

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Tekamlo (aliskiren and amlodipine) 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 Tekamlo 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

Contraindications: Concomitant use with ARBs or ACEIs in diabetes (4)	03/2012
Boxed Warning: Fetal Toxicity	02/2012
Warnings and Precautions: Fetal Toxicity (5.1)	02/2012
Warnings and Precautions (5.2, 5.4, 5.6, 5.10)	03/2012

INDICATIONS AND USAGE

Tekamlo is a combination of aliskiren, a renin inhibitor, and amlodipine, a dihydropyridine calcium channel blocker, indicated for the treatment of hypertension, to lower blood pressure:

- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals. (1)
- In patients not adequately controlled with monotherapy. (1)
- As a substitute for its titrated components. (1)

Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

DOSAGE AND ADMINISTRATION

- Add-on therapy or initial therapy: Initiate with 150 mg/5 mg. Titrate as needed up to a maximum of 300 mg/10 mg. (2.1, 2.3, 2.5)
- The blood pressure lowering effect is largely attained within 1-2 weeks. (2.2)
- Replacement therapy: may substitute for titrated components. (2.4)
- Administer one tablet daily with a routine pattern with regard to meals. (2.7)
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DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

Do not use with angiotensin receptor blockers (ARBs) or ACE inhibitors (ACEI) in patients with diabetes (4)

WARNINGS AND PRECAUTIONS

- Avoid concomitant use with ARBs or ACEI in patients with renal impairment (GFR < 60 mL/min) (5.2)
- Head and neck angioedema: Discontinue Tekamlo and monitor until signs and symptoms resolve. (5.3)
- Hypotension in volume- and/or salt-depleted patients: Correct imbalances before initiating therapy with Tekamlo. (5.4)
- Increased angina or myocardial infarction with calcium channel blockers may occur upon dosage initiation or increase. (5.5)
- Impaired renal function: Monitor serum creatinine periodically. (5.6)
- Patients with hepatic impairment: Titrate slowly. (5.7)
- Patients with heart failure: Titrate slowly. (5.8)
- Hyperkalemia: Monitor potassium levels periodically. (5.10)

ADVERSE REACTIONS

The most common adverse event (incidence $\geq 2\%$ and more common than with placebo) is peripheral edema. (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.

DRUG INTERACTIONS

- Cyclosporine: Avoid concomitant use (7, 12.3)
- Itraconazole: Avoid concomitant use (7, 12.3)
- NSAIDs use may lead to increased risk of renal impairment and loss of antihypertensive effect (7)
- If simvastatin is co-administered with amlodipine, do not exceed doses greater than 20 mg daily of simvastatin (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: 03/2012

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FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue Tekamlo 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

Tekamlo is indicated for the treatment of hypertension, alone or with other antihypertensive agents, 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. There are no controlled trials demonstrating risk reduction with Tekamlo.

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 one 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 also have 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 (for example, 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.

Initial Therapy

Use Tekamlo as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

Base the choice of Tekamlo as initial therapy on an assessment of potential benefits and risks.

Add-On Therapy

Switch a patient whose blood pressure is not adequately controlled with aliskiren alone or amlodipine besylate (or another dihydropyridine calcium channel blocker) to combination therapy with Tekamlo.

Replacement Therapy

Tekamlo may be substituted for its titrated components.

Patients with moderate or severe hypertension are at a relatively high risk for cardiovascular events (such as strokes, heart attacks, and heart failure), kidney failure, and vision problems, so prompt treatment is clinically relevant. Individualize the decision to use a combination as initial therapy by weighing factors such as baseline

blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination compared to monotherapy. Individual blood pressure goals may vary based upon the patient's risk.

Data from the high-dose multifactorial study [see *Clinical Studies (14)*] provide estimates of the probability of reaching a target blood pressure with Tekamlo compared to aliskiren or amlodipine monotherapy. The figures below provide estimates of the likelihood of achieving systolic or diastolic blood pressure control with Tekamlo 300 mg/10 mg, based upon baseline systolic or diastolic blood pressure. The curve of each treatment group was estimated by logistic regression modeling. The estimated likelihood at the right tail of each curve is less reliable because of a small number of subjects with high baseline blood pressures.

Figure 1: Probability of Achieving Systolic Blood Pressure (SBP) <140 mmHg

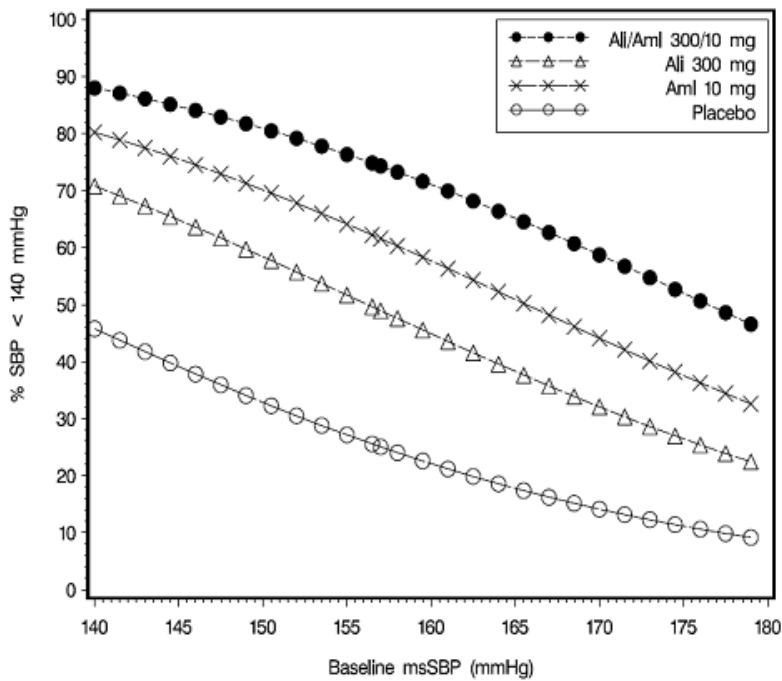


Figure 2: Probability of Achieving Diastolic Blood Pressure (DBP) <90 mmHg

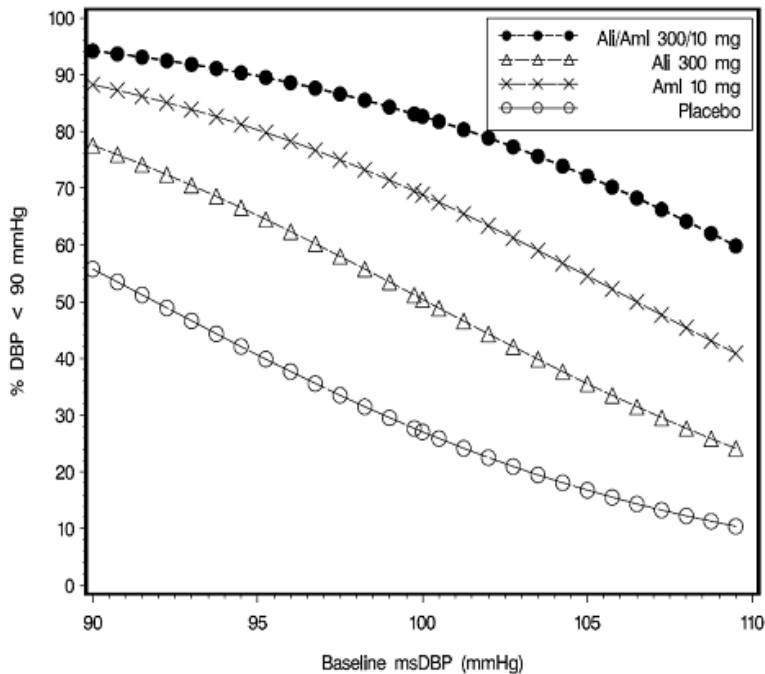


Figure 3: Probability of Achieving Systolic Blood Pressure (SBP) <130 mmHg

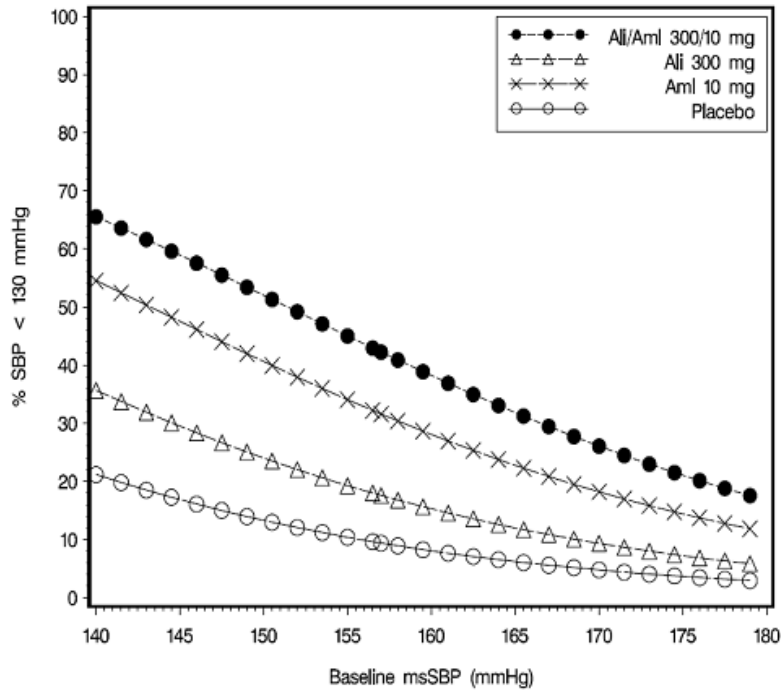
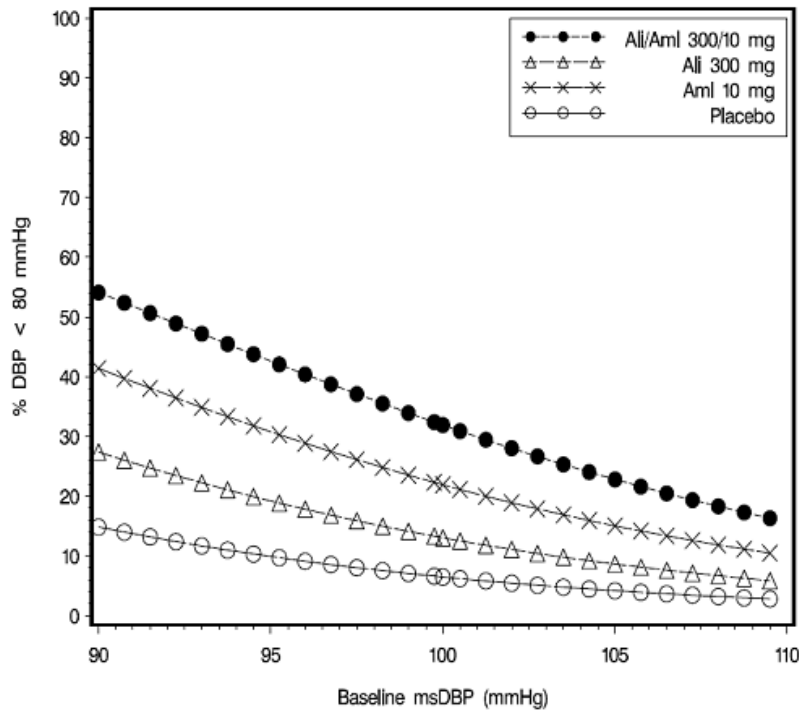


Figure 4: Probability of Achieving Diastolic Blood Pressure (DBP) <80 mmHg



The figures above provide an approximation of the likelihood of reaching a targeted blood pressure goal (e.g. SBP<140 mmHg or <130 mmHg) for the high dose groups evaluated in the study. At all levels of baseline blood pressure, the probability of achieving any given diastolic or systolic goal is greater with the combination than for either monotherapy. For example, the mean baseline SBP/DBP for patients participating in this multifactorial study was 157/100 mmHg. A patient with a baseline blood pressure of 157/100 mmHg has about a 49% likelihood of achieving a goal of <140 mmHg (systolic) and 50% likelihood of achieving <90 mmHg (diastolic) on aliskiren alone, and the likelihood of achieving these goals on amlodipine alone is about 62% (systolic) and 69% (diastolic). The likelihood of achieving these goals on Tekamlo rises to about 74% (systolic)

and 83% (diastolic). The likelihood of achieving these goals on placebo is about 25% (systolic) and 27% (diastolic) [see *Dosage and Administration (2)* and *Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

The blood pressure lowering effects are largely attained within 1-2 weeks.

2.2 Dose Selection

The recommended initial once-daily dose of Tekamlo is 150 mg/5 mg. Titrate as needed to a maximum of 300 mg/10 mg.

2.3 Dose Titration

If blood pressure remains uncontrolled after 2 to 4 weeks of therapy, titrate the dose to a maximum of Tekamlo 300 mg/10 mg once daily.

2.4 Initial Therapy

The usual recommended starting dose of Tekamlo is 150 mg/5 mg once daily as needed to control blood pressure. Titrate the dose to a maximum of 300 mg/10 mg once daily.

Tekamlo is not recommended for use as initial therapy in patients with intravascular volume depletion [see *Warnings and Precautions (5.4)*].

2.5 Add-on Therapy

Use Tekamlo for patients not adequately controlled with aliskiren alone or amlodipine besylate (or another dihydropyridine calcium channel blocker) alone.

Switch a patient who experiences dose-limiting adverse reactions on either component alone to Tekamlo containing a lower dose of that component in combination with the other to achieve similar blood pressure reductions.

2.6 Replacement Therapy

Switch patients receiving aliskiren and amlodipine besylate from separate tablets to a single tablet of Tekamlo containing the same component doses. When substituting for individual components, increase the dose of one or both of the components if blood pressure control has not been satisfactory.

2.7 Use with Other Antihypertensive Drugs

Tekamlo may be administered with some other antihypertensive agents. In diabetics, do not use in combination with angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACEIs) [see *Contraindications (4)*]. Concomitant use of aliskiren with an ARB or ACEI is not recommended in patients with GFR <60 ml/min [see *Warnings and Precautions (5.2)*]. It is not known whether Tekamlo decreases blood pressure further when added to maximum dosages of ACE inhibitors and beta blockers [see *Clinical Studies (14)*].

2.8 Relationship to Meals

Advise patients to establish a routine pattern for taking Tekamlo with regard to meals. High-fat meals decrease absorption substantially [see *Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

- 150 mg aliskiren/5 mg amlodipine tablets: Non-scored light yellow, ovaloid convex shaped film-coated tablet with a beveled edge with debossing “T2” on one side and “NVR” on the reverse side of the tablet.
- 150 mg aliskiren/10 mg amlodipine tablets: Non-scored yellow, ovaloid convex shaped film-coated tablet with a beveled edge with debossing “T7” on one side and “NVR” on the reverse side of the tablet.

- 300 mg aliskiren/5 mg amlodipine tablets: Non-scored dark yellow, ovaloid convex shaped film-coated tablet with a beveled edge with debossing “T11” on one side and “NVR” on the reverse side of the tablet.
- 300 mg aliskiren /10 mg amlodipine tablets: Non-scored brown yellow, ovaloid convex shaped film-coated tablet with a beveled edge with debossing “T12” on one side and “NVR” on the reverse side of the tablet.

4 CONTRAINDICATIONS

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

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

5.2 Renal Impairment/Hyperkalemia/Hypotension when Tekamlo is given in combination with ARBs or ACEI

Tekamlo is contraindicated in patients with diabetes who are receiving ARBs or ACEI because of the increased risk of renal impairment, hyperkalemia, and hypotension [*see Contraindications (4) and Clinical Trials (14.2)*].

Avoid use of Tekamlo with ARBs or ACEI in patients with moderate renal impairment (GFR <60 ml/min).

5.3 Head and Neck Angioedema

Aliskiren

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has 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 ACE inhibitors or angiotensin receptor antagonists. 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, since treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory involvement. Prompt administration of subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 ml) and measures to ensure a patent airway may be necessary.

Discontinue Tekamlo immediately in patients who develop angioedema and do not readminister.

5.4 Hypotension

In patients with an activated renin-angiotensin-aldosterone system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving renin-angiotensin-aldosterone system (RAAS) blockers. Correct these conditions prior to administration of Tekamlo, or start the treatment 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 Risk of Myocardial Infarction or Increased Angina

Rarely, initiation or change to the dose of a calcium channel blocker has resulted in the development of documented increased frequency, duration or severity of angina or acute myocardial infarction, particularly in patients with severe obstructive coronary artery disease. The mechanism of this effect has not been elucidated.

5.6 Impaired Renal Function

Monitor renal function periodically in patients treated with Tekamlo. Changes in renal function, including acute renal failure, can be caused by drugs that affect the renin-angiotensin system. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, severe heart failure, post-myocardial infarction or volume depletion) or patients receiving ARB, ACEI or non-steroidal anti-inflammatory (NSAID) therapy may be at particular risk for developing acute renal failure on Tekamlo [see *Contraindications (4)*, *Warnings (5.2)*, *Clinical Trials (14.2)*]. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function.

5.7 Patients with Hepatic Impairment

Amlodipine besylate

Amlodipine is extensively metabolized by the liver and the plasma elimination half-life is 56 hours in patients with impaired hepatic function, therefore, caution should be exercised when administering Tekamlo to patients with severe hepatic impairment.

5.8 Patients with Congestive Heart Failure

Amlodipine besylate

Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA Class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or left ventricular ejection fraction.

5.9 Cyclosporine or Itraconazole

Aliskiren

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)*].

5.10 Hyperkalemia

Aliskiren

Monitor serum potassium periodically in patients receiving aliskiren. Drugs that affect the renin-angiotensin system can cause hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes, combination use with ARBs or ACEI [see *Contraindications (4)*, *Warnings (5.2)*, and *Clinical Trials (14.2)*], NSAIDs, or potassium supplements or potassium sparing diuretics.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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

- Risk of fetal/neonatal morbidity and mortality [see *Warnings and Precautions (5.1)*]
- 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.

Tekamlo

Tekamlo has been evaluated for safety in more than 2800 patients, including 372 patients for 1 year or longer.

In a placebo-controlled study, there were 51% males, 62% Caucasians, 20% Blacks, 18% Hispanics, and 17% who were over 65 years of age. In this study, the overall incidence of adverse events on therapy with Tekamlo was similar to the individual components. Discontinuation of therapy due to a clinical adverse event in this study occurred in 1.7% of patients treated with Tekamlo (2.2% in the highest dose group) versus 1.5% of patients given placebo.

Peripheral edema is a known, dose-dependent adverse effect of amlodipine. The incidence of peripheral edema for Tekamlo in short-term double-blind placebo-controlled studies was lower than or equal to that of the corresponding amlodipine doses.

The adverse event in a placebo-controlled trial that occurred in at least 2% of patients treated with Tekamlo and at a higher incidence than placebo was peripheral edema (6.2% versus 1.0%). The incidence rate of peripheral edema at high dose was 8.9%.

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

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 ACEI [see *Contraindications (4)*, *Warnings (5.2)*, and *Clinical Trials (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) 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%), elevated uric acid (0.4% versus 0.1%), gout (0.2% versus 0.1%), and renal stones (0.2% versus 0%).

Single episodes of tonic-clonic seizures with loss of consciousness were reported in two 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 rechallenge in either case.

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

Amlodipine besylate

Amlodipine (Norvasc[®]) 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 <1% but >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, postural hypotension, vasculitis

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

Gastrointestinal: anorexia, constipation, dyspepsia,** 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: micturation frequency, micturation 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 $\leq 0.1\%$ 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.

Clinical Laboratory Test Abnormalities

RBC count, hemoglobin and hematocrit: Small mean changes from baseline were seen in RBC count, hemoglobin and hematocrit in patients treated with both Tekamlo and aliskiren monotherapy. 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, vs. 0% for placebo). No patients discontinued due to anemia.

Blood Urea Nitrogen (BUN) / Creatinine: In patients with hypertension not concomitantly treated with an ARB or ACEI, elevations in BUN (> 40 mg/dL) and creatinine (>2.0 mg/dL) in patients treated with Tekamlo were <1.0%.

Serum Potassium: In patients with hypertension not concomitantly treated with an ARB or ACEI, increases in serum potassium >5.5 mEq/L were infrequent (0.9% compared to 0.6% with placebo) [*see Contraindications (4) and Warnings and Precautions (5.10)*].

6.2 Post-marketing Experience

The following adverse reactions have been identified during postapproval use of either aliskiren or amlodipine. 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: angioedema requiring airway management and hospitalization

Aliskiren: Peripheral edema, severe cutaneous adverse reactions, including Stevens Johnson syndrome and toxic epidermal necrolysis

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.

7 DRUG INTERACTIONS

No drug interaction studies have been conducted with Tekamlo and other drugs, although studies with the individual aliskiren and amlodipine besylate components are described below.

Aliskiren

Cyclosporine: Avoid co-administration of cyclosporine with aliskiren.

Itraconazole: Avoid co-administration of itraconazole with aliskiren [*see Clinical Pharmacology (12.3)*].

Non-Steroidal Anti-Inflammatory Agents (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, co-administration of NSAIDs, including selective COX-2 inhibitors with agents that affect the renin-angiotensin system, 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.

Amlodipine besylate

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Grapefruit juice: Co-administration 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[®] (antacid): Co-administration 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: Co-administration 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: Co-administration 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: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Simvastatin: Co-administration 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. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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 Tekamlo as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester 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 Tekamlo, 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 Tekamlo 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 and amlodipine besylate. However, these studies have been conducted for aliskiren and amlodipine besylate 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^2), respectively, in rats and rabbits. (Actual animal doses were up to 600 $\text{mg}/\text{kg}/\text{day}$ in rats and up to 100 $\text{mg}/\text{kg}/\text{day}$ 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^2). Aliskiren was present in placentas, amniotic fluid and fetuses of pregnant rabbits.

Amlodipine

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

8.3 Nursing Mothers

It is not known whether aliskiren or amlodipine is 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 Tekamlo, a decision should be made whether to discontinue nursing or discontinue Tekamlo, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

Neonates with a history of in utero exposure to Tekamlo:

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

Tekamlo

In the short-term controlled clinical trials of Tekamlo, 17% of patients treated with Tekamlo were ≥ 65 years. 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.

Aliskiren

Impact of aging on aliskiren pharmacokinetics has been assessed, when compared to young adults (18-40 years), aliskiren mean AUC and C_{max} in elderly subjects (> 65 years) are increased by 57% and 28%, respectively. However, differences in efficacy and safety between the elderly and younger populations were minor, indicating that differences in exposure due to age do not significantly alter the clinical effect of the drug. Therefore, no starting dose adjustment in geriatric population is required.

Amlodipine

Other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%. In general dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal impairment

Safety and effectiveness of Tekamlo in patients with severe renal impairment ($\text{CrCL} < 30 \text{ ml}/\text{min}$) have not been established as patients with $\text{eGFR} < 30 \text{ ml}/\text{min}$ were excluded in clinical trials [*see Clinical Trials (14)*].

10 OVERDOSAGE

Aliskiren

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

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

Amlodipine besylate

Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m² basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdose of amlodipine is limited. Reports of intentional overdose include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

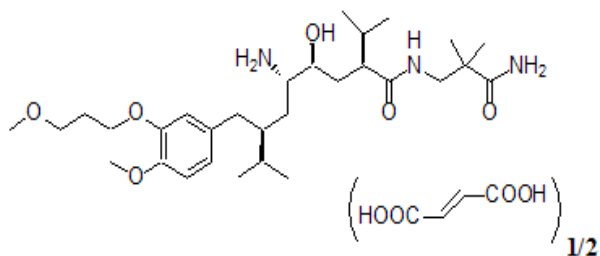
If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

11 DESCRIPTION

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

Aliskiren hemifumarate

Aliskiren hemifumarate is chemically described as (2*S*,4*S*,5*S*,7*S*)-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:

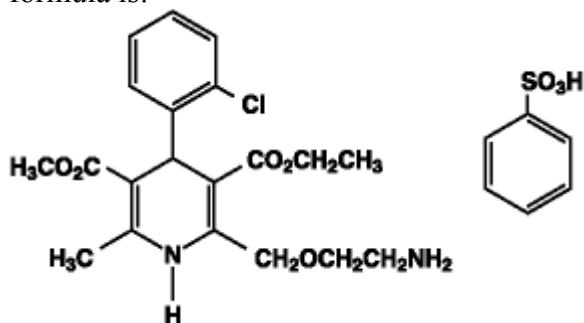


Molecular formula: C₃₀H₅₃N₃O₆ • 0.5 C₄H₄O₄

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 besylate

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.

Tekamlo tablets are formulated for oral administration to contain aliskiren hemifumarate and amlodipine besylate providing for the following available combinations: 150 mg/5 mg, 150 mg/10 mg, 300 mg/5 mg and 300 mg/10 mg aliskiren /amlodipine. The inactive ingredients for all strengths of the tablets may contain colloidal silicon dioxide, crospovidone, hypromellose, iron oxide red, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 angiotensin-converting enzyme (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 ACE inhibitors 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 besylate

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 ($pK_a=8.6$), 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.

Tekamlo

The effects of combined treatment of aliskiren and amlodipine arise from the actions of these two agents on different, but complementary mechanisms that regulate blood pressure, calcium channel-mediated vasoconstriction and RAAS-mediated effects on vascular tone and sodium excretion.

12.2 Pharmacodynamics

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 besylate

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 increase 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 105-114 mmHg) had about 50% greater response than patients with mild hypertension (diastolic pressure 90-104 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 co-administered 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[®] package insert.

Tekamlo

In a placebo-controlled study in hypertensive patients, amlodipine was associated with an increase in PRA (59-73% increase) whereas aliskiren monotherapy was associated with a 61-68% reduction in PRA. Aliskiren in combination with amlodipine reduced PRA (55-68% reduction).

12.3 Pharmacokinetics

Absorption and Distribution

Tekamlo

Following oral administration of the aliskiren/amlodipine combination tablets, the median peak plasma concentration times are within 3.0 hours for aliskiren and 8.0 hours for amlodipine. The rate and extent of absorption of aliskiren and amlodipine from Tekamlo are the same as when administered as individual tablets. When taken with food, mean AUC and C_{max} of aliskiren are decreased by 79% and 90%, respectively, while there is no impact of food on the AUC and C_{max} of amlodipine.

Aliskiren

Aliskiren is poorly absorbed (bioavailability about 2.5%) with an accumulation half life of about 24 hours. Steady state blood levels are reached in about 7-8 days. Following oral administration, peak plasma concentrations of aliskiren are reached within 1-3 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, aliskiren was administered without a fixed relation to meals.

Amlodipine besylate

Peak plasma concentrations of amlodipine are reached 6-12 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. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Metabolism and Elimination

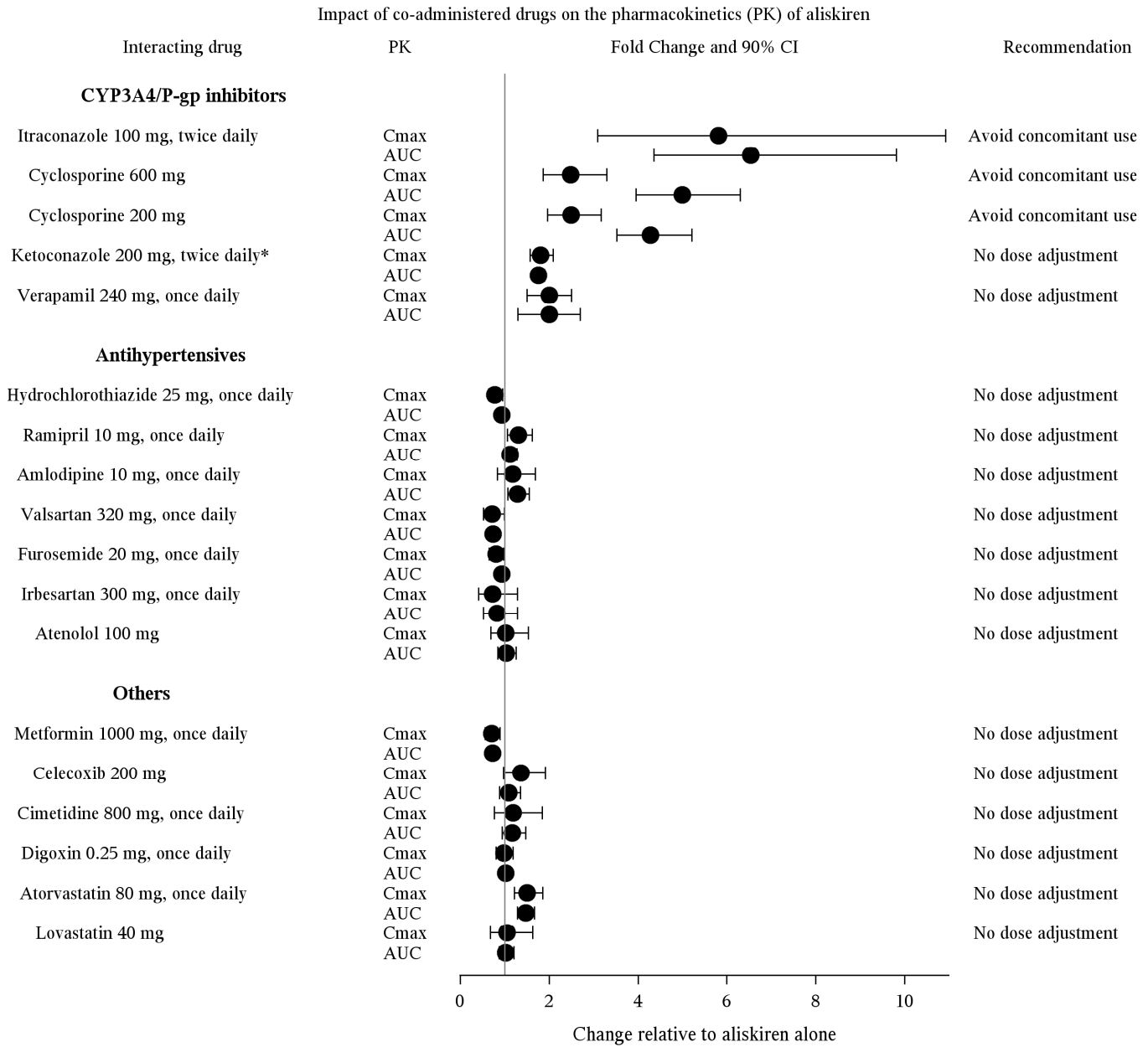
Aliskiren

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 CYP 3A4. Aliskiren does not inhibit the CYP450 isoenzymes (CYP 1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A) or induce CYP 3A4.

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.

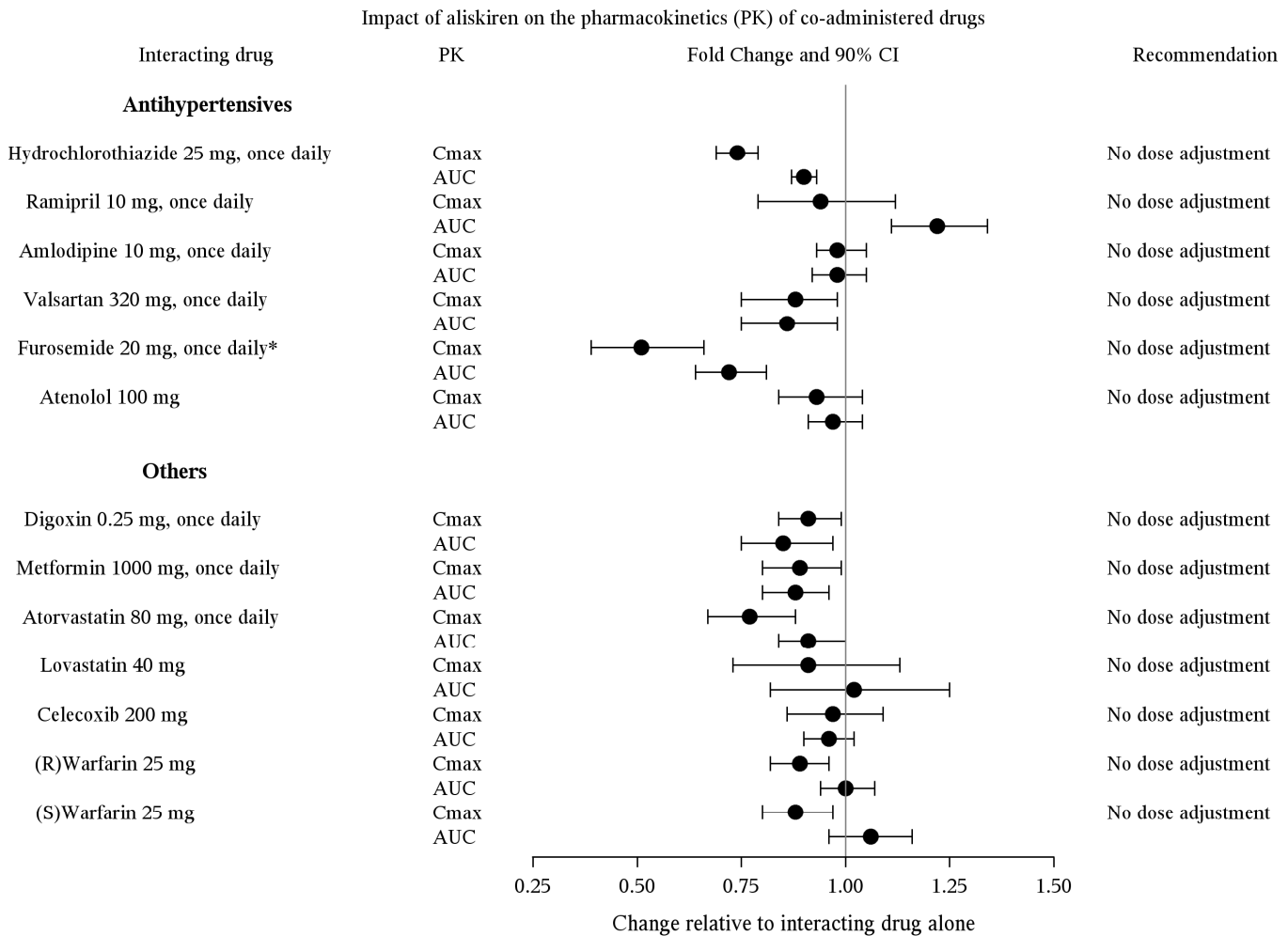
Drug interactions: The effect of co-administered drugs on the pharmacokinetics of aliskiren and vice versa, were studied in several single and multiple dose studies. Pharmacokinetic measures indicating the magnitude of these interactions are presented in Figure 5 (impact of co-administered drugs on aliskiren) and Figure 6 (impact on co-administered drugs).

Figure 5: The impact of co-administered drugs on the pharmacokinetics of aliskiren.



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

Figure 6: The impact of aliskiren on the pharmacokinetics of co-administered drugs.



*Patients receiving furosemide could find its effect diminished after starting aliskiren.

Amlodipine besylate

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 30-50 hours.

Special Populations

Pediatric Patients

The pharmacokinetics of Tekamlo have not been investigated in patients <18 years of age.

Geriatric Patients

The pharmacokinetics of aliskiren were studied in the elderly (≥65 years). Exposure (measured by AUC) is increased in elderly patients. Adjustment of the starting dose is not required in these patients.

Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40%-60%; therefore, a lower initial dose of amlodipine may be required.

Race

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

Renal Impairment

Aliskiren

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. Adjustment of the starting dose is not required in these patients [see *Warnings and Precautions (5.6)*].

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 was 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.

Amlodipine besylate

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose [see *Warnings and Precautions (5.6)*].

Hepatic Impairment

Aliskiren

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 [see *Warnings and Precautions (5.7)*].

Amlodipine besylate

Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40%-60%; therefore, a lower initial dose of amlodipine may be required [see *Warnings and Precautions (5.7)*].

Drug Interactions

Aliskiren exposure is increased slightly (AUC increased 29%) when aliskiren is co-administered with amlodipine, while amlodipine exposure remains unchanged when co-administered with aliskiren. The slight exposure increase of aliskiren in the presence of amlodipine is not clinically relevant.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with Aliskiren hemifumarate and Amlodipine besylate

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

Studies with Aliskiren hemifumarate

Carcinogenic potential was 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 750 or more 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 (AUC_{0-24hr}) 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 (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 rat bone marrow micronucleus assay.

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

Studies with Amlodipine besylate

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on mg/m² basis, similar to the maximum recommended human dose (MRHD) of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m² basis, about two and a half times the MRHD. (Calculations based on a 60 kg patient.)

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 mg amlodipine/kg/day (about 10 times the MRHD of 10 mg/day on a mg/m² basis).

13.2 Animal Toxicology and/or Pharmacology

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

Animal reproductive and developmental toxicology findings are described elsewhere [*see Use in Specific Populations (8.1)*].

14 CLINICAL STUDIES

14.1 Tekamlo

Tekamlo was studied in a total of 5549 patients with mild to moderate hypertension (diastolic blood pressure between 90 mmHg and 109 mmHg).

Aliskiren 150 mg and 300 mg and amlodipine besylate 5 mg and 10 mg were studied alone and in combination in an 8-week, randomized, double-blind, placebo-controlled, multifactorial study comparing the combinations 150 mg/5 mg, 150 mg/10 mg, 300 mg/5 mg and 300 mg/10 mg of aliskiren and amlodipine with their components and placebo. The combination of aliskiren and amlodipine resulted in placebo-adjusted decreases in systolic/diastolic blood pressure at trough of 14-17/9-11 mmHg compared to 4-9/3-5 mmHg for aliskiren alone and 9-14/6-8 mmHg for amlodipine alone.

Treatment with Tekamlo resulted overall in significantly greater reductions in diastolic and systolic blood pressure compared to the respective monotherapy components.

The antihypertensive effect of Tekamlo was similar in patients with and without diabetes, obese and non-obese patients, in patients ≥ 65 years of age and < 65 years of age, and in women and men.

A subgroup of 819 patients was studied with ambulatory blood pressure monitoring. The blood pressure lowering effect in the aliskiren/amlodipine group was maintained throughout the 24-hour period (see Figure 7 and Figure 8).

Figure 7: Mean Ambulatory Diastolic Blood Pressure at Endpoint by Treatment and Hour

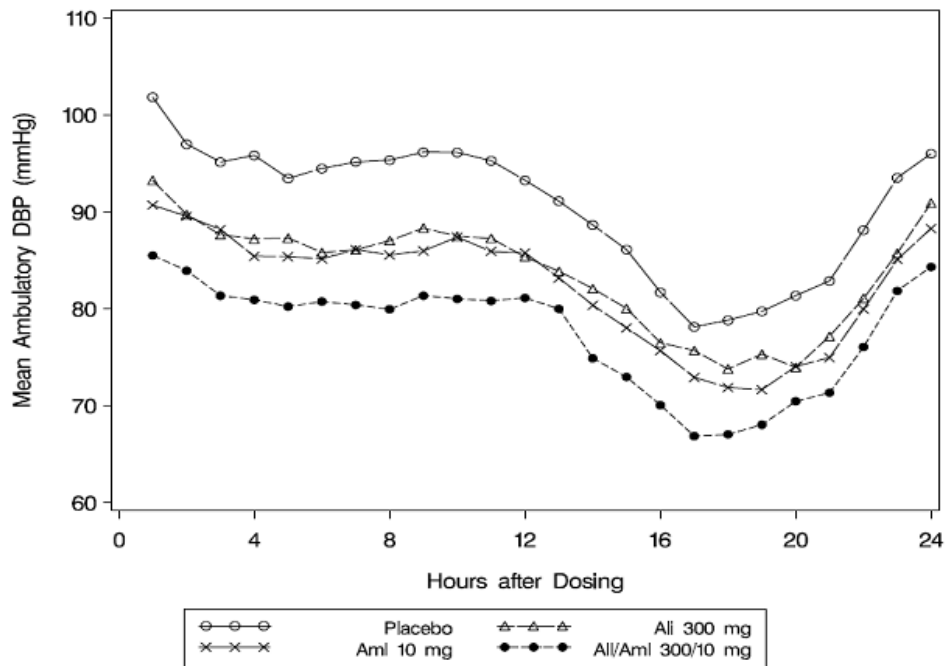
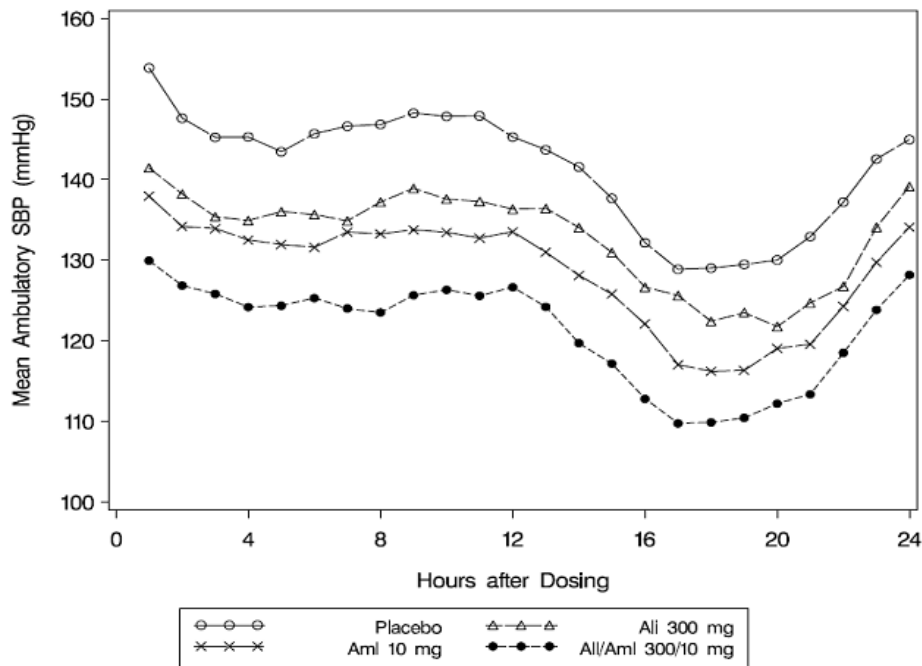


Figure 8: Mean Ambulatory Systolic Blood Pressure at Endpoint by Treatment and Hour



Two additional double-blind, active-controlled studies of similar design were conducted in which Tekamlo was administered as initial therapy in patients with moderate to severe hypertension (SBP 160-200 mmHg). Patients were randomized to receive either combination aliskiren/amlodipine or amlodipine monotherapy. The initial dose of aliskiren/amlodipine was 150 mg/5 mg for 1 week with forced titration to 300 mg/10 mg for 7 weeks. The initial dose of amlodipine was 5 mg for 1 week with forced titration to 10 mg for 7 weeks. In one study of 443 Black patients, at the primary endpoint of 8 weeks, the treatment difference between aliskiren/amlodipine and amlodipine was 5.2/3.8 mmHg. In the other study of 484 patients, at the primary endpoint of 8 weeks, the treatment difference between aliskiren/amlodipine and amlodipine was 7.1/3.8 mmHg.

The blood pressure lowering effects of Tekamlo are largely attained within 1-2 weeks.

There are no trials of the Tekamlo combination tablet demonstrating reductions in cardiovascular risk in patients with hypertension, but the amlodipine component has 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=4283) or placebo (n=4296). 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, non-fatal myocardial infarction, non-fatal 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 one month. After a median follow up of about 27 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 the table below.

Table 1: Incidence of selected adverse events in ALTITUDE

	Aliskiren N=4283		Placebo N=4296	
	Serious Adverse Events* (%)	Adverse Events (%)	Serious Adverse Events* (%)	Adverse Events (%)
Renal impairment [†]	4.7	12.4	3.3	10.4
Hypotension ^{††}	2.0	18.6	1.7	14.8
Hyperkalemia ^{†††}	1.1	36.9	0.3	27.1

[†]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 (2.7% aliskiren vs 2.0% placebo) and death (6.9% aliskiren vs. 6.4% placebo) were also numerically higher in aliskiren treated patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

Tekamlo (aliskiren and amlodipine) is supplied as follows:

150 mg aliskiren/5 mg amlodipine Tablets - Non-scored light yellow, ovaloid convex-shaped, film-coated tablet with a beveled edge with debossing “T2” on one side and “NVR” on the reverse side of the tablet. The tablet dimensions are approximately 16 x 6.3 mm.

150 mg aliskiren/10 mg amlodipine Tablets - Non-scored yellow, ovaloid convex shaped, film-coated tablet with a beveled edge with debossing “T7” on one side and “NVR” on the reverse side of the tablet. The tablet dimensions are approximately 16 x 6.3 mm.

300 mg aliskiren/5 mg amlodipine Tablets - Non-scored dark yellow, ovaloid convex-shaped, film-coated tablet with a beveled edge with debossing “T11” on one side and “NVR” on the reverse side of the tablet. The tablet dimensions are approximately 21 x 8.3 mm.

300 mg aliskiren/10 mg amlodipine Tablets - Non-scored brown yellow, ovaloid convex shaped, film-coated tablet with a beveled edge with debossing “T12” on one side and “NVR” on the reverse side of the tablet. The tablet dimensions are approximately 21 x 8.3 mm.

All strengths are packaged in bottles and unit-dose blister packages (10 strips of 10 tablets) as described below.

Table 2: Tekamlo Tablets Supply

Tablet	Color	Debossed		NDC 0078- XXXX-XX		
		Side 1	Side 2	Bottle of 30	Bottle of 90	Blister Packages of 100
Aliskiren hemifumarate /amlodipine besylate						
150 mg/5 mg	Light yellow	T2	NVR	0603-15	0603-34	0603-35
150 mg/10 mg	Yellow	T7	NVR	0604-15	0604-34	0604-35
300 mg/5 mg	Dark yellow	T11	NVR	0605-15	0605-34	0605-35
300 mg/10 mg	Brown yellow	T12	NVR	0606-15	0606-34	0606-35

Storage

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

Protect from heat and moisture.

Dispense in original container.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information)

Healthcare professionals should instruct their patients to read the Patient Package Insert before starting Tekamlo and to reread each time the prescription is renewed. Patients should be instructed to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

Pregnancy

Female patients of childbearing age should be told about the consequences of exposure to Tekamlo during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physician as soon as possible.

Symptomatic Hypotension

Caution patients receiving Tekamlo 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 Tekamlo 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.

Angioedema

Patients should be advised and told to report immediately any signs or symptoms suggesting 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.

Potassium Supplements

Tell patients receiving Tekamlo not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Relationship to Meals

Patients should establish a routine pattern for taking Tekamlo with regard to meals. High-fat meals decrease absorption substantially.

FDA-Approved Patient Labeling

Patient Information

Tekamlo™ (tĕk'-ăm-lō) Tekamlo (aliskiren and amlodipine) Tablets

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

What is the most important information I should know about Tekamlo?

Tekamlo 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 Tekamlo, tell your doctor right away.

What is Tekamlo?

Tekamlo is a prescription medicine that may be used:

- as the first medicine to lower your high blood pressure if your doctor decides that you are likely to need more than one medicine.
- to treat your high blood pressure when one medicine to lower your high blood pressure has not worked well enough.
- if you are already taking the medicines aliskiren and amlodipine to treat your high blood pressure.

Tekamlo contains:

- aliskiren, a direct renin inhibitor (DRI)
- amlodipine, a calcium channel blocker (CCB)

Your doctor may prescribe other medicines for you to take along with Tekamlo to treat your high blood pressure.

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

Who should not take Tekamlo?

- If you get pregnant, stop taking Tekamlo 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.
- If you have diabetes and are taking a kind of medicine called an angiotensin-receptor-blocker or angiotensin-converting-enzyme-inhibitor.
- **If you are allergic** (hypersensitive) to aliskiren, amlodipine or other dihydropyridines (calcium-channel blockers, a group of medicines to lower blood pressure to which amlodipine belongs) or any of the other ingredients of Tekamlo listed at the end of this leaflet.

What should I tell my doctor before taking Tekamlo?

Before taking Tekamlo, tell your doctor if you:

- have kidney problems

- have liver problems
- 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.
- have any other medical problems
- are pregnant or planning to become pregnant. **See “What is the most important information I should know about Tekamlo?”**
- are breastfeeding. It is not known if Tekamlo passes into your breast milk and if it can harm your baby. You and your doctor should decide if you will take Tekamlo 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. Tekamlo and certain other medicines may affect each other and cause side effects.

Especially tell your doctor if you take:

- a kind of medicine called angiotensin receptor blocker or angiotensin converting enzyme inhibitor
- water pills (also called “diuretics”)
- medicines for treating fungus or fungal infections
- cyclosporine (Gengraf[®], Neoral, Sandimmune), a medicine used to suppress the immune system
- potassium-containing medicines, potassium supplements, or salt substitutes containing potassium
- atorvastatin (Lipitor[®]) non-steroidal anti-inflammatory drugs (like ibuprofen or naproxen)

Know your medicines. Keep a list of all your medicines. Show this list to 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 Tekamlo?

- Take Tekamlo exactly as prescribed by your doctor. It is important to take Tekamlo every day to control your blood pressure.
- Take Tekamlo one time a day, about the same time each day.
- Take Tekamlo the same way every day, either with or without a meal.
- Your doctor may change your dose of Tekamlo if needed. Do not change the amount of Tekamlo you take without talking to your doctor.
- If you miss a dose of Tekamlo, 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 Tekamlo, call your doctor or a Poison Control Center, or go to the nearest hospital emergency room.

What are the possible side effects of Tekamlo?

Tekamlo may cause serious side effects:

- **Harm to an unborn baby, causing injury or death. See “What is the most important information I should know about Tekamlo?”**

- Aliskiren, one of the medicines in Tekamlo, can cause swelling of your face, lips, tongue, throat, arms and legs, or the whole body. Get medical help right away and 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 Tekamlo.
- **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. Lie down if you feel faint or get dizzy. Call your doctor right away.
- **Possible increased chest pain or risk of heart attack.** It is rare, but when you first start taking Tekamlo 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 a hospital emergency room.

The most common side effects of Tekamlo include:

- Swelling of your lower legs

Common side effects of Tekamlo include:

- diarrhea
- cough
- dizziness
- flu-like symptoms
- tiredness
- high levels of potassium in the blood (hyperkalemia)

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 Tekamlo. 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 Tekamlo?

- Store Tekamlo tablets at room temperature between 59oF to 86oF (15oC to 30oC).
- Keep the original prescription bottle and store in a dry place.
- Protect Tekamlo from heat and moisture.

Keep Tekamlo and all medicines out of the reach of children.

General information about Tekamlo

Medicines are sometimes prescribed for conditions not listed in the patient information leaflet. Do not take Tekamlo for a condition for which it was not prescribed. Do not give Tekamlo 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 Tekamlo. If you have questions about Tekamlo talk with your doctor. You can ask your doctor or pharmacist for information that is written for healthcare professionals.

For more information about Tekamlo, visit www.Tekamlo.com, or call 1-888-NOW-NOVA (1-888-669-6682).

What are the ingredients in Tekamlo?

Active Ingredients: Aliskiren hemifumarate and amlodipine

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

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. Tekamlo 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.

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