

Amlodipine and Valsartan Tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use amlodipine and valsartan safely and effectively. See full prescribing information for Amlodipine and Valsartan Tablets.

Amlodipine and Valsartan Tablets

Initial U.S. Approval: 2007

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **When pregnancy is detected, discontinue Amlodipine and Valsartan 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)**

INDICATIONS AND USAGE

Amlodipine and valsartan is the combination tablet of amlodipine, a dihydropyridine calcium channel blocker (DHP CCB), and valsartan, an angiotensin II receptor blocker (ARB). Amlodipine and valsartan is indicated for the treatment of hypertension, to lower blood pressure:

- In patients not adequately controlled on monotherapy (1)
- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals (1).

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

DOSAGE AND ADMINISTRATION

General Considerations:

- Majority of effect attained within 2 weeks (2.1)
- May be administered with other antihypertensive agents (2.1)

Hypertension

- May be used as add-on therapy for patients not controlled on monotherapy (2.2)
- Patients who experience dose-limiting adverse reactions on monotherapy may be switched to amlodipine and valsartan containing a lower dose of that component (2.2)
- May be substituted for titrated components (2.3)
- When used as initial therapy: Initiate with 5/160 mg, then titrate upwards as necessary to a maximum of 10/320 mg once daily (2.4)

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: FETAL TOXICITY

1 INDICATIONS AND USAGE

1.1 Hypertension

2 DOSAGE and ADMINISTRATION

- 2.1 General Considerations
- 2.2 Add-on Therapy
- 2.3 Replacement Therapy
- 2.4 Initial Therapy

3 DOSAGE FORMS and STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS and PRECAUTIONS

- 5.1 Fetal Toxicity
- 5.2 Hypotension
- 5.3 Risk of Myocardial Infarction or Increased Angina
- 5.4 Impaired Renal Function
- 5.5 Hyperkalemia

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue Amlodipine and Valsartan 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

1.1 Hypertension

Amlodipine and valsartan 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 the ARB class to which valsartan principally belongs. There are no controlled trials demonstrating risk reduction with amlodipine and valsartan.

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 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 anti-hypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy. Amlodipine and valsartan is indicated for the treatment of hypertension.

Amlodipine and valsartan may be used in patients whose blood pressure is not adequately controlled on either monotherapy.

Amlodipine and valsartan may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

The choice of amlodipine and valsartan as initial therapy for hypertension should be based on an assessment of potential benefits and risks including whether the patient is likely to tolerate the lowest dose of amlodipine and valsartan.

Patients with stage 2 hypertension (moderate or severe) are at a relatively higher risk for cardiovascular events (such as strokes, heart attacks, and heart failure), kidney failure and vision problems, so prompt treatment is clinically relevant. The decision to use a combination as initial therapy should be individualized and should be shaped by considerations 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 blood pressure goal with amlodipine and valsartan compared to amlodipine or valsartan monotherapy. The figures below provide estimates of the likelihood of achieving systolic or diastolic blood pressure control with amlodipine and valsartan 10/320 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 due to small numbers of subjects with high baseline blood pressures.

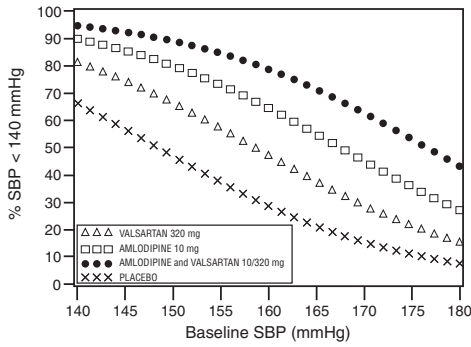


Figure 1: Probability of Achieving Systolic Blood Pressure <140 mmHg at Week 8

DOSAGE FORMS and STRENGTHS

Tablets (amlodipine/valsartan mg): 5/160, 10/160, 5/320, 10/320 (3)

CONTRAINDICATIONS

Known hypersensitivity to any component; Do not coadminister aliskiren with amlodipine and valsartan in patients with diabetes (4)

WARNINGS and PRECAUTIONS

- Hypotension: Correct volume depletion prior to initiation (5.2)
- Increased angina and/or myocardial infarction (5.3)
- Monitor renal function and potassium in susceptible patients (5.4, 5.5)

ADVERSE REACTIONS

In placebo-controlled clinical trials, discontinuation due to side effects occurred in 1.8% of patients in the amlodipine and valsartan treated patients and 2.1% in the placebo-treated group. The most common reasons for discontinuation of therapy with amlodipine and valsartan were peripheral edema and vertigo. The adverse experiences that occurred in clinical trials (≥2% of patients) at a higher incidence than placebo included peripheral edema, nasopharyngitis, upper respiratory tract infection and dizziness. (6.1)

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

DRUG INTERACTIONS

- If simvastatin is coadministered with amlodipine, do not exceed doses greater than 20 mg daily of simvastatin (7)
- NSAIDs use may lead to increased risk of renal impairment and loss of anti-hypertensive effect (7)
- Dual inhibition of the renin-angiotensin system: Increased risk of renal impairment, hypotension, and hyperkalemia (7)
- Lithium: Increases in serum lithium concentrations and lithium toxicity (7)

USE IN SPECIFIC POPULATIONS

Start amlodipine or add amlodipine at 2.5 mg in patients ≥75 years old or in patients with hepatic impairment. (8.5, 8.7)

Nursing Mothers: Avoid use while nursing – discontinue either nursing or drug (8.3)

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

Revised: 04/2014

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.3 Developmental Toxicity Studies

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE and HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

A patient who experiences dose-limiting adverse reactions on either component alone may be switched to amlodipine and valsartan containing a lower dose of that component in combination with the other to achieve similar blood pressure reductions. The clinical response to amlodipine and valsartan should be subsequently evaluated and if blood pressure remains uncontrolled after 3 to 4 weeks of therapy, the dose may be titrated up to a maximum of 10/320 mg.

2.3 Replacement Therapy

For convenience, patients receiving amlodipine and valsartan from separate tablets may instead wish to receive tablets of amlodipine and valsartan containing the same component doses.

2.4 Initial Therapy

A patient may be initiated on amlodipine and valsartan if it is unlikely that control of blood pressure would be achieved with a single agent. The usual starting dose is amlodipine and valsartan 5/160 mg once daily in patients who are not volume-depleted.

3 DOSAGE FORMS and STRENGTHS

5/160 mg tablets, debossed with p/574 (side 1/side 2)

10/160 mg tablets, debossed with p/575

5/320 mg tablets, debossed with p/576

10/320 mg tablets, debossed with p/577

4 CONTRAINDICATIONS

Do not use in patients with known hypersensitivity to any component.

Do not coadminister aliskiren with amlodipine and valsartan in patients with diabetes [see **DRUG INTERACTIONS (7)**].

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 amlodipine and valsartan as soon as possible. [see **Use in Specific Populations (8.1)**].

5.2 Hypotension

Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with amlodipine and valsartan in placebo-controlled studies. In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving angiotensin receptor blockers. Volume depletion should be corrected prior to administration of amlodipine and valsartan. Treatment with amlodipine and valsartan should start under close medical supervision.

Initiate therapy cautiously in patients with heart failure or recent myocardial infarction and in patients undergoing surgery or dialysis. Patients with heart failure or post-myocardial infarction patients given valsartan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials in heart failure patients, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), hypotension in post-myocardial infarction patients led to permanent discontinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopril-treated patients.

Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution, as with any other peripheral vasodilator, should be exercised when administering amlodipine, particularly in patients with severe aortic stenosis.

If excessive hypotension occurs with amlodipine and valsartan, the patient should be placed in a supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

5.3 Risk of Myocardial Infarction or Increased Angina

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

5.4 Impaired Renal Function

Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g. patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute renal failure on amlodipine and valsartan. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on amlodipine and valsartan [see **DRUG INTERACTIONS (7)**].

5.5 Hyperkalemia

Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically.

Some patients with heart failure have developed increases in potassium with valsartan therapy. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of amlodipine and valsartan may be required. [see **Adverse Reactions (6.1)**].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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 the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Studies with Amlodipine and Valsartan:

Amlodipine and valsartan has been evaluated for safety in over 2600 patients with hypertension; over 1440 of these patients were treated for at least 6 months and over 540 of these patients were treated for at least 1 year. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

The hazards [see **WARNINGS and PRECAUTIONS (5)**] of valsartan are generally independent of dose; those of amlodipine are a mixture of dose-dependent phenomena (primarily peripheral edema) and dose-independent phenomena, the former much more common than the latter.

The overall frequency of adverse reactions was neither dose-related nor related to gender, age, or race. In placebo-controlled clinical trials, discontinuation due to side effects occurred in 1.8% of patients in the amlodipine and valsartan-treated patients and 2.1% in the placebo-treated group. The most common reasons for discontinuation of therapy with amlodipine and valsartan were peripheral edema (0.4%), and vertigo (0.2%).

The adverse reactions that occurred in placebo-controlled clinical trials in at least 2% of patients treated with amlodipine and valsartan but at a higher incidence in amlodipine/valsartan patients (n=1437) than placebo (n=337) included peripheral edema (5.4% vs. 3.0%), nasopharyngitis (4.3% vs. 1.8%), upper respiratory tract infection (2.9% vs 2.1%) and dizziness (2.1% vs 0.9%).

Orthostatic events (orthostatic hypotension and postural dizziness) were seen in less than 1% of patients.

Other adverse reactions that occurred in placebo-controlled clinical trials with amlodipine and valsartan (≥ 0.2%) are listed below. It cannot be determined whether these events were causally related to amlodipine and valsartan.

Blood and Lymphatic System Disorders: lymphadenopathy

Cardiac Disorders: palpitations, tachycardia

Ear and Labyrinth Disorders: ear pain

Gastrointestinal Disorders: diarrhea, nausea, constipation, dyspepsia, abdominal pain, abdominal pain upper, gastritis, vomiting, abdominal discomfort, abdominal distention, dry mouth, colitis

General Disorders and Administration Site Conditions: fatigue, chest pain, asthma, pitting edema, pyrexia, edema

Immune System Disorders: seasonal allergies

Infections and Infestations: nasopharyngitis, sinusitis, bronchitis, pharyngitis, gastroenteritis, pharyngotonsillitis, bronchitis acute, tonsillitis

Injury and Poisoning: epicondylitis, joint sprain, limb injury

Metabolism and Nutrition Disorders: gout, non-insulin dependent diabetes mellitus, hypercholesterolemia

Musculoskeletal and Connective Tissue Disorders: arthralgia, back pain, muscle spasms, pain in extremity, myalgia, osteoarthritis, joint swelling, musculoskeletal chest pain

Nervous System Disorders: headache, sciatica, paresthesia, cervicobrachial syndrome, carpal tunnel syndrome, hyposthesia, sinus headache, somnolence

Psychiatric Disorders: insomnia, anxiety, depression

Renal and Urinary Disorders: hematuria, nephrolithiasis, pollakiuria

Reproductive System and Breast Disorders: erectile dysfunction

Respiratory, Thoracic and Mediastinal Disorders: cough, pharyngolaryngeal pain, sinus congestion, dyspnea, epistaxis, productive cough, dysphonia, nasal congestion

Skin and Subcutaneous Tissue Disorders: pruritus, rash, hyperhidrosis, eczema, erythema

Vascular Disorders: flushing, hot flush

Isolated cases of the following clinically notable adverse reactions were also observed in clinical trials: exanthema, syncope, visual disturbance, hypersensitivity, tinnitus, and hypotension.

Studies with Amlodipine:

Norvasc[®] has been evaluated for safety in more than 11000 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, tremor

Gastrointestinal: anorexia, dysphagia, pancreatitis, gingival hyperplasia

General: allergic reaction, hot flashes, malaise, rigors, weight gain, weight loss

Musculoskeletal System: arthrosis, muscle cramps

Psychiatric: sexual dysfunction (male and female), nervousness, abnormal dreams, depersonalization

Respiratory System: dyspnea

Skin and Appendages: angioedema, erythema multiforme, rash erythematous, rash maculopapular

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

Urinary System: micturition frequency, micturition disorder, nocturia

Autonomic Nervous System: sweating increased

Metabolic and Nutritional: hyperglycemia, thirst

Hemopoietic: leukopenia, purpura, thrombocytopenia

Other events reported with amlodipine at a frequency of ≥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.

Adverse reactions reported for amlodipine for indications other than hypertension may be found in the prescribing information for Norvasc.

Studies with Valsartan:

Diovan[®] has been evaluated for safety in more than 4000 hypertensive patients in clinical trials. In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129-patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively (<0.001).

Other adverse reactions, not listed above, occurring in >0.2% of patients in controlled clinical trials with valsartan are:

Body as a Whole: allergic reaction, asthma

Musculoskeletal: muscle cramps

Neurologic and Psychiatric: paresthesia

Respiratory: sinusitis, pharyngitis

Urogenital: impotence

Other reported events seen less frequently in clinical trials were: angioedema.

Adverse reactions reported for valsartan for indications other than hypertension may be found in the prescribing information for Diovan.

Clinical Lab Test Findings:

Creatinine: In hypertensive patients, greater than 50% increases in creatinine occurred in 0.4% of patients receiving amlodipine and valsartan and 0.6% receiving placebo. In heart failure patients, greater than 50% increases in creatinine were observed in 3.9% of valsartan-treated patients compared to 0.9% of placebo-treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients and 3.4% of captopril-treated patients.

Liver Function Tests: Occasional elevations (greater than 150%) of liver chemistries occurred in amlodipine and valsartan-treated patients.

Serum Potassium: In hypertensive patients, greater than 20% increases in serum potassium were observed in 2.8% of valsartan-treated patients compared to 3.4% of placebo-treated patients. In heart failure patients, greater than 20% increases in serum potassium were observed in 10% of valsartan-treated patients compared to 5.1% of placebo-treated patients.

Blood Urea Nitrogen (BUN): In hypertensive patients, greater than 50% increases in BUN were observed in 5.5% of amlodipine and valsartan-treated patients compared to 4.7% of placebo-treated patients. In heart failure patients, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients compared to 6.3% of placebo-treated patients.

Neutropenia: Neutropenia was observed in 1.9% of patients treated with Diovan and 0.8% of patients treated with placebo.

6.2 Postmarketing Experience

Amlodipine: Gynecomastia has been reported infrequently and a causal relationship is

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

If massive overdose should occur, initiate active cardiac and respiratory monitoring. 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, 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 two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption.

Information on Valsartan

Limited data are available related to overdose in humans. The most likely effect of overdose with valsartan would be peripheral vasodilation, hypotension and tachycardia; bradycardia could occur from parasympathetic (vaga) stimulation. Depressed level of consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension should occur, supportive treatment should be instituted.

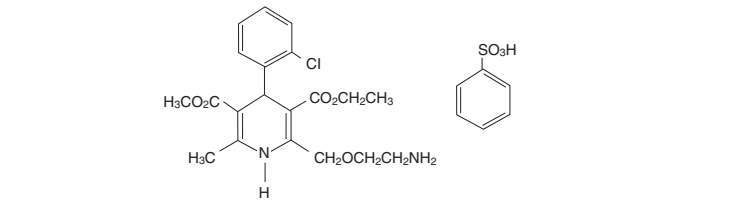
Valsartan is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for the salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 37 times, respectively, the maximum recommended human dose (MRHD) on a mg/m² basis). (Calculations assume an oral dose of 320 mg/day and a 60 kg patient.)

11. DESCRIPTION

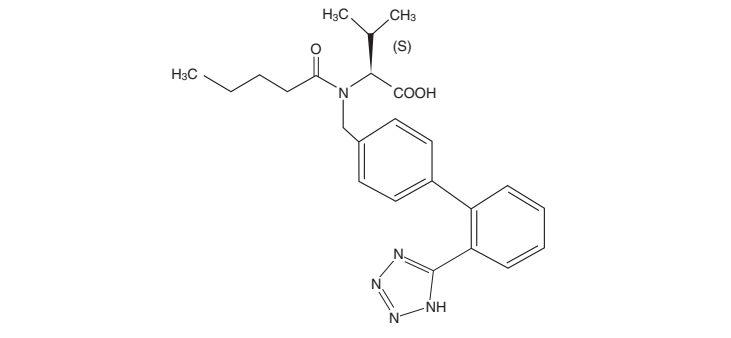
Amlodipine and valsartan is a fixed combination of amlodipine and valsartan.

Amlodipine and valsartan contains the besylate salt of amlodipine, a dihydropyridine calcium-channel blocker (CCB). Amlodipine besylate is a white to pale yellow crystalline powder, slightly soluble in water and sparingly soluble in ethanol. Amlodipine besylate's chemical name is 3-Ethyl-5-methyl(4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate; its structural formula is



Its molecular formula is C₂₀H₂₅ClN₂O₆•C₆H₅O₃S and its molecular weight is 567.1.

Valsartan is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT₁ receptor subtype. Valsartan is a white fine powder, soluble in ethanol and methanol and slightly soluble in water. Valsartan's chemical name is N-(1-oxopentyl)-N-[(2-[(1H-tetrazol-5-yl) [1,1'-biphenyl]-4-yl)methyl]-L-valine; its structural formula is



Its molecular formula is C₂₄H₂₉N₅O₃ and its molecular weight is 435.5.

Amlodipine and valsartan tablets are formulated in four strengths for oral administration with a combination of amlodipine besylate, equivalent to 5 mg or 10 mg of amlodipine free-base, with 160 mg or 320 mg of valsartan providing for the following available combinations: 5/160 mg, 10/160 mg, 5/320 mg and 10/320 mg.

The inactive ingredients for all strengths of the tablets are colloidal silicon dioxide, crospovidone, magnesium stearate and microcrystalline cellulose. The film coating contains polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

Valsartan

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT₂ receptor found in many tissues, but AT₂ is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT₁ receptor than for the AT₂ receptor. The increased plasma levels of angiotensin following AT₁ receptor blockade with valsartan may stimulate the unblocked AT₂ receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT₁ receptor about one-200th that of valsartan itself.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

12.2 Pharmacodynamics

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 to 114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90 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 the therapeutic dose range to intact animals and man, even when coadministered with beta-blockers to man. Similar findings, however, have been observed in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Amlodipine does not change sinoatrial nodal function or atrioventricular (AV) 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 (ECG) 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.

Valsartan

Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.

Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

In multiple dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic blood pressure, usually with little or no orthostatic change. Valsartan has indications other than hypertension which can be found in the Diovan package insert.

Amlodipine and Valsartan

Amlodipine and valsartan has been shown to be effective in lowering blood pressure. Both amlodipine and valsartan lower blood pressure by reducing peripheral resistance, but calcium influx blockade and reduction of angiotensin II vasoconstriction are complementary mechanisms.

12.3 Pharmacokinetics

Amlodipine

Peak plasma concentrations of amlodipine are reached 6 to 12 hours after administration of amlodipine alone. 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 21 L/kg. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

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 of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Valsartan

Following oral administration of valsartan alone peak plasma concentrations of valsartan are reached in 2 to 4 hours. Absolute bioavailability is about 25% (range 10% to 35%). Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%.

The steady state volume of distribution of valsartan after intravenous administration is 17 L indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

Valsartan shows bi-exponential decay kinetics following intravenous administration with an average elimination half-life of about 6 hours. The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. *In vitro* metabolism studies involving recombinant CYP 450 enzymes indicated that the CYP 2C9 isoenzyme is responsible for the formation of valeryl-4-hydroxy valsartan. Valsartan does not inhibit CYP 450 isozymes at clinically relevant concentrations. CYP 450 mediated drug interaction between valsartan and coadministered drugs are unlikely because of the low extent of metabolism.

Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

Amlodipine and Valsartan

Following oral administration of amlodipine and valsartan in normal healthy adults, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6 to 8 hours, respectively. The rate and extent of absorption of valsartan and amlodipine from amlodipine and valsartan are the same as when administered as individual tablets. The bioavailabilities of amlodipine and valsartan are not altered by the coadministration of food.

Special Populations

Geriatric

Studies with Amlodipine: Elderly patients have decreased clearance of amlodipine with a resulting increase in peak plasma levels, elimination half-life and AUC.

Studies with Valsartan: Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary.

Gender

Studies with Valsartan: Pharmacokinetics of valsartan does not differ significantly between males and females.

Renal Insufficiency

Studies with Amlodipine: The pharmacokinetics of amlodipine is not significantly influenced by renal impairment.

Studies with Valsartan: There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance <10 mL/min). Valsartan is not removed from the plasma by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan.

Hepatic Insufficiency

Studies with Amlodipine: Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40% to 60%.

Studies with Valsartan: On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex and weight). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease.

Drug Interactions

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® (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 (Viagra®[®] *) 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.

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. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

CYP3A4 inhibitors: Coadministration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensives 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 (i.e., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with Amlodipine

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 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 MRHD of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m² basis, about 2.5 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).

Studies with Valsartan

There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at concentrations calculated to provide doses of up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.4 and 6 times, respectively, the MRHD of 320 mg/day on a mg/m² basis. (Calculations based on a 60 kg patient.)

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli*, a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with Chinese hamster ovary cells, and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses of up to 200 mg/kg/day. This dose is about 6 times the MRHD on a mg/m² basis.

13.3 Developmental Toxicity Studies

Studies with Amlodipine

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses of up to 10 mg amlodipine/kg/day (respectively, about 10 and 20 times the MRHD of 10 mg amlodipine on a mg/m² basis) during their respective periods of major organogenesis. (Calculations based on a patient weight of 60 kg.) However, litter size was significantly decreased (by about 50%) and the number of intrauterine resorptions was significantly increased (about 5-fold) for rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day 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. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Studies with Valsartan

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses of up to 600 mg/kg/day and to pregnant rabbits at oral doses of up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits, respectively, are about 9, 6 and 0.1 times the MRHD of 320 mg/day on a mg/m² basis. (Calculations based on a patient weight of 60 kg.)

Studies with Amlodipine Besylate and Valsartan

In the oral embryo-fetal development study in rats using amlodipine besylate plus valsartan at doses equivalent to 5 mg/kg/day amlodipine plus 80 mg/kg/day valsartan, 10 mg/kg/day amlodipine plus 160 mg/kg/day valsartan, and 20 mg/kg/day amlodipine plus 320 mg/kg/day valsartan, treatment-related maternal and fetal effects (developmental delays and alterations noted in the presence of significant maternal toxicity) were noted with the high dose combination. The no-observed-adverse-effect level (NOAEL) for embryo-fetal effects was 10 mg/kg/day amlodipine plus 160 mg/kg/day valsartan. On a systemic exposure [AUC(0-∞)] basis, these doses are, respectively, 4.3 and 2.7 times the systemic exposure [AUC(0-∞)] in humans receiving the MRHD (10/320 mg/60 kg).

14 CLINICAL STUDIES

Amlodipine and valsartan was studied in 2 placebo-controlled and 4 active-controlled trials in hypertensive patients. In a double-blind, placebo controlled study, a total of 1012 patients with mild-to-moderate hypertension received treatments of 3 combinations of amlodipine and valsartan (5/80, 5/160, 5/320 mg) or amlodipine alone (5 mg), valsartan alone (80, 160, or 320 mg) or placebo. All doses with the exception of the 5/320 mg dose were initiated at the randomized dose. The high dose was titrated to that dose after a week at a dose of 5/160 mg. At week 8, the combination treatments were statistically significantly superior to their monotherapy components in reduction of diastolic and systolic blood pressures.

Amlodipine dosage	Valsartan dosage							
	0 mg		80 mg		160 mg		320 mg	
	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted
0 mg	-6.4	—	-9.5	-3.1	-10.9	-4.5	-13.2	-6.7
5 mg	-11.1	-4.7	-14.2	-7.8	-14.0	-7.6	-15.7	-9.3

*Mean Change and Placebo-Subtracted Mean Change from Baseline (mmHg) at Week 8 in Sitting Diastolic Blood Pressure. Mean baseline diastolic BP was 99.3 mmHg.

Table 2: Effect of Amlodipine and Valsartan on Sitting Systolic Blood Pressure

Amlodipine dosage	Valsartan dosage							
	0 mg		80 mg		160 mg		320 mg	
	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted
0 mg	-6.2	—	-12.9	-6.8	-14.3	-8.2	-16.3	-10.1
5 mg	-14.8	-8.6	-20.7	-14.5	-19.4	-13.2	-22.4	-16.2

*Mean Change and Placebo-Subtracted Mean Change from Baseline (mmHg) at Week 8 in Sitting Systolic Blood Pressure. Mean baseline systolic BP was 132.8 mmHg.

In a double-blind, placebo controlled study, a total of 1246 patients with mild to moderate hypertension received treatments of 2 combinations of amlodipine and valsartan (10/160, 10/320 mg) or amlodipine alone (10 mg), valsartan alone (160 or 320 mg) or placebo. With the exception of the 10/320 mg dose, treatment was initiated at the randomized dose. The high dose was initiated at a dose of 5/160 mg and titrated to the randomized dose after 1 week. At week 8, the combination treatments were statistically significantly superior to their monotherapy components in reduction of diastolic and systolic blood pressures.

Amlodipine dosage	Valsartan dosage					
	0 mg		160 mg		320 mg	
	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted
0 mg	-8.2	—	-12.8	-4.5	-12.8	-4.5
10 mg	-15.0	-6.7	-17.2	-9.0	-18.1	-9.9

*Mean Change and Placebo-Subtracted Mean Change from Baseline (mmHg) at Week 8 in Sitting Diastolic Blood Pressure. Mean baseline diastolic BP was 99.1 mmHg.

Table 4: Effect of Amlodipine and Valsartan on Sitting Systolic Blood Pressure

Amlodipine dosage	Valsartan dosage					
	0 mg		160 mg		320 mg	
	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted
0 mg	-11.0	—	-18.1	-7.0	-18.5	-7.5
10 mg	-22.2	-11.2	-26.6	-15.5	-26.9	-15.9

*Mean Change and Placebo-Subtracted Mean Change from Baseline (mmHg) at Week 8 in Sitting Systolic Blood Pressure. Mean baseline systolic BP was 156.7 mmHg.

In a double-blind, active-controlled study, a total of 947 patients with mild to moderate hypertension who were not adequately controlled on valsartan 160 mg received treatments of 2 combinations of amlodipine and valsartan (10/160, 5/160 mg), or valsartan alone (160 mg). At week 8, the combination treatments were statistically significantly superior to the monotherapy component in reduction of diastolic and systolic blood pressures.

Table 5: Effect of Amlodipine and Valsartan on Sitting Diastolic/Systolic Blood Pressure

Treatment Group	Diastolic BP		Systolic BP	
	Mean Change*	Treatment Difference**	Mean Change*	Treatment Difference**
Amlodipine and Valsartan 10/160 mg	-11.4	-4.8	-13.9	-5.7
Amlodipine and Valsartan 5/160 mg	-9.6	-3.1	-12.0	-3.9
Valsartan 160 mg	-6.6	—	-8.2	—

*Mean Change from Baseline at Week 8 in Sitting Diastolic/Systolic Blood Pressure. Mean baseline BP was 149.5/96.5 (systolic/diastolic) mmHg.

**Treatment Difference = difference in mean BP reduction between amlodipine and valsartan and the control group (Valsartan 160 mg).

In a double-blind, active-controlled study, a total of 944 patients