

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

AMTURNIDE™ (aliskiren, amlodipine and hydrochlorothiazide) tablets, for oral use  
Initial U.S. Approval: 2010

### WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

- When pregnancy is detected, discontinue Amturnide as soon as possible. (5.1)
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)

### RECENT MAJOR CHANGES

Warnings and Precautions (5.1, 5.2, 5.6) 03/2015

### INDICATIONS AND USAGE

Amturnide is a combination of aliskiren, a renin inhibitor, amlodipine besylate, a dihydropyridine calcium channel blocker, and hydrochlorothiazide (HCTZ), a thiazide diuretic. Amturnide is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions:

- Not indicated for initial therapy. (1)

### DOSAGE AND ADMINISTRATION

- Dose once-daily. Titrate as needed to a maximum dose of 300/10/25 mg.
- Amturnide may be used as add-on/switch therapy for patients not adequately controlled on any 2 of the following: aliskiren, dihydropyridine calcium channel blockers, and thiazide diuretics. (2.2)
- Amturnide may be substituted for its individual components. (2.3)

### DOSAGE FORMS AND STRENGTHS

Tablets (aliskiren/ amlodipine/ HCTZ): 150/5/12.5, 300/5/12.5, 300/5/25, 300/10/12.5, 300/10/25 mg. (3)

### CONTRAINDICATIONS

- Do not use with angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEIs) in patients with diabetes. (4)

- Anuria (4)
- Hypersensitivity to sulfonamide derived drugs or to any of the components (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 Angioedema.(5.3)
- Hypotension: Correct imbalances in volume and/or salt-depleted patients.(5.4)
- Increased angina or myocardial infarction may occur upon dosage initiation or increase in amlodipine. (5.5)
- Impaired Renal Function: Monitor serum creatinine periodically. (5.6)
- Systemic lupus erythematosus activation or exacerbation. (5.8)
- Hyperkalemia: Monitor potassium levels periodically. (5.10)
- Acute Myopia and Secondary Angle Closure Glaucoma. (5.12)

### ADVERSE REACTIONS

The most common adverse events (incidence  $\geq 2\%$ ) are: peripheral edema, dizziness, headache and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Cyclosporine or Itraconazole: Avoid concomitant use (5.11, 7, 12.3)
- Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): Increased risk of renal impairment and loss of antihypertensive effect. (7)
- Simvastatin: Avoid doses greater than 20 mg daily. (7)
- Antidiabetic Drugs: Antidiabetic dosage adjustment may be required. (7)
- Cholestyramine and Colestipol: Reduce absorption of thiazides. (7)
- Lithium: Increased risk of lithium toxicity when used with diuretics.(7)

### USE IN SPECIFIC POPULATIONS

Nursing Mothers: Discontinue drug or nursing. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 03/2015

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## FULL PRESCRIBING INFORMATION

### WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue Amlturnide as soon as possible. (5.1)**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)**

## 1 INDICATIONS AND USAGE

Amlturnide is indicated for the treatment of hypertension, 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, including amlodipine and hydrochlorothiazide (HCTZ). There are no controlled trials demonstrating risk reduction with Amlturnide.

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.

This fixed combination drug is not indicated for initial therapy of hypertension.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 General Considerations

Dose once-daily. The dosage may be increased after 2 weeks of therapy. The maximum recommended dose of Amlturnide is 300/10/25 mg.

### 2.2 Add-on/Switch Therapy

Use Amlturnide for patients not adequately controlled with any 2 of the following: aliskiren, dihydropyridine calcium channel blockers, and thiazide diuretics.

Switch a patient who experiences dose-limiting adverse reactions attributed to an individual component—while on any dual combination of the components of Amlturnide—to Amlturnide at a lower dose of that component to achieve similar blood pressure reductions.

### 2.3 Replacement Therapy

For patients receiving aliskiren, amlodipine, and HCTZ from separate tablets, substitute Amlturnide containing the same component doses.

### 2.4 Relationship to Meals

Patients should establish a routine pattern for taking Amlturnide, either with or without a meal. High-fat meals decrease absorption of aliskiren substantially [*see Clinical Pharmacology (12.3)*].

### 3 DOSAGE FORMS AND STRENGTHS

Tablets are convex ovaloid with a beveled edge, film-coated, and unscored, in the following strengths:

Aliskiren/Amlodipine/HCTZ (mg)	Color	Embossing Side 1/side 2
150/5/12.5	Violet white	YIY/NVR
300/5/12.5	Light pink	LIL/NVR
300/5/25	Pale orange brown	OIO/NVR
300/10/12.5	Light red	UIU/NVR
300/10/25	Brown	VIV/NVR

### 4 CONTRAINDICATIONS

Do not use aliskiren with ARBs or ACEIs in patients with diabetes [*see Warnings and Precautions (5.2) and Clinical Studies (14.2)*].

Amturnide is contraindicated in patients with anuria or hypersensitivity to sulfonamide derived drugs like HCTZ or to any of the components [*see Warnings and Precautions (5.8) and Adverse Reactions (6.1)*]. Hypersensitivity reactions may range from urticaria to anaphylaxis.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Fetal Toxicity

Pregnancy Category D

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 Amturnide as soon as possible [*see Use in Specific Populations (8.1)*].

Thiazides cross the placenta, and use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice, thrombocytopenia, and possible other adverse reactions that have occurred in adults.

#### 5.2 Renal Impairment/Hyperkalemia/Hypotension when Amturnide is Given in Combination with ARBs or ACEIs

Amturnide is 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 (14.2)*].

#### 5.3 Anaphylactic Reactions and Head and Neck Angioedema

##### Aliskiren

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 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 Amturnide immediately in patients who develop anaphylactic reactions or angioedema, and do not re-administer [*see Dosage and Administration (2.1) Contraindications (4)*].

#### 5.4 Hypotension

Symptomatic hypotension may occur after initiation of treatment with Amturnide in patients with marked volume depletion, patients with salt depletion, or with combined use of aliskiren and other agents acting on the RAAS. The

volume or salt depletion should be corrected prior to administration of Amlodipine, 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.

#### Amlodipine besylate

Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

### **5.5 Risk of Myocardial Infarction or Increased Angina**

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly with severe obstructive coronary artery disease.

### **5.6 Impaired Renal Function**

Monitor renal function periodically in patients treated with Amlodipine. Changes in renal function, including acute renal failure, can be caused by drugs that affect the RAAS and by diuretics. Patients whose renal function 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 of developing acute renal failure on Amlodipine [see *Warnings and Precautions (5.2)*, *Drug Interactions (7)*, and *Use in Specific Populations (8.7)* and *Clinical Studies (14.2)*]. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Amlodipine [see *Dosage and Administration (2.1)*].

### **5.7 Hypersensitivity Reactions**

#### Hydrochlorothiazide (HCTZ)

Hypersensitivity reactions to HCTZ may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

### **5.8 Systemic Lupus Erythematosus**

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus (SLE).

### **5.10 Serum Electrolyte Abnormalities**

#### Amlodipine

In a short-term controlled trial the incidence of patients with hypertension not concomitantly treated with an ARB or ACEI who developed hypokalemia (serum potassium less than 3.5 mEq/L) was 11.0% of Amlodipine-treated patients compared to 19.0% of amlodipine/HCTZ patients, 4.4% of aliskiren/HCTZ patients, and 2.1% of aliskiren/amlodipine patients; the incidence of hyperkalemia (serum potassium greater than 5.5 mEq/L) was 3.0% compared to 2.0% of amlodipine/HCTZ patients, 0.7% of aliskiren/HCTZ patients, and 0.7% of aliskiren/amlodipine patients. No Amlodipine-treated patients discontinued due to increase or decrease of serum potassium.

#### Aliskiren

Monitor serum potassium periodically in patients receiving aliskiren. 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 (14.2)*], NSAIDs, or potassium supplements or potassium-sparing diuretics.

#### Hydrochlorothiazide (HCTZ)

HCTZ can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which appears difficult to treat despite potassium repletion.

If hypokalemia is accompanied by clinical signs (e.g., muscular weakness, paresis, or ECG alterations), Amlodipine should be discontinued. Correction of hypokalemia and any coexisting hypomagnesemia is recommended prior to the initiation of thiazides.

### 5.11 Cyclosporine or Itraconazole

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

### 5.12 Acute Myopia and Secondary Angle-Closure Glaucoma

HCTZ, a sulfonamide, can cause an idiosyncratic reaction, resulting in transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue HCTZ as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

### 5.13 Metabolic Disturbances

#### Hydrochlorothiazide (HCTZ)

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

HCTZ may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients.

HCTZ decreases urinary calcium excretion and may cause elevation of serum calcium. Monitor calcium levels in patients with hypercalcemia receiving Amturnide.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Studies 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.

#### Amturnide

Amturnide has been evaluated for safety in 1155 patients treated with Amturnide, including 182 patients for over 1 year.

In a short-term controlled trial, there were 60.5% males, 84.1% Caucasians, 10% blacks, 6.4% Hispanics, and 19.1% who were 65 years of age and older. In this study, the overall incidence of adverse events on therapy with Amturnide was similar to that observed with the individual components. The overall frequency of adverse events was similar between men and women and black and Caucasian patients. Discontinuation of therapy because of a clinical adverse event in this study occurred in 3.6% of patients treated with Amturnide versus 2.4% in aliskiren/amlodipine, 0.7% in aliskiren/HCTZ, and 2.7% in amlodipine/HCTZ.

**Table 1. Adverse Events in a Short-term Controlled Trial that Occurred in at Least 2% of Patients Treated with Amturnide**

	<b>Amturnide</b>	<b>Ali/amlo</b>	<b>Ali/HCTZ</b>	<b>Amlo/HCTZ</b>
Edema peripheral	7.1%	8.0%	2.0%	4.1%
Dizziness	3.6%	2.4%	3.4%	1.7%
Headache	3.6%	3.1%	4.0%	5.1%
Nasopharyngitis	2.6%	0.7%	2.0%	3.4%

In a long-term safety trial, the safety profile was similar to that seen in the short-term controlled trial.

#### Aliskiren

Aliskiren has been evaluated for safety in 6460 patients, including 1740 treated for longer than 6 months, and 1250 for longer than 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event, including uncontrolled hypertension, occurred in 2.2% of patients treated with aliskiren, 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 (14.2)*].

Two cases of angioedema with respiratory symptoms were reported with aliskiren 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 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 compared with 0.5% with placebo. In a long-term active-controlled study with aliskiren and HCTZ arms, the incidence of edema involving the face, hands, or whole body was 0.4% in both treatment arms.

Aliskiren 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 similar to those seen at 300 mg for men or younger patients (all rates about 2%). 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.

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

Other adverse reactions with increased rates for aliskiren compared to placebo included rash (1% versus 0.3%), and renal stones (0.2% versus 0%).

Single episodes of tonic-clonic seizures with loss of consciousness were reported in 2 patients treated with aliskiren in the clinical trials. One patient had 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 was discontinued and there was no re-challenge in either case.

No clinically meaningful changes in vital signs or in ECG (including QTc interval) were observed in patients treated with aliskiren.

### Amlodipine

Amlodipine (Norvasc<sup>®</sup>) has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. Other adverse events that have been reported at less than 1% but greater than 0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain were:

**Cardiovascular:** arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, tachycardia, vasculitis

**Central and Peripheral Nervous System:** neuropathy peripheral, paresthesia, tremor, vertigo

**Gastrointestinal:** anorexia, constipation, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia

**General:** allergic reaction, asthenia,\*\* back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease

**Musculoskeletal System:** arthralgia, arthrosis, muscle cramps,\*\* myalgia

**Psychiatric:** sexual dysfunction (male\*\* and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization

**Respiratory System:** dyspnea, epistaxis

**Skin and Appendages:** angioedema, erythema multiforme, pruritus,\*\* rash,\*\* rash erythematous, rash maculopapular

\*\*These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

**Special Senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus

**Urinary System:** micturition frequency, micturition disorder, nocturia

**Autonomic Nervous System:** dry mouth, sweating increased

**Metabolic and Nutritional:** hyperglycemia, thirst

**Hemopoietic:** leukopenia, purpura, thrombocytopenia

Other events reported with amlodipine at a frequency of less than or equal to 0.1% of patients include: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia. Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

### HCTZ

Other adverse reactions not listed above that have been reported with HCTZ, without regard to causality, are listed below:

**Body as a Whole:** weakness

**Digestive:** pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation

**Hematologic:** aplastic anemia, agranulocytosis, hemolytic anemia

**Hypersensitivity:** photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions

**Musculoskeletal:** muscle spasm

**Nervous System/Psychiatric:** restlessness

**Renal:** renal failure, renal dysfunction, interstitial nephritis

**Skin:** erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis

**Special Senses:** transient blurred vision, xanthopsia

### **Clinical Laboratory Test Abnormalities**

Clinical laboratory findings for Amturnide in patients with hypertension not concomitantly treated with an ARB or ACEI were obtained in a controlled trial of Amturnide administered at the maximal dose of 300/10/25 mg compared to maximal doses of dual therapies, i.e., aliskiren/amlodipine 300/10 mg, aliskiren/HCTZ 300/25 mg and amlodipine/HCTZ 10/25 mg.

### **RBC Count, Hemoglobin, and Hematocrit**

Small mean changes from baseline were seen in RBC count, hemoglobin and hematocrit in patients treated with Amturnide. This effect is also seen with other agents acting on the renin angiotensin system. In aliskiren monotherapy trials, these decreases led to slight increases in rates of anemia compared to placebo (0.1% for any aliskiren use, 0.3% for aliskiren 600 mg daily, versus 0% for placebo). No patients discontinued Amturnide because of anemia.

### **Blood Urea Nitrogen (BUN)/Creatinine**

No patients with hypertension not concomitantly treated with an ARB or ACEI treated with Amturnide had elevations in BUN greater 40 mg/dL or creatinine greater 2.0 mg/dL.

### **Liver Function Tests**

Occasional elevations (greater than 150% from baseline) in ALT (SGPT) were observed in 2.7% of patients treated with Amturnide, compared with 1.7% to 2.7% in patients treated with the dual combinations. No patients were discontinued due to abnormal liver function tests.

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of either aliskiren, amlodipine or HCTZ. 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:

### *Aliskiren:*

*Hypersensitivity:* anaphylactic reactions and angioedema requiring airway management and hospitalization.

Peripheral edema, severe cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, urticaria, hepatic enzyme increase with clinical symptoms of hepatic dysfunction, pruritus, erythema, nausea, vomiting.

### *Amlodipine:*

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

### *Hydrochlorothiazide (HCTZ):*

Acute renal failure, renal disorder, aplastic anemia, erythema multiforme, pyrexia, muscle spasm, asthenia, acute angle-closure glaucoma, bone marrow failure, worsening of diabetes control, hypokalemia, blood lipids increased, hyponatremia, hypomagnesemia, hypercalcemia, hyperchloremic alkalosis, impotence, visual impairment.

Pathological changes in the parathyroid gland of patients with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcemia occurs, further diagnostic evaluation is necessary.

## 7 DRUG INTERACTIONS

No drug interaction studies have been conducted between Amturnide and other drugs. In a phase III sub-study, there was no clinically relevant change in the exposure of aliskiren, amlodipine, and HCTZ observed with Amturnide compared to the dual combinations of aliskiren and amlodipine, amlodipine and HCTZ, and aliskiren and HCTZ. Studies with the individual aliskiren, amlodipine, and HCTZ components are described below.

### *Aliskiren*

*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 on aliskiren and other agents that affect the RAAS [see *Warnings and Precautions (5.4, 5.6, 5.10)*].

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.

### Amlodipine

*Simvastatin*: Coadministration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

*CYP3A4 Inhibitors*: Coadministration with CYP3A4 inhibitors (moderate and strong) result in increased systemic exposure to amlodipine warranting dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is coadministered with CYP3A4 inhibitors to determine the need for dose adjustment.

*CYP3A4 Inducers*: No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Blood pressure should be monitored when amlodipine is coadministered with CYP3A4 inducers.

### HCTZ

When administered concurrently, the following drugs may interact with thiazide diuretics.

*Antidiabetic drugs (oral agents and insulin)*: Dosage adjustment of the antidiabetic drug may be required.

*Lithium*: Diuretic agents increase the risk of lithium toxicity. Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitoring of serum lithium levels is recommended during concomitant use.

*Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and COX-2 selective agents*: When Amturnide and NSAIDs are used concomitantly, observe the patient to determine if the desired effect of the diuretic is obtained.

*Ion-exchange Resins*: Staggering the dosage of HCTZ and resin (e.g., cholestyramine, colestipol) such that HCTZ is administered at least 4 hours before or 4 to 6 hours after the administration of resins would potentially minimize the interaction [see *Clinical Pharmacology (12.3)*].

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category D [See *Warnings and Precautions (5.1)*]

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 Amturnide as soon as possible. These adverse outcomes are usually associated with use of drugs in the second and third trimesters of pregnancy. 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. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

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. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Amturnide, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. 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 Amturnide for hypotension, oliguria, and hyperkalemia [see *Use in Specific Populations (8.4)*].

### Animal Data

No reproductive toxicity studies have been conducted with the combination of aliskiren, amlodipine besylate and HCTZ. However, these studies have been conducted for aliskiren, amlodipine besylate, and HCTZ alone.

### Aliskiren

In developmental toxicity studies, pregnant rats and rabbits received oral aliskiren hemifumarate during organogenesis at doses up to 20 and 7 times the maximum recommended human dose (MRHD) based on body surface area (mg/m<sup>2</sup>), 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/m<sup>2</sup>). Aliskiren was present in placentas, amniotic fluid and fetuses of pregnant rabbits.

### Amlodipine

No evidence of teratogenicity or embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold). Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

### HCTZ

When pregnant mice and rats were given HCTZ at doses up to 3000 and 1000 mg/kg/day, respectively (about 600 and 400 times the MRHD), during their respective periods of major organogenesis, there was no evidence of fetal harm.

Thiazides can cross the placenta, and concentrations reached in the umbilical vein approach those in the maternal plasma. HCTZ, like other diuretics, can cause placental hypoperfusion. It accumulates in the amniotic fluid, with reported concentrations up to 19 times higher than in umbilical vein plasma. Use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice or thrombocytopenia. Since they do not prevent or alter the course of EPH (Edema, Proteinuria, Hypertension) gestosis (pre eclampsia), these drugs should not be used to treat hypertension in pregnant women. The use of HCTZ for other indications (e.g., heart disease) in pregnancy should be avoided.

## **8.3 Nursing Mothers**

It is not known whether aliskiren or amlodipine is excreted in human milk, but thiazides are excreted in human milk. Both aliskiren and amlodipine are secreted in the milk of lactating rats. Because of the potential for serious adverse reactions in human milk-fed infants from Amturnide, a decision should be made whether to discontinue nursing or discontinue Amturnide, taking into account the importance of the drug to the mother.

## **8.4 Pediatric Use**

Safety and effectiveness of Amturnide in pediatric patients have not been established.

### Neonates with a history of in utero exposure to Amturnide

If oliguria or hypotension occurs, direct attention towards 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**

As individual components, exposure to aliskiren, amlodipine and HCTZ is increased in elderly patients, thus consider lower initial doses of Amturnide [see *Clinical Pharmacology (12.3)*].

In the short-term controlled clinical trial of Amturnide, 19% of patients treated with Amturnide were 65 years and 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 Hepatic Impairment**

Exposure to amlodipine is increased in patients with hepatic insufficiency, thus consider using lower doses of Amturnide [see *Clinical Pharmacology (12.3)*].

### Hydrochlorothiazide (HCTZ)

Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

## **8.7 Renal Impairment**

Exposure to HCTZ increases in patients with renal insufficiency, thus consider using lower doses of Amturnide [see *Clinical Pharmacology (12.3)*].

Safety and effectiveness of Amturnide in patients with severe renal impairment [creatinine clearance (CrCl) less than 30 mL/min] have not been established as these patients were excluded in clinical trials [see *Warnings and Precautions (5.6), Clinical Pharmacology (12.3) and Clinical Studies (14)*].

## 10 OVERDOSAGE

### Aliskiren

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

Aliskiren is poorly dialyzed. Therefore, hemodialysis is not adequate to treat aliskiren overexposure [see *Clinical Pharmacology (12.3)*].

### Amlodipine

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported. In humans, experience with intentional overdosage of amlodipine is limited.

Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 mg or more of amlodipine/kg or higher in dogs (11 or more times the MRHD on a mg/m<sup>2</sup> basis) caused a marked peripheral vasodilation and hypotension.

If massive overdose occurs, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. If hypotension occurs, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine), with attention to circulating volume and urine output. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. Administration of activated charcoal to healthy volunteers immediately or up to 2 hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption.

### HCTZ

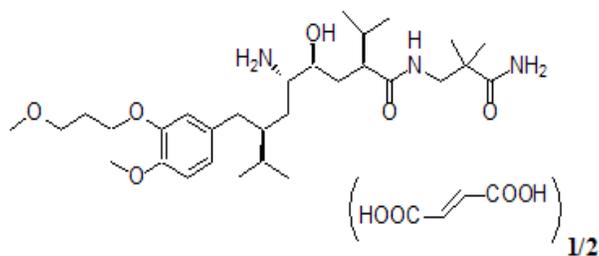
The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree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

## 11 DESCRIPTION

Amturnide is a single tablet for oral administration of aliskiren hemifumarate (an orally active, nonpeptide, potent direct renin inhibitor), amlodipine besylate (a dihydropyridine calcium channel blocker) and HCTZ (a thiazide diuretic).

### Aliskiren hemifumarate

Aliskiren hemifumarate is chemically described as (2S,4S,5S,7S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide hemifumarate, and its structural formula is:

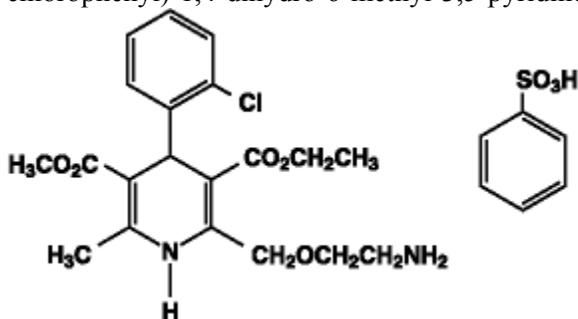


Molecular formula: C<sub>30</sub>H<sub>53</sub>N<sub>3</sub>O<sub>6</sub> • 0.5 C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>

Aliskiren hemifumarate is a white to slightly yellowish powder with a molecular weight of 609.8 (free base- 551.8). It is highly soluble in water, and freely soluble in methanol, ethanol and isopropanol.

### Amlodipine

Amlodipine besylate, USP is chemically described as 3-ethyl 5-methyl ( $\pm$ )-2-[(2-aminoethoxy)methyl]-4-(*o*-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulfonate and its structural formula is:



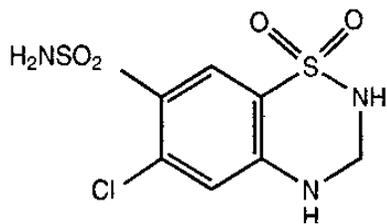
Molecular formula:  $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$

Amlodipine besylate is a white to pale yellow crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol.

### HCTZ

HCTZ, USP is a white, or practically white, practically odorless, crystalline powder. It is slightly soluble in water; freely soluble in sodium hydroxide solution, in *n*-butylamine, and in dimethylformamide; sparingly soluble in methanol; and insoluble in ether, in chloroform, and in dilute mineral acids. HCTZ is chemically described as 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

HCTZ is a thiazide diuretic. Its empirical formula is  $C_7H_8ClN_3O_4S_2$ , its molecular weight is 297.73, and its structural formula is:



The inactive ingredients for all strengths of the tablets may contain colloidal silicon dioxide, crospovidone, hypromellose, iron oxide red, iron oxide yellow, iron oxide black, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

#### Amturnide

The effects of combined treatment of aliskiren, amlodipine and HCTZ arise from the actions of these 3 agents on different but complementary mechanisms that regulate blood pressure. Together, inhibition of the RAAS, inhibition of calcium channel-mediated vasoconstriction, and increase of sodium chloride excretion lowers blood pressure to a greater degree than the individual components.

#### Aliskiren

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 presynaptic 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.

### Amlodipine

Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

### HCTZ

The mechanism of action of the antihypertensive effect of thiazides is unknown.

HCTZ is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of HCTZ reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of agents that block the production or function of angiotensin II tends to reverse the potassium loss associated with these diuretics.

## **12.2 Pharmacodynamics**

### Amturide

In an active-controlled trial which established the clinical efficacy of Amturide in hypertensive patients, Amturide was associated with a 34% reduction in PRA compared to a 63% reduction with aliskiren/amlodipine, 64% reduction with aliskiren/HCTZ and a 170% elevation with amlodipine/HCTZ.

### Aliskiren

PRA reductions in clinical trials ranged from approximately 50% to 80%, were not dose-related and did not correlate with blood pressure reductions. The clinical implications of the differences in effect on PRA are not known.

### Amlodipine

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once-daily administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105 mmHg to 114 mmHg) had about 50% greater response than patients with mild hypertension (diastolic pressure 90 mmHg to 104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressure (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in therapeutic dose range to intact animals and man, even when coadministered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects of electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

Amlodipine has indications other than hypertension, which can be found in the Norvasc<sup>®</sup> package insert.

### HCTZ

After oral administration of HCTZ, diuresis begins within 2 hours, peaks in about 4 hours, and lasts about 6 to 12 hours.

#### Drug Interactions

##### Hydrochlorothiazide (HCTZ)

*Alcohol, barbiturates, or narcotics:* Potentiation of orthostatic hypotension may occur.

*Skeletal muscle relaxants:* Possible increased responsiveness to muscle relaxants such as curare derivatives.

*Digitalis glycosides:* Thiazide-induced hypokalemia or hypomagnesemia may predispose the patient to digoxin toxicity.

## **12.3 Pharmacokinetics**

### Absorption and Distribution

#### Amturnide

Following oral administration of the fixed combination of aliskiren, amlodipine, and HCTZ, peak concentrations were achieved within 1 to 2 hours, 6 to 12 hours, and 1 to 4 hours for aliskiren, amlodipine and HCTZ, respectively. The rate and extent of absorption of aliskiren, amlodipine, and HCTZ following administration of the fixed combination are similar to when they are administered as individual dosage forms.

When Amturnide is taken with food, mean AUC and C<sub>max</sub> of aliskiren are decreased by 78% and 89%, respectively. There is no impact of food on the exposures of amlodipine and HCTZ.

#### Aliskiren

Aliskiren is poorly absorbed (bioavailability about 2.5%). 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<sub>max</sub> 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.

#### Amlodipine

Peak plasma concentrations of amlodipine are reached 6 to 12 hours after an oral administration of amlodipine. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of amlodipine is not altered by the presence of food.

The apparent volume of distribution of amlodipine is about 21 L/kg. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

### HCTZ

The estimated absolute bioavailability of HCTZ after oral administration is about 70%. Peak plasma HCTZ concentrations ( $C_{max}$ ) are reached within 2 to 5 hours after oral administration. There is no clinically significant effect of food on the bioavailability of HCTZ.

HCTZ binds to albumin (40% to 70%) and distributes into erythrocytes. Following oral administration, plasma hydrochlorothiazide concentrations decline bi-exponentially, with a mean distribution half-life of about 2 hours and an elimination half-life of about 10 hours.

### **Metabolism and Elimination**

#### **Aliskiren**

The effective half-life for aliskiren is 24 hours. Steady state blood levels are reached in about 7 to 8 days. 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/1b) was found to be the major efflux system involved in absorption and disposition 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.

#### **Amlodipine**

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism, with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Elimination of amlodipine from the plasma is biphasic, with a terminal elimination half-life of about 30 to 50 hours. Steady state plasma levels are reached after once-daily dosing for 7 to 8 days.

#### **HCTZ**

About 70% of an orally administered dose of HCTZ is eliminated in the urine as unchanged drug.

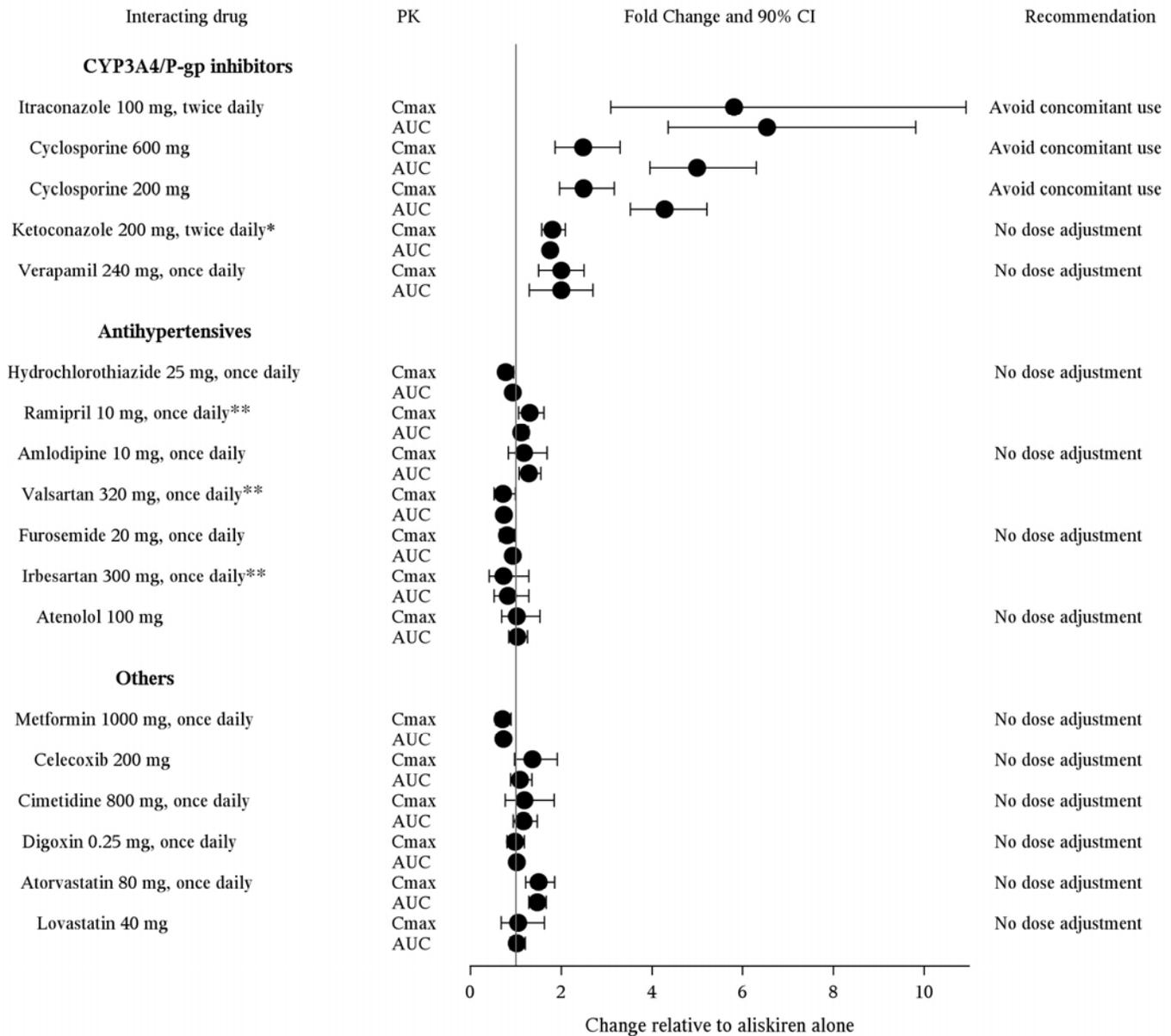
### **Drug Interactions**

#### **Aliskiren**

The effects 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**

Impact of co-administered drugs on the pharmacokinetics (PK) of aliskiren

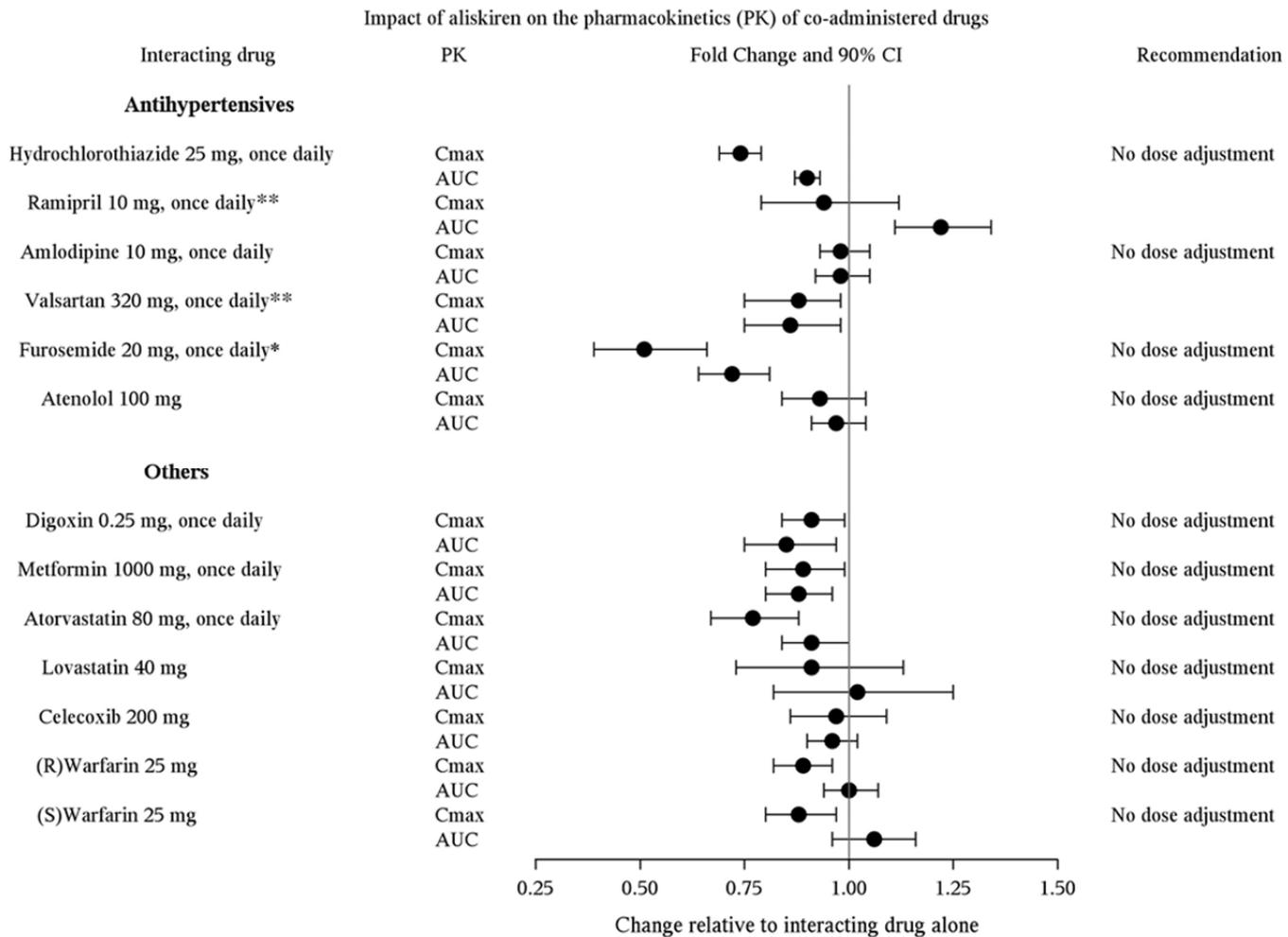


\*Ketoconazole: A 400 mg once daily dose was not studied, but would be expected to increase aliskiren blood levels further.

\*\*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<sub>max</sub> 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)].

### Amlodipine

In vitro data in human plasma indicate that amlodipine has no effect on the protein binding of digoxin, phenytoin, warfarin, and indomethacin.

*Cimetidine*: Coadministration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

*Grapefruit juice*: Coadministration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

*Maalox*<sup>®</sup> (antacid): Coadministration of the antacid Maalox with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

*Sildenafil*: A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

*Atorvastatin:* Coadministration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.

*Digoxin:* Coadministration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

*Ethanol (alcohol):* Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

*Warfarin:* Coadministration of amlodipine with warfarin did not change the warfarin prothrombin response time.

*Simvastatin:* Coadministration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone.

*CYP3A inhibitors:* Coadministration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin coadministration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent.

### Hydrochlorothiazide (HCTZ)

*Drugs that alter gastrointestinal motility:* The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, pro-kinetic drugs may decrease the bioavailability of thiazide diuretics.

*Cholestyramine:* In a dedicated drug interaction study, administration of cholestyramine 2 hours before HCTZ resulted in a 70% reduction in exposure to HCTZ. Further, administration of HCTZ 2 hours before cholestyramine, resulted in 35% reduction in exposure to hydrochlorothiazide.

*Antineoplastic agents (e.g., cyclophosphamide, methotrexate):* Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.

### Special Populations

#### Pediatric Patients

The pharmacokinetics of Amlodipine have not been investigated in patients younger than 18 years of age.

#### Geriatric Patients

Impact of aging on aliskiren pharmacokinetics has been assessed. When compared to young adults (18 to 40 years), aliskiren mean AUC and  $C_{max}$  in elderly subjects (65 years and older) are increased by 57% and 28%, respectively. In the elderly, clearance of amlodipine is decreased with resulting increases in peak plasma levels, elimination half-life and area-under-the-plasma-concentration curve. Limited data suggest that the systemic clearance of HCTZ is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers [see *Use in Specific Populations (8.5)*].

#### Race

With Amlodipine, pharmacokinetic differences due to race have not been studied. The pharmacokinetic differences among blacks, Caucasians, and Japanese are minimal with aliskiren therapy.

#### Hepatic Impairment

The pharmacokinetics of aliskiren is not significantly affected in patients with mild-to-severe liver disease. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40% to 60% [see *Warnings and Precautions (5.6) and Use in Specific Populations (8.6)*].

#### Renal Impairment

The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal impairment. 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.

The pharmacokinetics of aliskiren following administration of a single oral dose of 300 mg was evaluated in 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.

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment.

In a study in individuals with impaired renal function, the mean elimination half-life of HCTZ was doubled in individuals with mild/moderate renal impairment ( $30 < \text{CrCl} < 90 \text{ mL/min}$ ) and tripled in severe renal impairment ( $\text{CrCl}$  less than or equal to  $30 \text{ mL/min}$ ), compared to individuals with normal renal function ( $\text{CrCl}$  greater than  $90 \text{ mL/min}$ ) [see *Warnings and Precautions* (5.7) and *Use in Specific Populations* (8.7)].

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Studies with Aliskiren hemifumarate, Amlodipine besylate and HCTZ

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

#### Studies with Aliskiren hemifumarate

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  $1500 \text{ mg aliskiren/kg/day}$ . 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  $750$  or more  $\text{mg/kg/day}$  in both species, with a colonic adenoma identified in one rat and a cecal adenocarcinoma identified in another, rare tumors in the strain of rat studied. On a systemic exposure ( $\text{AUC}_{0-24\text{h}}$ ) basis,  $1500 \text{ mg/kg/day}$  in the rat was about 4 times and in the mouse about 1.5 times the MRHD ( $300 \text{ mg aliskiren/day}$ ). Mucosal hyperplasia in the cecum or colon of rats was also observed at doses of  $250 \text{ mg/kg/day}$  (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 rat bone marrow micronucleus assay.

Fertility of male and female rats was unaffected at doses of up to aliskiren  $250 \text{ mg/kg/day}$  (8 times the MRHD of aliskiren  $300 \text{ mg/60 kg}$  on a  $\text{mg/m}^2$  basis).

#### Studies with Amlodipine besylate

Rats and mice treated with amlodipine maleate in the diet for up to 2 years, at concentrations calculated to provide daily dosage levels of  $0.5$ ,  $1.25$ , and  $2.5 \text{ mg amlodipine/kg/day}$ , showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on  $\text{mg/m}^2$  basis, similar to the MRHD of  $10 \text{ mg amlodipine/day}$ . For the rat, the highest dose was, on a  $\text{mg/m}^2$  basis, about twice the MRHD.

Mutagenicity studies conducted with amlodipine maleate revealed no drug-related effects at either the gene or chromosome level.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to  $10 \text{ mg amlodipine/kg/day}$  (about 8 times the MRHD of  $10 \text{ mg/day}$  on a  $\text{mg/m}^2$  basis).

#### Studies with HCTZ

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of HCTZ in female mice (at doses of up to approximately  $600 \text{ mg/kg/day}$ ) or in male and female rats (at doses of up to approximately  $100 \text{ mg/kg/day}$ ). These doses in mice and rats are about 117 and 39 times, respectively, the MRHD of  $25 \text{ mg/day}$ , when based on a  $\text{mg/m}^2$  basis of a  $60 \text{ kg}$  individual. The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

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

HCTZ was not teratogenic and had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation. These doses of HCTZ in mice and rats represent 19 and 1.5 times, respectively, the MRHD on a mg/m<sup>2</sup> basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.)

## 13.2 Animal Toxicology and/or Pharmacology

### Reproductive Toxicology Studies

[See Use in Specific Populations (8.1).]

## 14 CLINICAL STUDIES

### 14.1 Amturnide

Amturnide was studied in a double-blind, active-controlled study in 1181 treated hypertensive patients, of whom 773 were classified as moderately hypertensive (SBP 160 to 180 mmHg) and 408 as severely hypertensive (SBP 180 to 200 mmHg) at baseline. The mean baseline systolic/diastolic blood pressure for all randomized patients was approximately 173/105 mmHg. A total of 61% of patients were male, 19% were 65 years or older, 84% were Caucasian, and 10% were black.

At study initiation, patients assigned to the dual combination treatments received lower doses of their treatment combination (aliskiren 150 mg plus amlodipine 5 mg, aliskiren 150 mg plus HCTZ 12.5 mg, or amlodipine 5 mg plus HCTZ 12.5 mg), while patients assigned to the Amturnide arm received aliskiren/HCTZ 150/12.5 mg. After 3 days, Amturnide patients were titrated to aliskiren/amlodipine/HCTZ 150/5/12.5 mg, while all other patients continued receiving their initial doses. After 4 weeks, all patients were titrated to their full target doses of aliskiren/amlodipine/HCTZ 300/10/25 mg, aliskiren/amlodipine 300/10, aliskiren/HCTZ 300/25 mg, or amlodipine/HCTZ 10/25 mg.

Amturnide produced greater reductions in blood pressure than did any of the 3 dual combination treatments (p value less than 0.001 for both diastolic and systolic blood pressure reductions). The reductions in systolic/diastolic blood pressure with Amturnide were 9.9/6.3 mmHg greater than with aliskiren/HCTZ, 7.2/3.6 mmHg greater than with amlodipine/HCTZ, and 6.6/2.6 mmHg greater than with aliskiren/amlodipine.

In the severe hypertensive patients, Amturnide produced greater reductions in blood pressure than each of the 3 dual combination treatments (p value less than 0.001 for both diastolic and systolic blood pressure reductions). The reductions in systolic/diastolic blood pressure with Amturnide were 16.3/8.2 mmHg greater than with aliskiren/HCTZ, 9.6/4.8 mmHg greater than with amlodipine/HCTZ, and 11.4/4.9 mmHg greater than with aliskiren/amlodipine.

The distribution of reductions in blood pressure on each treatment are shown in Figure 3 for diastolic blood pressure and in Figure 4 for systolic blood pressure. For example, Figure 3 shows that 50% of patients on Amturnide had more than 20.2 mmHg reduction in diastolic blood pressure compared to 18.7 mmHg on aliskiren/amlodipine combination, 12.7 mmHg on aliskiren/HCTZ combination, and 15.3 mmHg on amlodipine/HCTZ combination. Similarly, Figure 4 shows that 50% of patients on Amturnide had more than 36.3 mmHg reduction in systolic blood pressure compared to 30.8 mmHg on aliskiren/amlodipine combination, 28.3 mmHg on aliskiren/HCTZ combination, and 31.0 mmHg on amlodipine/HCTZ combination. The time course over which blood pressure effects developed is shown in Figures 5 and 6. As the trial had no placebo control, the treatment effects shown in Figures 3–6 include a placebo effect of unknown size.

The antihypertensive effect of Amturnide was similar in patients with and without diabetes, obese and non-obese patients, in patients 65 years of age and older and less than 65 years of age, and in women and men.

Figure 3. Distribution of Diastolic Blood Pressure Responses on Amluride and Combinations of Two Drugs

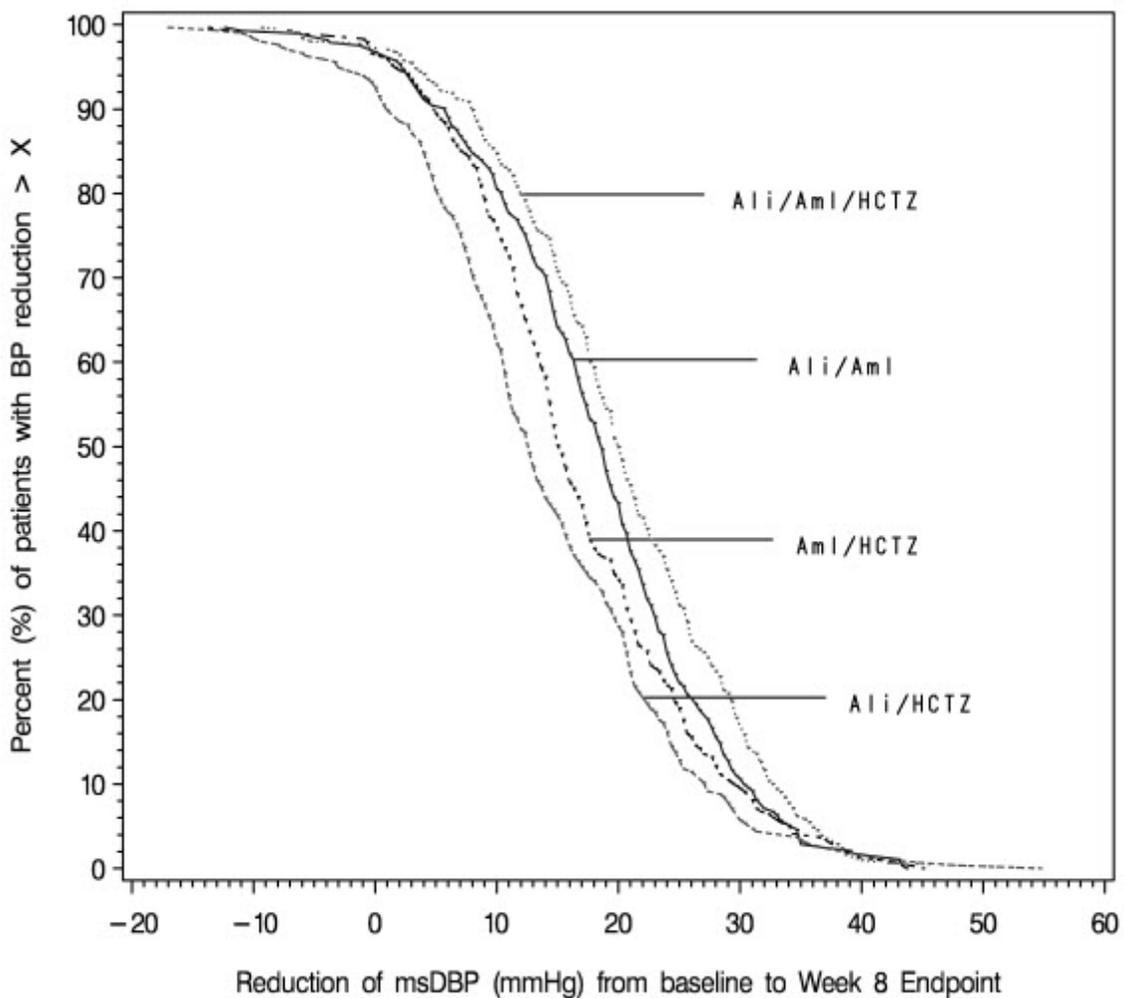
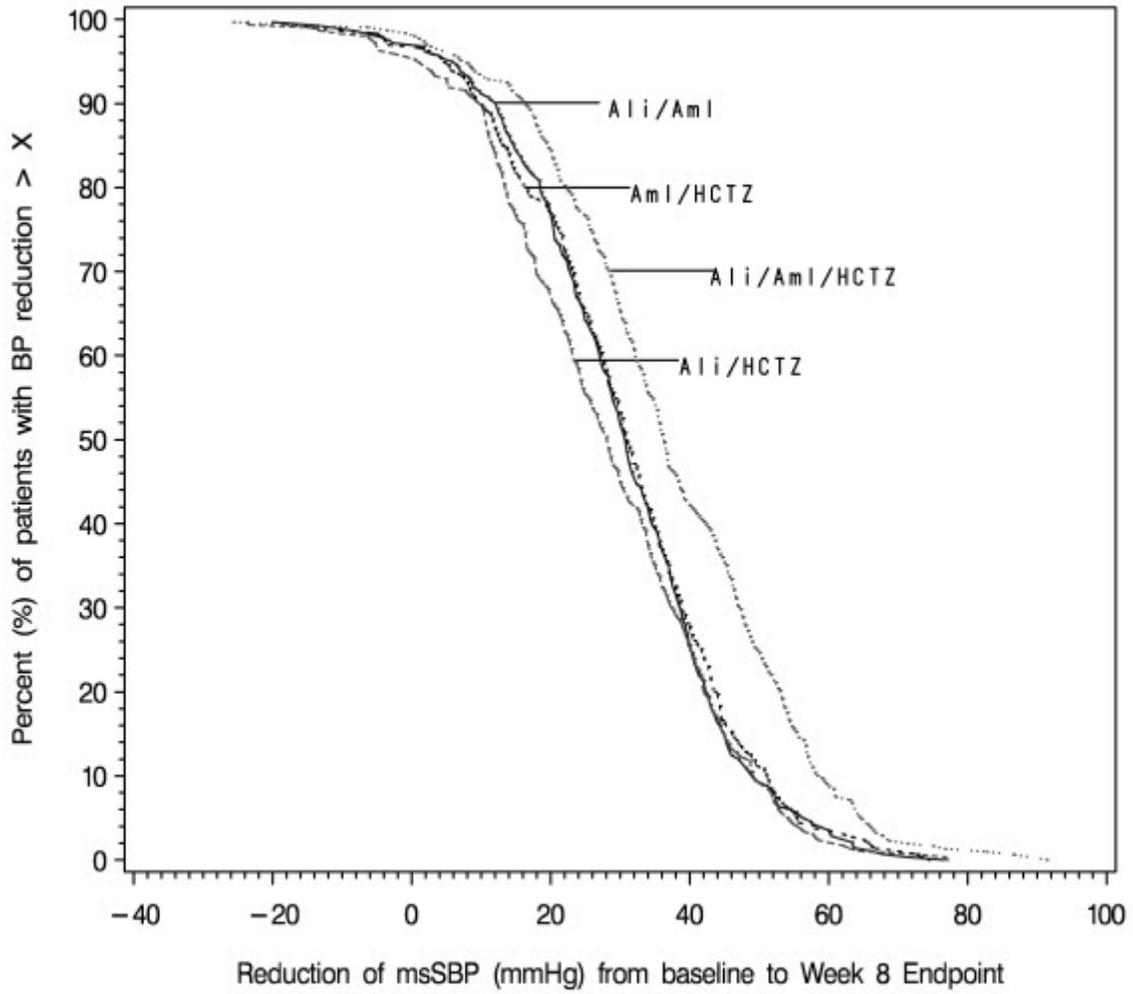
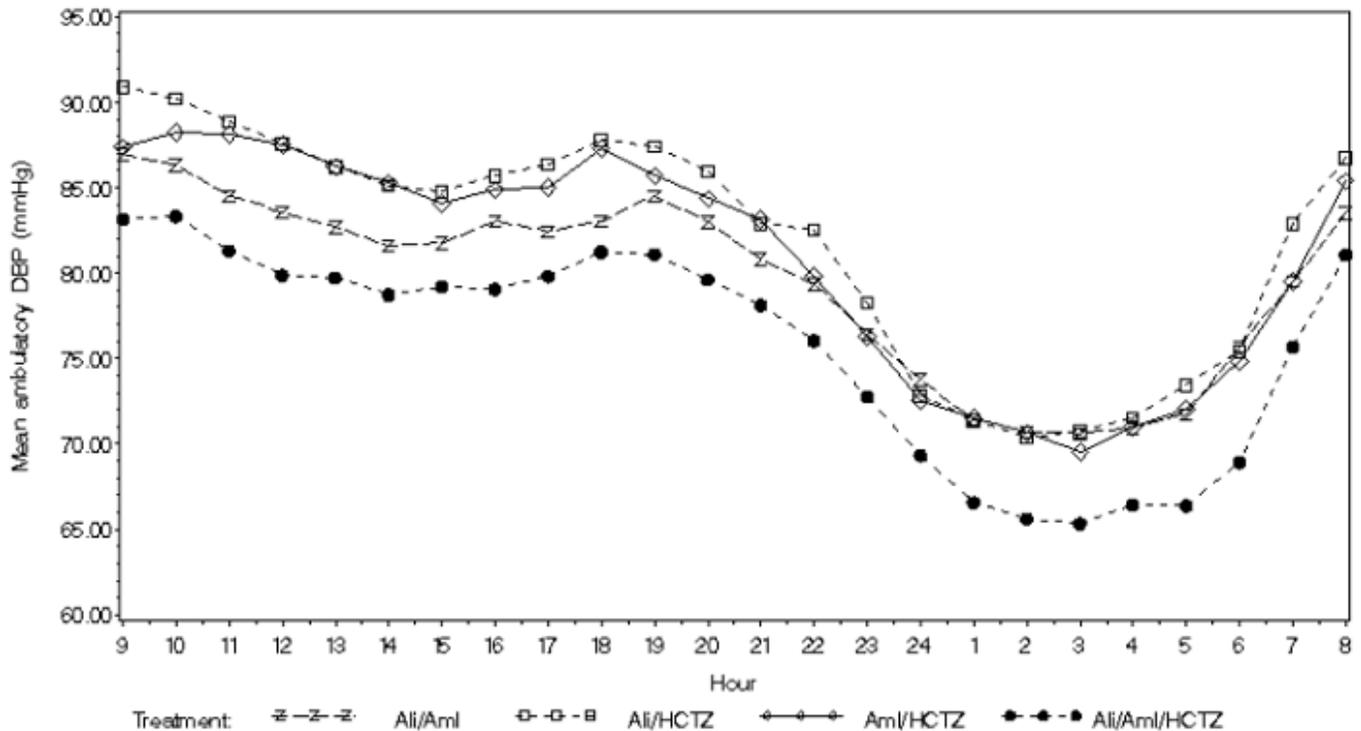


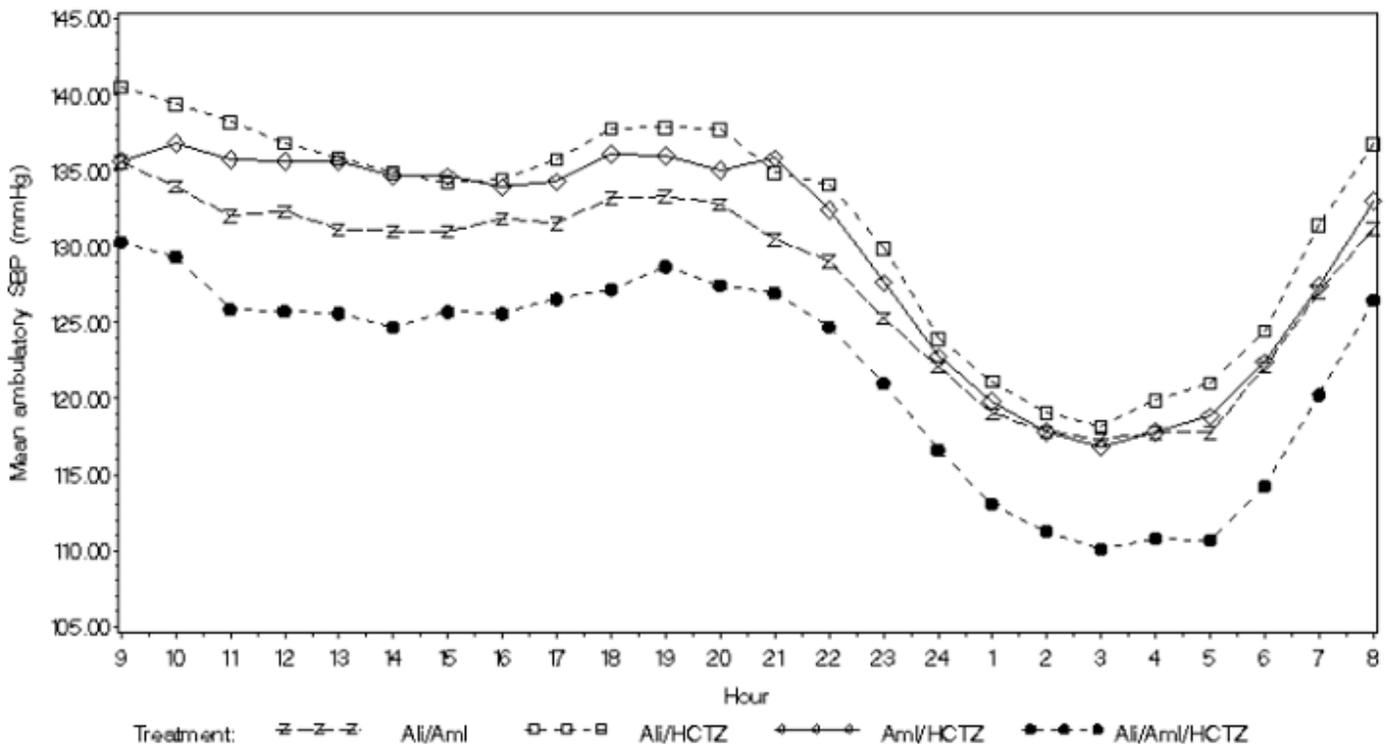
Figure 4. Distribution of Systolic Blood Pressure Responses on Amluride and Combinations of Two Drugs



**Figure 5. Mean Ambulatory Diastolic Blood Pressure at Endpoint by Treatment and Clock Hour**



**Figure 6. Mean Ambulatory Systolic Blood Pressure at Endpoint by Treatment and Clock Hour**



There are no trials of the Amlturnide triple combination tablet demonstrating reductions in cardiovascular risk in patients with hypertension, but 2 of the components, amlodipine and HCTZ, have demonstrated such benefits.

**14.2 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 2.

**Table 2: 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 (%)
<b>Renal impairment</b> †	5.7	14.5	4.3	12.4
<b>Hypotension</b> ††	2.3	19.9	1.9	16.3
<b>Hyperkalemia</b> †††	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.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Tablets are convex ovaloid with a beveled edge, film-coated, and unscored, in the following strengths and packages:

Aliskiren/Amlodipine/HCTZ (mg)	Color	Embossing Side 1/side 2	NDC 0078-XXXX-XX		
			Bottle/30	Bottle/90	Blister/100
150/5/12.5	Violet white	YIY/NVR	0610-15	0610-34	0610-35
300/5/12.5	Light pink	LIL/NVR	0611-15	0611-34	0611-35
300/5/25	Pale orange brown	OIO/NVR	0612-15	0612-34	0612-35
300/10/12.5	Light red	UIU/NVR	0613-15	0613-34	0613-35
300/10/25	Brown	VIV/NVR	0614-15	0614-34	0614-35

### Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) in original container.

Protect from heat and moisture.

Dispense in original container.

## 17 PATIENT COUNSELING INFORMATION

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

### Pregnancy

Advise female patients of childbearing age about the consequences of exposure to Amturnide during pregnancy. Discuss treatment options with women planning to become pregnant. Advise patients to report pregnancies to their physicians as soon as possible.

### **Symptomatic Hypotension**

Caution patients receiving Amturnide that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. Tell patients that if syncope occurs, discontinue Amturnide until the physician has been consulted.

Caution all 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.

### **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 physician. Angioedema, including laryngeal edema, may occur at any time during treatment with Amturnide.

### **Potassium Supplements**

Tell patients receiving Amturnide 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 Amturnide either with or without a meal. High-fat meals decrease absorption substantially.

T201X-XX  
March 2015

## Patient Information

### Amturnide™ (AM-turn-ide)

#### (aliskiren, amlodipine and hydrochlorothiazide) Tablets

Read the Patient Information leaflet that comes with Amturnide before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition and treatment. If you have any questions about Amturnide, ask your doctor or pharmacist.

#### **What is the most important information I should know about Amturnide?**

**Amturnide can cause harm or death to an unborn baby. Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant. If you get pregnant while taking Amturnide, tell your doctor right away.**

#### **What is Amturnide?**

Amturnide is a prescription medicine used to lower blood pressure (hypertension). Amturnide is not for use as the first medicine to treat your high blood pressure.

Amturnide contains 3 different prescription medicines:

- aliskiren, a direct renin inhibitor (DRI)
- amlodipine, a calcium channel blocker (CCB) and
- hydrochlorothiazide (HCTZ), a diuretic (water pill)

It is not known if Amturnide is safe and works in children under 18 years of age.

#### **What is high blood pressure (hypertension)?**

Blood pressure is the force of blood in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too much.

High blood pressure makes the heart work harder to pump blood through the body and causes damage to blood vessels. Amturnide can help your blood vessels relax so your blood pressure is lower. Medicines that lower your blood pressure may lower your chance of having a stroke or heart attack.

#### **Who should not take Amturnide?**

Do not take Amturnide if you:

- get pregnant. Stop taking Amturnide and call your doctor right away. If you plan to become pregnant, talk to your doctor about other treatment options for your high blood pressure.
- have diabetes and are taking a kind of medicine called an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI).
- have low or no urine output
- are allergic to aliskiren, hydrochlorothiazide, amlodipine or other medicines that contain sulfonamide. See the end of this leaflet for a complete list of ingredients in Amturnide.

#### **What should I tell my doctor before taking Amturnide?**

**Before taking Amturnide, tell your doctor if you:**

- have a kidney problem

- have liver problems
- have signs of systemic lupus erythematosus (SLE). Amturnide can make your SLE active or worse.
- have ever had an allergic reaction to another blood pressure medicine. Symptoms may include: swelling of the face, lips, tongue, throat, arms and legs, and trouble breathing (angioedema).
- suffer from heart disorders or if you experienced a heart attack
- have any other medical problems
- are pregnant or planning to become pregnant. **See “What is the most important information I should know about Amturnide?”**
- are breastfeeding. It is not known if Amturnide passes into your breast milk and if it can harm your baby. You and your doctor should decide if you will take Amturnide or breastfeed. You should not do both.

**Tell your doctor about all the medicines you take** including prescription and nonprescription medicines, vitamins and herbal supplements. Amturnide and certain other medicines may affect each other and cause side effects.

**Especially tell your doctor if you are taking:**

- a kind of medicine to control blood pressure called angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI)
- medicines used to lower blood pressure, water pills (also called “diuretics”), especially potassium-sparing diuretics
- medicines for treating fungus or fungal infections (like itraconazole or ketoconazole)
- cyclosporine (Gengraf<sup>®</sup>, Neoral, Sandimmune), a medicine used to suppress the immune system
- potassium-containing medicines, potassium supplements, or salt substitutes containing potassium
- cholesterol lowering medicines
  - simvastatin (Zocor<sup>®</sup>) or atorvastatin (Lipitor<sup>®</sup>)
  - cholestyramine (Questran, Questran Light, Cholestyramine Light, Locholest Light, Locholest, Prevalite)
  - colestipol (Colestipol hydrochloride, Colestid, Flavored Colestid)
- medicines used to treat diabetes, including insulin
- lithium, a medicine used to treat some types of depression.
- nonsteroidal anti-inflammatory drugs (NSAIDs) (like ibuprofen or naproxen), including selective Cyclooxygenase-2 inhibitors (COX-2 inhibitors). Ask your doctor if you are not sure if you are taking one of these medicines.
- medicines used to treat AIDS or HIV infections (such as ritonavir, indinavir)

Ask your doctor if you are not sure whether you are taking one of the medicines listed above.

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine. Your doctor or pharmacist will know what medicines are safe to take together.

**How should I take Amturnide?**

- Take Amluride exactly as prescribed by your doctor. It is important to take Amluride every day to control your blood pressure.
- Take Amluride 1 time a day, at about the same time each day.
- Take Amluride the same way every day, either with or without a meal.
- Your doctor may change your dose of Amluride if needed. Do not change the amount of Amluride you take without talking to your doctor.
- If you miss a dose of Amluride, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Just take the next dose at your regular time.
- If you take too much Amluride, call your doctor or a Poison Control Center, or go to the nearest hospital emergency room.

### **What should I avoid while taking Amluride?**

**Drinking alcohol.** Drinking alcohol during treatment with Amluride can cause you to have low blood pressure. **See “What are the possible side effects of Amluride?”**

### **What are the possible side effects of Amluride?**

Amluride may cause serious side effects, including:

- **Harm to an unborn baby causing injury or death.** See “What is the most important information I should know about Amluride?”
- **Severe Allergic Reactions and Angioedema (hypersensitivity).** Aliskiren, one of the medicines in Amluride, can cause difficulty breathing or swallowing, tightness of the chest, hives, general rash, swelling, itching, dizziness, vomiting, or abdominal pain (signs of a severe allergic reaction called anaphylactic reaction). Aliskiren can also cause swelling of your face, lips, tongue, throat, arms and legs, or the whole body (signs of angioedema). Stop taking Amluride and get medical help right away. Tell your doctor if you get any one or more of these symptoms. Serious allergic reactions can happen at any time while you are taking Amluride.
- **Low blood pressure (hypotension).** Your blood pressure may get too low if you also take water pills, are on a low-salt diet, get dialysis treatments, have heart problems, or get sick with vomiting or diarrhea. Drinking alcohol and taking certain medicines (barbiturates or narcotics) can cause low blood pressure to get worse. Lie down if you feel faint or dizzy, and call your doctor right away.
- **Worsening chest pain or heart attack.** When you first start taking Amluride or increase your dose, you may have a heart attack or your angina may get worse. If that happens, call your doctor right away or go directly to the nearest hospital emergency room.
- **Allergic reactions:** Hydrochlorothiazide, one of the medicines in Amluride, can cause allergic reactions.
- **Active or Worsened Systemic Lupus Erythematosus (SLE).** One of the medicines in Amluride may cause your lupus to become active or get worse. Tell your doctor if your lupus gets worse or becomes active while taking Amluride.
- **Amluride may affect your potassium levels.** Your doctor will do blood tests to check your potassium levels.
- **Eye problems.** One of the medicines in Amluride can cause eye problems that may lead to vision loss. Symptoms of eye problems can happen within hours to weeks of starting Amluride. Tell your doctor right away if you have:
  - decrease in vision

- o eye pain

- **Renal impairment or failure.** Aliskiren, one of the medicines in Amturnide, may cause renal disorder with symptoms such as severely decreased urine output or decreased urine output (signs of renal impairment or failure).

**The most common side effects of Amturnide include:**

- swelling of your ankles, feet, and hands
- dizziness
- headache
- stuffy or runny nose and sore throat

**Common side effects of Amturnide include:**

- diarrhea
- cough
- tiredness
- high levels of potassium in the blood (hyperkalemia)

Less common side effects include rash, severe skin reactions (signs may include severe blistering of the lips, eyes or mouth, rash with fever and skin peeling) and liver disorder (signs may include nausea, loss of appetite, dark colored urine or yellowing of skin and eyes), stomach pain, nausea, flushing (hot or warm feeling in your face), arrhythmia (irregular heartbeat), heart palpitations (very fast heartbeat)

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of Amturnide. For more information ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How do I store Amturnide?**

- Store Amturnide tablets at room temperature between 59°F to 86°F (15°C to 30°C).
- Keep Amturnide in the original container.
- Protect Amturnide from heat and moisture.

**Keep Amturnide and all medicines out of the reach of children.**

**General information about Amturnide.**

Medicines are sometimes prescribed for conditions not listed in the patient information leaflet. Do not take Amturnide for a condition for which it was not prescribed. Do not give Amturnide to other people, even if they have the same condition or symptoms you have. It may harm them.

This leaflet summarizes the most important information about Amturnide. If you have questions about Amturnide, talk with your doctor or pharmacist. You can ask your doctor or pharmacist for information that is written for healthcare professionals.

**For more information about Amturnide, visit [www.Amturnide.com](http://www.Amturnide.com), or call 1-888-NOW-NOVA (1-888-669-6682).**

**What are the ingredients in Amturnide?**

Active ingredients: aliskiren hemifumarate, amlodipine besylate, and hydrochlorothiazide.

Inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, iron oxide red, iron oxide yellow, iron oxide black, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide.

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