aliskiren tablets. Drugs that affect the RAAS can cause hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes, combination use with ARBs or ACEIs [*See Contraindications (4), Warnings and Precautions (5.2), and Clinical Studies (14.3)*], NSAIDs, or potassium supplements or potassium sparing diuretics.

5.7 Cyclosporine or Itraconazole

When aliskiren was given with cyclosporine or itraconazole, the blood concentrations of aliskiren were significantly increased. Avoid concomitant use of aliskiren with cyclosporine or itraconazole [*See Drug Interactions (7)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Fetal Toxicity [*See Warnings and Precautions (5.1)*]
- Anaphylactic Reactions and Head and Neck Angioedema [*See Warnings and Precautions (5.3)*]
- Hypotension [*See Warnings and Precautions (5.4)*]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

Adult Hypertension

Data described below reflect the evaluation of the safety of aliskiren tablets in more than 6,460 patients, including over 1,740 treated for longer than 6 months, and more than 1,250 patients for longer than 1 year. In placebo-controlled clinical trials, discontinuation of therapy due to a clinical adverse event, including uncontrolled hypertension, occurred in 2.2% of patients treated with aliskiren tablets versus 3.5% of patients given placebo. These data do not include information from the ALTITUDE study which evaluated the use of aliskiren in combination with ARBs or ACEIs [*See Contraindications (4), Warnings and Precautions (5.2), and Clinical Studies (14.3)*].

Angioedema: Two cases of angioedema with respiratory symptoms were reported with aliskiren tablets use in the clinical studies. Two other cases of periorbital edema without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.06%.

In addition, 26 other cases of edema involving the face, hands, or whole body were reported with aliskiren tablets use including 4 leading to discontinuation.

In the placebo-controlled studies, however, the incidence of edema involving the face, hands, or whole body was 0.4% with aliskiren tablets compared with 0.5% with placebo. In a long-term active-control study with aliskiren tablets and hydrochlorothiazide (HCTZ) arms, the incidence of edema involving the face, hand or whole body was 0.4% in both treatment arms [*See Warnings and Precautions (5.2)*].

Gastrointestinal: Aliskiren tablets produces dose-related gastrointestinal (GI) adverse reactions. 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 and older) 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% to 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.

Cough: Aliskiren tablets were associated with a slight increase in cough in the placebo-controlled studies (1.1% for any aliskiren tablets use versus 0.6% for placebo). In active-controlled trials with ACE inhibitor (ramipril, lisinopril) arms, the rates of cough for the aliskiren tablets arms were about one-third to one-half the rates in the ACE inhibitor arms.

Seizures: Single episodes of tonic-clonic seizures with loss of consciousness were reported in 2 patients treated with aliskiren tablets in the clinical trials. One of these patients did have predisposing causes for seizures and had a negative electroencephalogram (EEG) and cerebral imaging following the seizures (for the other patient EEG and imaging results were not reported). Aliskiren tablets were discontinued and there was no rechallenge.

Other adverse effects with increased rates for aliskiren tablets compared to placebo included rash (1% versus 0.3%), elevated uric acid (0.4% versus 0.1%), gout (0.2% versus 0.1%) and renal stones (0.2% versus 0%).

Aliskiren’s effect on ECG intervals was studied in a randomized, double-blind, placebo and active-controlled (moxifloxacin), 7-day repeat dosing study with Holter-monitoring and 12 lead ECGs throughout the interposing interval. No effect of aliskiren on QT interval was seen.

Pediatric Hypertension

Aliskiren has been evaluated for safety in 267 pediatric hypertensive patients 6 to 17 years of age; including 208 patients treated for 52 weeks [*See Clinical Studies (14.4)*]. These studies did not reveal any unanticipated adverse reactions. Adverse reactions in pediatric patients 6 years of age and older are expected to be similar to those seen in adults.

Clinical Laboratory Findings

In controlled clinical trials, clinically relevant changes in standard laboratory parameters were rarely associated with the administration of aliskiren tablets in patients with hypertension not concomitantly treated with an ARB or ACEI. In multiple-dose studies in hypertensive patients, aliskiren tablets had no clinically important effects on total cholesterol, HDL, fasting triglycerides, or fasting glucose.

Blood Urea Nitrogen, Creatinine: In patients with hypertension not concomitantly treated with an ARB or ACEI, minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 7% of patients treated with aliskiren tablets alone versus 6% on placebo [*See Warnings and Precautions (5.2)*].

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.08 g/dL and 0.16 volume percent, respectively, for all aliskiren monotherapy) were observed. The decreases were dose-related and were 0.24 g/dL and 0.79 volume percent for 600 mg daily. This effect is also seen with other agents acting on the renin angiotensin system, such as angiotensin inhibitors and ARBs, and may be mediated by reduction of angiotensin II which stimulates erythropoietin production via the AT1 receptor. These decreases led to slight increases in rates of anemia with aliskiren compared to placebo were observed (0.1% for any aliskiren use, 0.3% for aliskiren 600 mg daily, versus 0% for placebo). No patients discontinued therapy due to anemia.

Serum Potassium: In patients with hypertension not concomitantly treated with an ARB or ACEI, increases in serum potassium greater than 5.5 mEq/L were infrequent (0.9% compared to 0.6% with placebo) [*See Contraindications (4) and Warnings and Precautions (5.6)*].

Serum Uric Acid: Aliskiren monotherapy produced small median increases in serum uric acid levels (about 6 micromol/L) while HCTZ produced larger increases (about 30 micromol/L). The combination of aliskiren with HCTZ appears to be additive (about 40 micromol/L increase). The increases in uric acid appear to lead to slight increases in uric acid-related AEs: elevated uric acid (0.4% versus 0.1%), gout (0.2% versus. 0.1%), and renal stones (0.2% versus 0%).

Creatine Kinase: Increases in creatine kinase of greater than 300% were recorded in about 1% of aliskiren monotherapy patients versus 0.5% of placebo patients. Five cases of creatine kinase rises, 3 leading to discontinuation and 1 diagnosed as subclinical rhabdomyolysis, and another as myositis, were reported as adverse events with aliskiren use in the clinical trials. No cases were associated with renal dysfunction.

6.2 Postmarketing Experience

The following adverse reactions have been reported in aliskiren postmarketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity: anaphylactic reactions and angioedema requiring airway management and hospitalization
Urticaria

Peripheral edema

Hepatic enzyme increase with clinical symptoms of hepatic dysfunction

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis
Pruritus

Erythema

Hyponatremia

Nausea, Vomiting

7 DRUG INTERACTIONS

Cyclosporine: Avoid coadministration of cyclosporine with aliskiren [*see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)*].

Itraconazole: Avoid coadministration of itraconazole with aliskiren [*see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)*].

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) including selective Cyclooxygenase-2 inhibitors (COX-2 inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors with agents that affect the RAAS, including aliskiren, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving aliskiren and NSAID therapy.

The antihypertensive effect of aliskiren may be attenuated by NSAIDs.

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS): The concomitant use of aliskiren with other agents acting on the RAAS such as ACEIs or ARBs is associated with an increased risk of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two drugs that inhibit the renin-angiotensin system do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of aliskiren with ACE inhibitors or ARBs, particularly in patients with CrCl less than 60 mL/min. Monitor blood pressure, renal function, and electrolytes in patients taking aliskiren and other agents that affect the RAAS [*see Warnings and Precautions (5.4, 5.5, 5.6)*].

The concomitant use of aliskiren with an ARB or an ACEI in diabetic patients is contraindicated [*see Contraindications (4)*].

Furosemide: Oral coadministration of aliskiren and furosemide reduced exposure to furosemide. Monitor diuretic effects when furosemide is coadministered with aliskiren.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Aliskiren can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death [*see Clinical Considerations*]. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. When pregnancy is detected, discontinue aliskiren as soon as possible.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major malformations and miscarriage in clinically recognized pregnancies is 2 to 4%, and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal Adverse Reactions

Use of drugs that act on the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, oligohydramnios, fetal lung hypoplasia and skeletal deformations, including skull hypoplasia, hypotension, and death. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus.

In patients taking aliskiren during pregnancy, perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of *in utero* exposure to aliskiren for hypotension, oliguria, and hyperkalemia. If oliguria or hypotension occur in neonates with a history of *in utero* exposure to aliskiren, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and substituting for disordered renal function.

Data

Animal Data

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), respectively, in rats and rabbits. (Actual animal doses were up to 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.

8.2 Lactation

Risk Summary

There is no information regarding the presence of aliskiren in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions, including hypotension, hyperkalemia and renal impairment in nursing infants, advise a nursing woman that breastfeeding is not recommended during treatment with aliskiren tablets.

8.4 Pediatric Use

Aliskiren tablets are contraindicated in patients less than 2 years of age [*see Contraindications (4)*]. Aliskiren tablets are indicated for treatment of hypertension in pediatric patients 6 years of age and older weighing 50 kg or more. The safety and effectiveness of aliskiren have been established in pediatric patients 6 years of age and older weighing 20 kg or more, but aliskiren tablets are not approved in patients 6 years of age and older weighing 20 kg to less than 50 kg because of the lack of an appropriate dosage form. Use of aliskiren tablets in pediatric patients 6 years and older is supported by evidence from a pharmacokinetic trial and two randomized, double-blind clinical trials in pediatric patients with hypertension 6 years to 17 years of age weighing 20 kg or more [*see Clinical Pharmacology (12.3), Clinical Studies (14.4)*]. The safety and effectiveness of aliskiren tablets have not been established in pediatric patients younger than 6 years of age and patients less than 20 kg. Avoid use in patients 2 years to less than 6 years and patients weighing less than 20 kg due to the limited information about aliskiren metabolism and exposures in this age group. No data are available in pediatric patients weighing less than 20 kg or in pediatric patients with a glomerular filtration rate <30 mL/min/1.73 m².

Juvenile Animal Toxicity Data

Toxicology studies in juvenile animals the approximate human age equivalent of children less than 2 years of age identified 85-to 385-fold increased systemic exposure to aliskiren compared to adult rats. The increased aliskiren exposure in juvenile rats was attributed to immaturity in aliskiren drug transporters and metabolizing enzymes. Increased aliskiren exposures were associated with premature deaths. Although a definitive pathology-based cause of death could not be ascertained, the premature deaths were attributed to the immaturity in aliskiren metabolism. The nonclinical findings suggest a distinct age-dependent relationship between dose and exposure.

Neonates with a history of *in utero* exposure to aliskiren tablets

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

8.5 Geriatric Use

Of the total number of patients receiving aliskiren in clinical studies, 1,275 (19%) were 65 years or older and 231 (3.4%) were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Safety and effectiveness of

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Renin is secreted by the kidney in response to decreases in blood volume and renal perfusion. 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. Ang II also inhibits renin release, thus providing a negative feedback to the system. This cycle, from renin through angiotensin to aldosterone and its associated negative feedback loop, is known as the renin-angiotensin-aldosterone system (RAAS). Aliskiren is a direct renin inhibitor, decreasing plasma renin activity (PRA) and inhibiting the conversion of angiotensinogen to Ang I. Whether aliskiren affects other RAAS components, e.g., ACE or non-ACE pathways, is not known.

All agents that inhibit the RAAS, including renin inhibitors, suppress the negative feedback loop, leading to a compensatory rise in plasma renin concentration. When this rise occurs during treatment with ACEIs and ARBs, the result is increased levels of PRA. During treatment with aliskiren, however, the effect of increased renin levels is blocked so that PRA, Ang I and Ang II are all reduced, whether aliskiren is used as monotherapy or in combination with other antihypertensive agents.

12.2 Pharmacodynamics

In placebo-controlled clinical trials, PRA was decreased in a range of 50% to 80%. This reduction in PRA was not dose-related and did not correlate with blood pressure reductions. The clinical implications of the differences in effect on PRA are not known.

12.3 Pharmacokinetics

Aliskiren is poorly absorbed (bioavailability about 2.5%) with an approximate accumulation half-life of 24 hours. Steady state blood levels are reached in about 7 to 8 days.

Absorption and Distribution

Following oral administration, peak plasma concentrations of aliskiren are reached within 1 to 3 hours. When taken with a high-fat meal, mean AUC and C_{max} of aliskiren are decreased by 71% and 85% respectively. In the clinical trials of aliskiren, it was administered without requiring a fixed relation of administration to meals.

Metabolism and Elimination

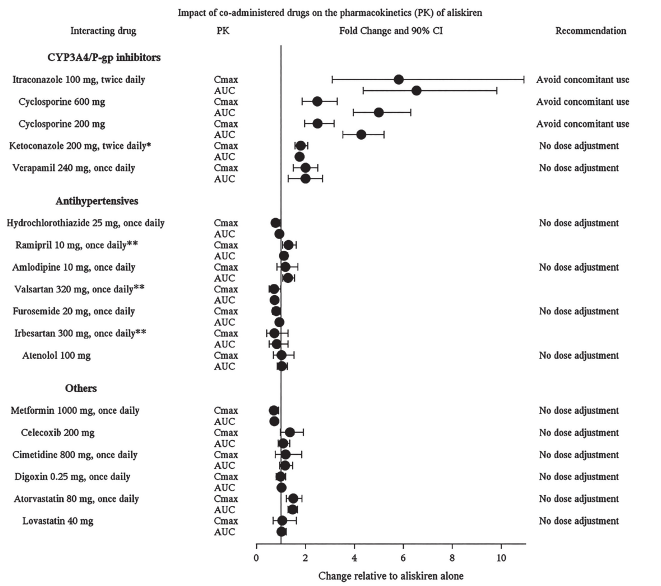
About one-fourth of the absorbed dose appears in the urine as parent drug. How much of the absorbed dose is metabolized is unknown. Based on the *in vitro* studies, the major enzyme responsible for aliskiren metabolism appears to be CYP3A4. Aliskiren does not inhibit the CYP450 isoenzymes (CYP 1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A) or induce CYP3A4.

Transporters: Pgp (MDR1/Mdr1a/b1) was found to be the major efflux system involved in intestinal absorption and elimination via biliary excretion of aliskiren in preclinical studies. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter.

Drug Interactions

The effect of coadministered drugs on the pharmacokinetics of aliskiren and vice versa, were studied in several single- and multiple-dose studies. Pharmacokinetic measures indicating the magnitude of these interactions are presented in Figure 1 (impact of coadministered drugs on aliskiren) and Figure 2 (impact of aliskiren on coadministered drugs).

Figure 1: The Impact of Coadministered Drugs on the Pharmacokinetics of Aliskiren

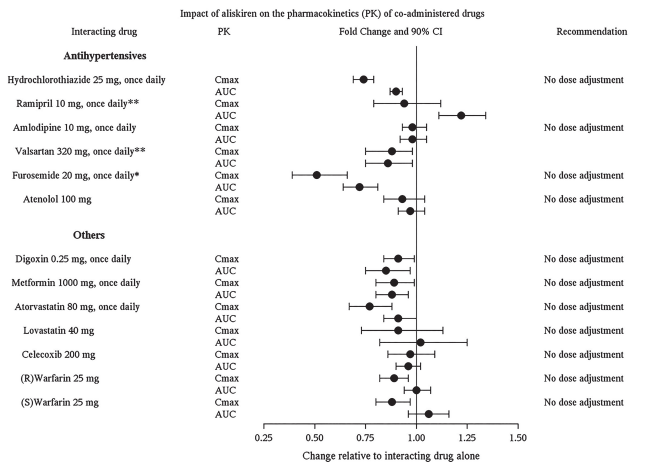


*Ketoconazole: A 400 mg once daily dose was not studied, but would be expected to increase aliskiren blood levels further.

**Ramipril, valsartan, irbesartan: In general, avoid combined use of aliskiren with ACE inhibitors or ARBs, particularly in patients with CrCl less than 60 mL/min (*see Drug Interactions (7)*).

Warfarin: There was no clinically significant effect of a single dose of warfarin 25 mg on the pharmacokinetics of aliskiren.

Figure 2: The Impact of Aliskiren on the Pharmacokinetics of Coadministered Drugs



*Furosemide: Patients receiving furosemide could find its effects diminished after starting aliskiren. In patients with heart failure, coadministration of aliskiren (300 mg/day) reduced plasma AUC and C_{max} of oral furosemide (60 mg/day) by 17% and 27%, respectively, and reduced 24-hour urinary furosemide excretion by 29%. This change in exposure did not result in statistically significant difference in total urine volume and urinary sodium excretion over 24 hours. However, a transient decrease in urinary sodium excretion and urine volume effects up to 12 hours were observed when furosemide was coadministered with aliskiren 300 mg/day.

**Ramipril, valsartan: In general, avoid combined use of aliskiren with ACE inhibitors or ARBs, particularly in patients with CrCl less than 60 mL/min (*see Drug Interactions (7)*).

Specific Populations

Renally Impaired Patients: Aliskiren was evaluated in adult patients with varying degrees of renal insufficiency. The rate and extent of exposure (AUC and C_{max}) of aliskiren in subjects with renal impairment did not show a consistent correlation with the severity of renal impairment. Adjustment of the starting dose is not required in these patients (*see Warnings and Precautions (5,2)*).

The pharmacokinetics of aliskiren following administration of a single oral dose of 300 mg was evaluated in adult patients with End Stage Renal Disease (ESRD) undergoing hemodialysis. When compared to matched healthy subjects, changes in the rate and extent of aliskiren exposure (C_{max} and AUC) in ESRD patients undergoing hemodialysis were not clinically significant.

Timing of hemodialysis did not significantly alter the pharmacokinetics of aliskiren in ESRD patients. Therefore, no dose adjustment is warranted in ESRD patients receiving hemodialysis.

Hepatically Impaired Patients: The pharmacokinetics of aliskiren were not significantly affected in patients with mild to severe liver disease. Consequently, adjustment of the starting dose is not required in these patients.

Pediatric Patients:

The pharmacokinetics of aliskiren were evaluated in an 8-day pharmacokinetic study in 39 pediatric patients with hypertension 6 years to 17 years of age. Aliskiren was given as daily doses of 2 mg/kg (0.67 times the lowest approved recommended dosage in a 50 kg pediatric patient) or 6 mg/kg (the highest recommended approved dosage in a 50 kg pediatric patient), administered as mini-tablets (3.125 mg oral pellets). The pharmacokinetic parameters of aliskiren were similar to those in adults, and the results of this study do not suggest that age or gender have any significant effect on aliskiren systemic exposure in patients 6 years to 17 years of age. Exposure decreased with increase in body weight.

In an 8-week randomized double blind study with aliskiren monotherapy in 267 pediatric patients with hypertension 6 years to 17 years of age [*see Clinical Studies (14.4)*], fasting trough aliskiren concentrations at Day 28 demonstrated similar drug trough exposure levels to those observed in other trials using similar aliskiren doses in both adults and pediatric patients.

Geriatric Patients: Exposure (measured by AUC) is increased in elderly patients 65 years and older. Adjustment of the starting dose is not required in these patients.

Racial or Ethnic Groups: The pharmacokinetic differences between blacks, Caucasians, and Japanese are minimal.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic (rasH2) mouse study with aliskiren hemifumarate at oral doses of up to 1500 mg aliskiren/kg/day. Although there were no statistically significant increases in tumor incidence associated with exposure to aliskiren, mucosal epithelial hyperplasia (with or without erosion/ulceration) was observed in the lower gastrointestinal tract at doses of greater than or equal to 750 mg/kg/day in both species, with a colonic adenoma identified in 1 rat and a cecal adenocarcinoma identified in another, rare tumors in the strain of rat studied. On a systemic exposure (AUC_{0-24h}) basis, 1500 mg/kg/day in the rat is about 4 times and in the mouse about 1.5 times the maximum recommended human dose (MRHD) (300 mg aliskiren/day). Mucosal hyperplasia in the cecum or colon of rats was also observed at doses of 250 mg/kg/day (the lowest tested dose) as well as at higher doses in 4- and 13-week studies.

Aliskiren hemifumarate was devoid of genotoxic potential in the Ames reverse mutation assay with *S. typhimurium* and *E. coli*, the *in vitro* Chinese hamster ovary cell chromosomal aberration assay, the *in vitro* Chinese hamster V79 cell gene mutation test and the *in vivo* mouse bone marrow micronucleus assay.

Fertility of male and female rats was unaffected at doses of up to 250 mg aliskiren/kg/day (8 times the MRHD of 300 mg aliskiren tablets/60 kg on a mg/m² basis.)

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies: Reproductive toxicity studies of aliskiren hemifumarate did not reveal any evidence of teratogenicity at oral doses up to 600 mg aliskiren/kg/day (20 times the MRHD of 300 mg/day on a mg/m² basis) in pregnant rats or up to 100 mg aliskiren/kg/day (7 times the MRHD on a mg/m² basis) in pregnant rabbits. Fetal birth weight was adversely affected in rabbits at 50 mg/kg/day (3.2 times the MRHD on a mg/m² basis). Aliskiren was present in placenta, amniotic fluid and fetuses of pregnant rabbits.

14 CLINICAL STUDIES

14.1 Aliskiren Monotherapy

The antihypertensive effects of aliskiren tablets have been demonstrated in 6 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 are shown in Table 2.

Table 2: Reductions in Seated Trough Cuff Blood Pressure (mmHg systolic/diastolic) in the Placebo-Controlled Studies

Study	Placebo mean change	Aliskiren daily dose, mg			
		75	150	300	600
		Placebo-subtracted	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted
1	2.9/3.3	5.7/4*	5.9/4.5*	11.2/7.5*	--
2	5.3/6.3	--	6.1/2.9*	10.5/5.4*	10.4/5.2*
3	10.8/6	2.2/1.7	2.1/1.7	5.1/3.7*	--
4	7.5/6.9	1.9/1.8	4.8/2*	8.3/3.3*	--
5	3.8/4.9	--	9.3/5.4*	10.9/6.2*	12.1/7.6*
6	4.6/4.1	--	--	8.4/4.9†	--

*p value less than 0.05 versus placebo by ANCOVA with Dunnett's procedure for multiple comparisons

†p value less than 0.05 versus placebo by ANCOVA for the pairwise comparison.

The studies included approximately 2,730 patients given doses of 75 mg (0.5 times the lowest recommended dosage) to 600 mg (twice the highest recommended dosage) of aliskiren and 1,231 patients given placebo. The recommended dosage of aliskiren tablets is either 150 or 300 mg once daily [*see Dosage and Administration (2.1)*]. As shown in Table 2, there is some increase in response with administered dose in all studies, with reasonable effects seen at 150 mg to 300 mg, and no clear further increases at 600 mg. A substantial proportion (85% to 90%) of the blood pressure-lowering effect was observed within 2 weeks of treatment. Studies with ambulatory blood pressure monitoring showed reasonable control throughout the interdosing interval; the ratios of mean daytime to mean nighttime ambulatory BP range from 0.6 to 0.9.

Patients in the placebo-controlled trials continued open-label aliskiren for up to 1 year. A persistent blood pressure-lowering effect was demonstrated by a randomized withdrawal study (patients randomized to continue drug or placebo), which showed a statistically significant difference between patients kept on aliskiren and those randomized to placebo. With cessation of treatment, blood pressure 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 blood pressure in all demographic subgroups, although black patients tended to have smaller reduction than Caucasians and Asians, as has been seen with ACEIs and ARBs.

There are no studies of aliskiren tablets or members of the direct renin inhibitors demonstrating reductions in cardiovascular risk in patients with hypertension.

14.2 Aliskiren in Combination with Other Antihypertensives

Hydrochlorothiazide (HCTZ)

Aliskiren 75, 150, and 300 mg (0.5 times the recommended lowest dosage, the lowest recommended dosage, and the maximum recommended dosage, respectively) and 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. Blood pressure reductions with the combinations were greater than the reductions with the monotherapies as shown in Table 4. In general, the combination of aliskiren and angiotensin receptor blocker should be avoided [*see Contraindications (4)*, *Warnings and Precautions (5)*, and *Drug Interactions (7)*].

Table 3: Placebo-Subtracted Reductions in Seated Trough Cuff Blood Pressure (mmHg systolic/diastolic) in Combination with Hydrochlorothiazide

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

Valsartan

Aliskiren 150 mg and 300 mg and valsartan 160 mg and 320 mg were studied alone and in combination in an 8-week, 1,797-patient, randomized, double-blind, placebo-controlled, parallel-group, 4-arm, dose-escalation study. The dosages of aliskiren and valsartan were started at 150 mg and 160 mg, respectively, and increased at 4 weeks to 300 mg and 320 mg, respectively. Seated trough cuff blood pressure was measured at baseline, 4, and 8 weeks. Blood pressure reductions with the combinations were greater than the reductions with the monotherapies as shown in Table 4. In general, the combination of aliskiren and angiotensin receptor blocker should be avoided [*see Contraindications (4)*, *Warnings and Precautions (5)*, and *Drug Interactions (7)*].

Table 4: Placebo-Subtracted Reductions in Seated Trough Cuff Blood Pressure (mmHg systolic/diastolic) in Combination with Valsartan

Aliskiren, mg	Placebo mean change	Valsartan, mg		
		0	160	320
0	4.6/4.1*	--	5.6/3.9	8.2/5.6
150	--	5.4/2.7	10.0/5.7	--
300	--	8.4/4.9	--	12.6/8.1

* The placebo change is 5.2/4.8 for week 4 endpoint which was used for the dose groups containing aliskiren 150 mg or valsartan 160 mg.

Amlodipine

Aliskiren 150 mg and 300 mg and amlodipine besylate 5 mg and 10 mg were studied alone and in combination in an 8-week, 1,685-patient, randomized, double-blind, placebo-controlled, multifactorial study. Treatment with aliskiren and amlodipine resulted overall in significantly greater reductions in diastolic and systolic blood pressure compared to the respective monotherapy components as shown in Table 5.

Table 5: Placebo-Subtracted Reductions in Seated Trough Cuff Blood Pressure (mmHg systolic/diastolic) in Combination with Amlodipine

Aliskiren, mg	Placebo mean change	Amlodipine, mg		
		0	5	10
0	6.8/5.4	--	9.0/5.6	14.3/8.5
150	--	3.9/2.6	13.9/8.6	17.1/10.8
300	--	8.6/4.9	15.0/9.6	16.4/11.1

14.3 Aliskiren in Patients with Diabetes Treated with ARB or ACEI (ALTITUDE study)

Patients with diabetes with renal disease (defined either by the presence of albuminuria or reduced GFR) were randomized to aliskiren 300 mg daily (n=4296) or placebo (n=4310). All patients were receiving background therapy with an ARB or ACEI. The primary efficacy outcome was the time to the first event of the primary composite endpoint consisting of cardiovascular death, resuscitated sudden death, nonfatal myocardial infarction, nonfatal stroke, unplanned hospitalization for heart failure, onset of end stage renal disease, renal death, and doubling of serum creatinine concentration from baseline sustained for at least 1 month. After a median follow-up of about 32 months, the trial was terminated early for lack of efficacy. Higher risk of renal impairment, hypotension and hyperkalemia was observed in aliskiren compared to placebo-treated patients, as shown in Table 6.

Table 6: Incidence of Selected Adverse Events During the Treatment Phase in ALTITUDE

	Aliskiren N=4272		Placebo N=4285	
	Serious Adverse Events* (%)	Adverse Events (%)	Serious Adverse Events* (%)	Adverse Events (%)
Renal impairment †	5.7	14.5	4.3	12.4
Hypotension ††	2.3	19.9	1.9	16.3
Hyperkalemia †††	1.0	38.9	0.5	28.8

*renal failure, renal failure acute, renal failure chronic, renal impairment

††dizziness, dizziness postural, hypotension, orthostatic hypotension, presyncope, syncope

††† Given the variable baseline potassium levels of patients with renal insufficiency on dual RAAS therapy, the reporting of adverse event of hyperkalemia was at the discretion of the investigator.

* A Serious Adverse Event (SAE) is defined as: an event which is fatal or life-threatening, results in persistent or significant disability/incapacity, constitutes a congenital anomaly/birth defect, requires inpatient hospitalization or prolongation of existing hospitalization, or is medically significant (i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes previously listed).

The risk of stroke (3.4% aliskiren versus 2.7% placebo) and death (8.4% aliskiren versus 8.0% placebo) were also numerically higher in aliskiren treated patients.

14.4 Pediatric Hypertension

The efficacy of aliskiren was evaluated in an 8-week randomized, double-blind trial in 267 pediatric patients with hypertension 6 years to 17 years of age (Study CSPP100A2365; NCT01150357). The majority of patients (82%) had primary hypertension, 59% had a BMI ≥95th percentile, 20% had an estimated GFR between 60 and 90 mL/min/1.73m² and < 2% had an estimated GFR < 60 mL/min/1.73m². The mean age was 11.8 years and 74% of patients were Caucasian. In the initial 4-week-dose-response phase of the trial patients were randomized to weight-based low, mid and high dosing groups. At the end of this phase, patients entered a 4-week randomized withdrawal phase in which they were re-randomized in each weight category in a 1:1 ratio to continue the same dose of aliskiren or take placebo.

During the initial dose-response phase, aliskiren reduced both systolic and diastolic blood pressure in a weight-based dose-dependent manner. Sitting systolic blood pressure, the trial's primary endpoint, was reduced by 4.8, 5.6 and 8.7 mmHg from baseline in the low, medium and high dose groups, respectively. In the randomized withdrawal phase, the mean difference between the high dose group of aliskiren and placebo in the mean change in sitting systolic blood pressure was 2.7 mmHg.

Following the 8-week trial, 208 patients were enrolled in a 52-week extension trial in which patients were randomized in a 1:1 ratio (irrespective of whether they were on placebo or aliskiren at the end of the 8-week study) to receive either aliskiren or enalapril (CSPP100A2365E1; NCT01151410). The extension study included 3 dose levels based on weight; optional dose up-titrations were allowed during the study to control blood pressure.

At the end of 52 weeks, reductions in blood pressure from baseline were similar in patients receiving aliskiren (7.6/3.9 mmHg) and enalapril (7.9/4.9 mmHg).

16 HOW SUPPLIED/STORAGE AND HANDLING

Aliskiren tablets are supplied as a pink colored, film-coated, biconvex round tablet containing 150 mg of aliskiren. Tablet is debossed with "E" on one side and "590" on the other side.

Aliskiren tablets are supplied as a brown colored, film-coated, ovaloid shaped biconvex tablet containing 300 mg of aliskiren. Tablet is debossed with "E" on one side and "591" on the other side.

All strengths are packaged in bottles as described below.

150 mg tablets: Bottles of 30 (NDC 49884-424-11)

300 mg tablets: Bottles of 30 (NDC 49884-425-11)

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from moisture.

Dispense in original container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Information for Patients

Pregnancy: Advise female patients of child-bearing age about the consequences of exposure to aliskiren tablets during pregnancy. Discuss treatment options with women planning to become pregnant. Advise patients to report pregnancies to their physicians as soon as possible.

Lactation: Advise nursing women that breastfeeding is not recommended during treatment with aliskiren tablets [*see Use in Specific Populations (8.2)*].

Anaphylactic Reactions and Angioedema: Advise patients to immediately report any signs or symptoms suggesting a severe allergic reaction (difficulty breathing or swallowing, tightness of the chest, hives, general rash, swelling, itching, dizziness, vomiting, or abdominal pain) or angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physicians. Angioedema, including laryngeal edema, may occur at any time during treatment with aliskiren tablets.

Symptomatic Hypotension: Advise patients that lightheadedness can occur, especially during the first days of aliskiren tablets therapy, and that it should be reported to the prescribing physician. Advise patients that if syncope occurs, aliskiren tablets should be discontinued until the physician has been consulted.

Caution patients that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Potassium Supplements: Advise patients receiving aliskiren tablets not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Relationship to Meals: Advise patients to establish a routine pattern for taking aliskiren tablets with regard to meals. High-fat meals decrease absorption substantially.

PATIENT INFORMATION

Aliskiren Tablets

(al[®] is kye[®] ren)

What is the most important information I should know about aliskiren tablets?

Aliskiren tablets can cause harm or death to your unborn baby.

- Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant.
- If you become pregnant during treatment with aliskiren tablets, stop taking aliskiren tablets and tell your doctor right away.