AMLODIPINE AND VALSARTAN- amlodipine besylate and valsartan tablet
Lupin Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AMLODIPINE AND VALSARTAN TABLETS safely and effectively. See full prescribing information for AMLODIPINE AND VALSARTAN TABLETS.

AMLODIPINE and VALSARTAN tablets, for oral use.
Initial U.S. Approval: 2007

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

- When pregnancy is detected, discontinue amlodipine and valsartan tablets 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 tablet is the combination tablet of amlodipine, a dihydropyridine calcium channel blocker (DHP CCB), and valsartan, an angiotensin II receptor blocker (ARB). Amlodipine and valsartan tablets are 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 tablets 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)

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 tablets-treated patients and 2.1% in the placebo-treated group. The most common reasons for discontinuation of therapy with amlodipine and valsartan tablets 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 Lupin Pharmaceuticals, Inc. at 1-800-399-2561 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)
- NSAID 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

Nursing Mothers: Avoid use while nursing – discontinue either nursing or drug (8.3)
Geriatric Patients: Not recommended for initial therapy (8.5)
Hepatic Impairment: Not recommended for initial therapy (8.7)
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2015

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FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue amlodipine and valsartan tablets 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 tablets are 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 tablets.

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

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

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

Amlodipine and valsartan tablets 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 tablets 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 tablets.

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 tablets 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 tablets 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

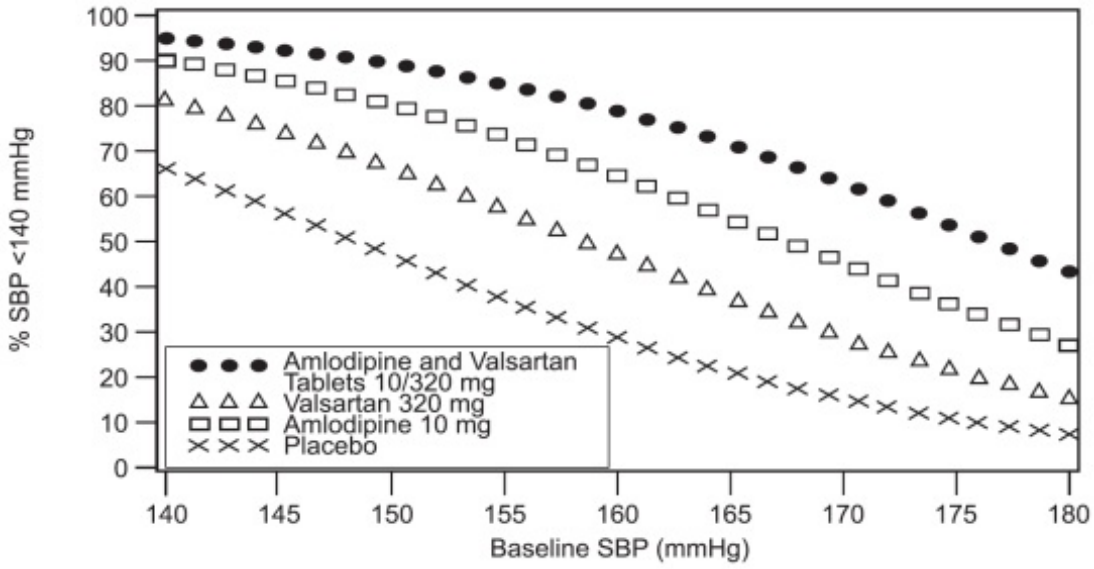


Figure 2: Probability of Achieving Diastolic Blood Pressure <90 mmHg at Week 8

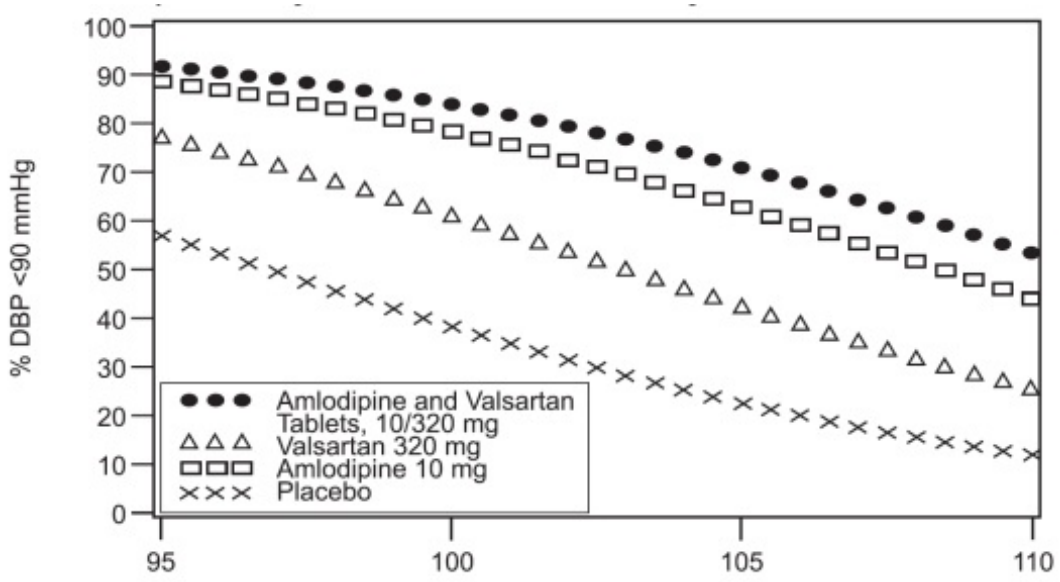


Figure 3: Probability of Achieving Systolic Blood Pressure <130 mmHg at Week 8

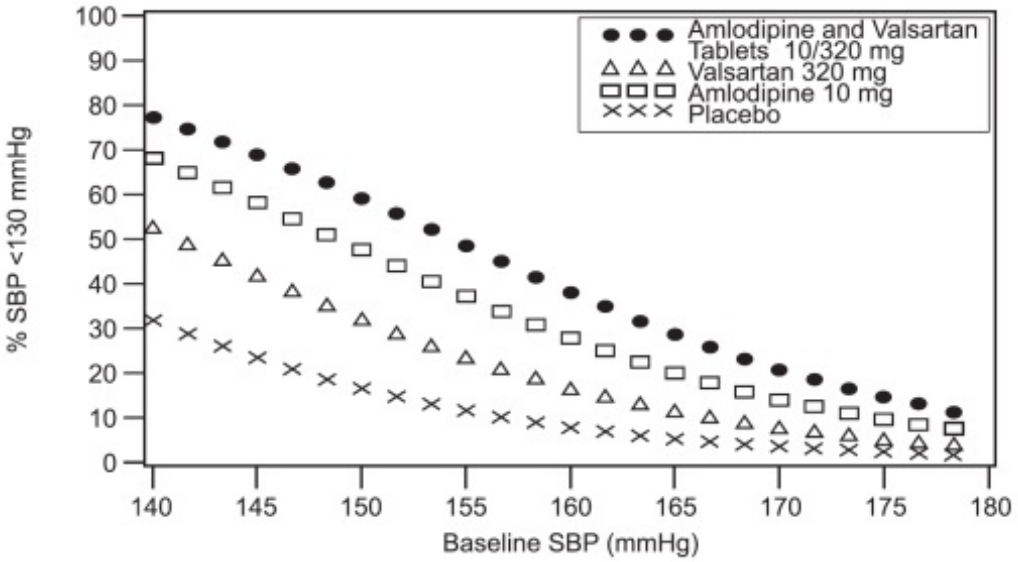
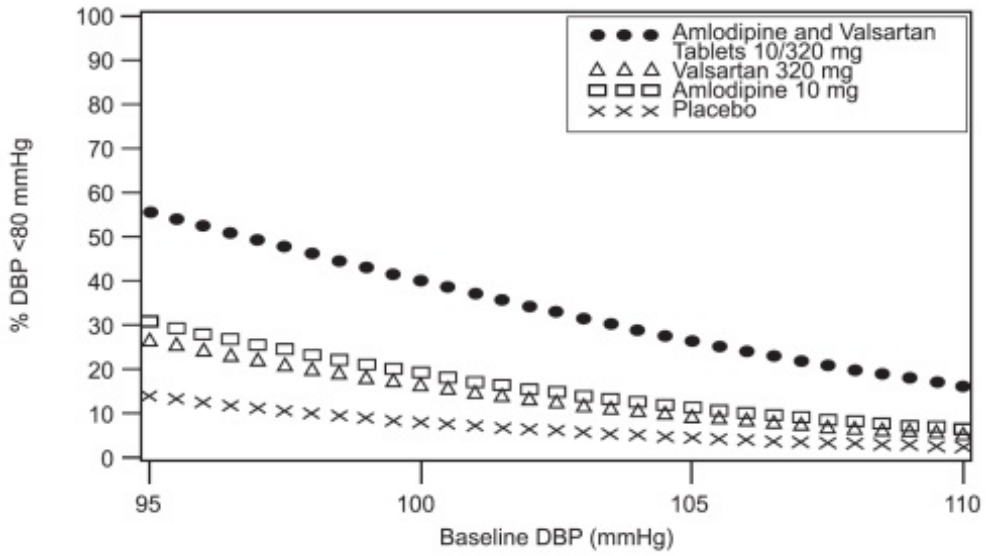


Figure 4: Probability of Achieving Diastolic Blood Pressure <80 mmHg at Week 8



For example, a patient with a baseline blood pressure of 160/100 mmHg has about a 67% likelihood of achieving a goal of <140 mmHg (systolic) and 80% likelihood of achieving <90 mmHg (diastolic) on amlodipine alone, and the likelihood of achieving these goals on valsartan alone is about 47% (systolic) or 62% (diastolic). The likelihood of achieving these goals on amlodipine and valsartan tablets rises to about 80% (systolic) or 85% (diastolic). The likelihood of achieving these goals on placebo is about 28% (systolic) or 37% (diastolic).

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

Dose once daily. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of one 10/320mg tablet once daily as needed to control blood pressure. The majority of the antihypertensive effect is attained within 2 weeks after initiation of therapy or a change in dose.

Amlodipine and valsartan tablets may be administered with or without food.

Amlodipine and valsartan tablets may be administered with other antihypertensive agents.

2.2 Add-on Therapy

A patient whose blood pressure is not adequately controlled with amlodipine (or another dihydropyridine calcium-channel blocker) alone or with valsartan (or another angiotensin II receptor blocker) alone may be switched to combination therapy with amlodipine and valsartan tablets.

A patient who experiences dose-limiting adverse reactions on either component alone may be switched to amlodipine and valsartan tablets 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 tablets 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 tablets containing the same component doses.

2.4 Initial Therapy

A patient may be initiated on amlodipine and valsartan tablets if it is unlikely that control of blood pressure would be achieved with a single agent. The usual starting dose is amlodipine and valsartan

tablets 5/160 mg once daily in patients who are not volume-depleted.

3 DOSAGE FORMS AND STRENGTHS

5/160 mg tablets, debossed with LU/Q12 (side 1/side 2)

10/160 mg tablets, debossed with LU/Q14

5/320 mg tablets, debossed with LU/Q13

10/320 mg tablets, debossed with LU/Q15

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 tablets 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 tablets 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 tablets. Treatment with amlodipine and valsartan tablets 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 tablets, 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 tablets. 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 tablets *[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 tablets 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 Tablets:

Amlodipine and valsartan tablets 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 tablets-treated patients and 2.1% in the placebo-treated group. The most common reasons for discontinuation of therapy with amlodipine and valsartan tablets 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 tablets but at a higher incidence in amlodipine/valsartan patients (n=1437) than placebo (n=337) included peripheral edema (5.4% vs. 3%), 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 tablets (≥ 0.2%) are listed below. It cannot be determined whether these events were causally related to

amlodipine and valsartan tablets.

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, asthenia, 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, hypoesthesia, 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 flushes, 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 ($p<0.001$).

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, asthenia

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 tablets 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 tablets-treated patients.

Serum Potassium:

In hypertensive patients, greater than 20% increases in serum potassium were observed in 2.8% of amlodipine and valsartan tablets-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 tablets-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 uncertain. 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.

Valsartan:

The following additional adverse reactions have been reported in postmarketing experience with valsartan:

Blood and Lymphatic:

Decrease in hemoglobin, decrease in hematocrit, neutropenia,

Hypersensitivity:

There are rare reports of angioedema. Some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Amlodipine and valsartan tablets should not be re-administered to patients who have had angioedema.

Digestive:

Elevated liver enzymes and very rare reports of hepatitis

Renal:

Impaired renal function, renal failure

Clinical Laboratory Tests:

Hyperkalemia

Dermatologic:

Alopecia, bullous dermatitis

Vascular:

Vasculitis Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

7 DRUG INTERACTIONS

No drug interaction studies have been conducted with amlodipine and valsartan tablets and other drugs, although studies have been conducted with the individual amlodipine and valsartan components.

Amlodipine

Impact of Other Drugs on Amlodipine

CYP3A Inhibitors*:*

Co-administration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A inhibitors to determine the need for dose adjustment *[see*

CLINICAL PHARMACOLOGY (12.3)].

***CYP3A Inducers**:*

No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A inducers.

***Sildenafil**:*

Monitor for hypotension when sildenafil is co-administered with amlodipine *[see Clinical Pharmacology (12.2)]*.

Impact of Amlodipine on Other Drugs

Simvastatin:

Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily *[see Clinical Pharmacology (12.3)]*.

Immunosuppressants:

Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate *[see Clinical Pharmacology (12.3)]*.

Valsartan

No clinically significant pharmacokinetic interactions were observed when valsartan was co-administered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.

Warfarin:

Co-administration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including valsartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving valsartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including valsartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

***Potassium*:**

Concomitant use of valsartan with other agents that block the renin-angiotensin system, potassium sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium or other drugs that may increase potassium levels (e.g., heparin) may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine. If co-medication is considered necessary, monitoring of serum potassium is advisable.

CYP 450 Interactions:

In vitro metabolism studies indicate that CYP 450 mediated drug interactions between valsartan and co-administered drugs are unlikely because of low extent of metabolism *[see PHARMACOKINETICS, Valsartan (12.3)]*.

Transporters:

The results from an in vitro study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Coadministration of

inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

Dual Blockade of the Renin-Angiotensin System (RAS):

Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function, and electrolytes in patients on amlodipine and valsartan and other agents that affect the RAS.

Do not coadminister aliskiren with amlodipine and valsartan in patients with diabetes. Avoid use of aliskiren with amlodipine and valsartan in patients with renal impairment (GFR <60 mL/min).

Lithium:

Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists, including valsartan. Monitor serum lithium levels during concomitant use.

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 amlodipine and valsartan tablets as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimesters of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue amlodipine and valsartan tablets, 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 amlodipine and valsartan tablets for hypotension, oliguria, and hyperkalemia. *[see USE IN SPECIFIC POPULATIONS (8.4)]*

8.2 Labor and Delivery

The effect of amlodipine and valsartan tablets on labor and delivery has not been studied.

8.3 Nursing Mothers

It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while amlodipine is administered.

It is not known whether valsartan is excreted in human milk. Valsartan was excreted into the milk of lactating rats; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because many drugs are excreted into human milk and because of the potential for adverse reactions in nursing infants from amlodipine and valsartan tablets, a decision should be made whether to

discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of amlodipine and valsartan tablets in pediatric patients have not been established.

Neonates with a history of in utero exposure to amlodipine and valsartan tablets:

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

8.5 Geriatric Use

In controlled clinical trials, 323 (22.5%) hypertensive patients treated with amlodipine and valsartan tablets were ≥65 years and 79 (5.5%) were ≥75 years. No overall differences in the efficacy or safety of amlodipine and valsartan tablets were observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

Amlodipine

The recommended starting dose of amlodipine 2.5 mg is not available strength with amlodipine and valsartan tablets.

Clinical studies of amlodipine besylate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40% to 60%.

Valsartan

In the controlled clinical trials of valsartan, 1214 (36.2%) of hypertensive patients treated with valsartan were ≥65 years and 265 (7.9%) were ≥75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Safety and effectiveness of amlodipine and valsartan tablets in patients with severe renal impairment (CrCl< 30 mL/min) have not been established. No dose adjustment is required in patients with mild (CrCl 60 to 90 mL/min) or moderate (CrCl 30 to 60 mL/min) renal impairment.

8.7 Hepatic Impairment

Amlodipine

Exposure to amlodipine is increased in patients with hepatic insufficiency *[see CLINICAL PHARMACOLOGY (12.3)]*. The recommended initial dose of amlodipine in patients with hepatic impairment is 2.5 mg, which is not an available strength with amlodipine and valsartan tablets.

Valsartan

No dose adjustment is necessary for patients with mild-to-moderate disease. No dosing recommendations can be provided for patients with severe liver disease.

10 OVERDOSAGE

Amlodipine:

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

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional overdosage 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.

Valsartan:

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

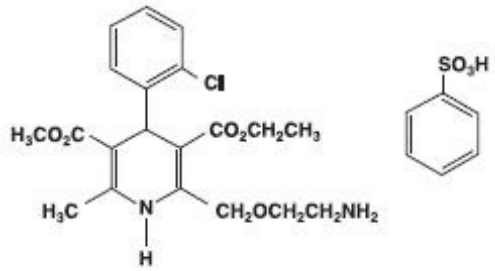
Valsartan is not removed from the plasma by hemodialysis.

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/m^2 basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

11 DESCRIPTION

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

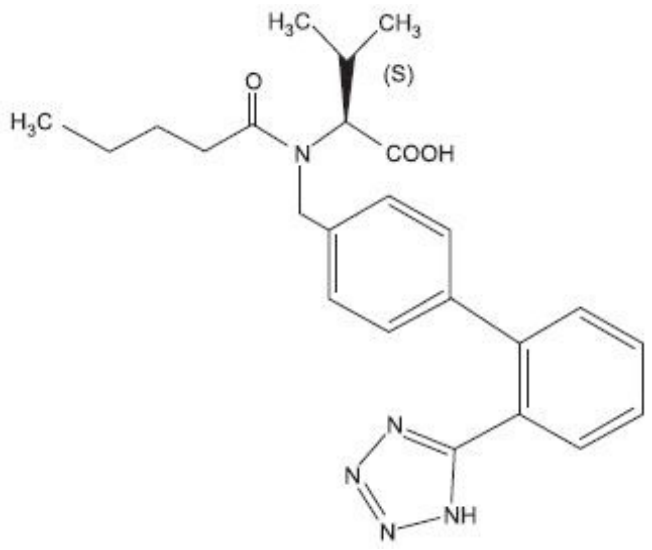
Amlodipine and valsartan tablets contain the besylate salt of amlodipine, a dihydropyridine calcium-channel blocker (CCB). Amlodipine besylate is a white to pale yellow crystalline powder, slightly soluble in water and sparingly soluble in ethanol. Amlodipine besylate's chemical name is 3-Ethyl-5-methyl(4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-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



Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ and its molecular weight is 567.1.

Valsartan is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT_1 receptor subtype. Valsartan is a white to practically 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 empirical formula is $C_{24}H_{29}N_5O_3$ and its molecular weight is 435.5.

Amlodipine and valsartan tablets are formulated in 4 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, croscarmellose sodium, crospovidone, magnesium stearate and microcrystalline cellulose. The film coating contains hypromellose, polyethylene glycol, iron oxide yellow and titanium dioxide. Additionally, the 5/160 mg and 5/320 mg strengths contain iron oxide red.

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 AT_1 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 AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The increased plasma levels of angiotensin following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 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 normal 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.

Drug Interactions:

Sildenafil

When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect *[see DRUG INTERACTIONS (7)]*.

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 tablets

Amlodipine and valsartan tablets have 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 biexponential 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 tablets

Following oral administration of amlodipine and valsartan tablets 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 tablets 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:

Amlodipine

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

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:

Valsartan

Pharmacokinetics of valsartan does not differ significantly between males and females.

Renal Insufficiency:

Amlodipine

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

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:

Amlodipine

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

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.

Impact of other drugs on amlodipine:

Co-administered cimetidine, magnesium-and aluminum hydroxide antacids, sildenafil, and grapefruit juice have no impact on the exposure to amlodipine.

CYP3A inhibitors

Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A (e.g., itraconazole, clarithromycin) may increase the plasma concentrations of amlodipine to a greater extent *[see DRUG INTERACTIONS (7)]*.

Impact of amlodipine on other drugs:

Co-administered amlodipine does not affect the exposure to atorvastatin, digoxin, ethanol and 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 *[see DRUG INTERACTIONS (7)]*.

Cyclosporine

A prospective study in renal transplant patients (N=11) showed on an average of 40% increase in trough cyclosporine levels when concomitantly treated with amlodipine *[see DRUG INTERACTIONS (7)]*.

Tacrolimus

A prospective study in healthy Chinese volunteers (N=9) with CYP3A5 expressers showed a 2.5-to 4-fold increase in tacrolimus exposure when concomitantly administered with amlodipine compared to tacrolimus alone. This finding was not observed in CYP3A5 non-expressers (N= 6). However, a 3-fold increase in plasma exposure to tacrolimus in a renal transplant patient (CYP3A5 non-expresser) upon initiation of amlodipine for the treatment of post-transplant hypertension resulting in reduction of tacrolimus dose has been reported. Irrespective of the CYP3A5 genotype status, the possibility of an interaction cannot be excluded with these drugs *[see DRUG INTERACTIONS (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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/m^2 basis, similar to the MRHD of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m^2 basis, about 2.5 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/m^2 basis).

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/m^2 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/m^2 basis.

13.3 Developmental Toxicity Studies

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/m^2 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 deaths 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.

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/m^2 basis. (Calculations based on a patient weight of 60 kg.)

Amlodipine Besylate and Valsartan

In the oral embryofetal 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 embryofetal effects was 10 mg/kg/day amlodipine plus 160 mg/kg/day valsartan. On a systemic exposure [$AUC_{(0-\infty)}$] basis, these doses are, respectively, 4.3, and 2.7 times the systemic exposure [$AUC_{(0-\infty)}$] in humans receiving the MRHD (10/320 mg/60 kg).

14 CLINICAL STUDIES

Amlodipine and valsartan tablets were 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.

Table 1: Effect of Amlodipine and Valsartan Tablets on Sitting Diastolic 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	-6.4	---	-9.5	-3.1	-10.9	-4.5	-13.2	-6.7
5 mg	-11.1	-4.7	-14.2	-7.8	-14	-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 Tablets 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 152.8 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.

Table 3: Effect of Amlodipine and Valsartan Tablets on Sitting Diastolic 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	-8.2	---	-12.8	-4.5	-12.8	-4.5
10 mg	-15	-6.7	-17.2	-9	-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 Tablets 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	---	-18.1	-7	-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 Tablets on Sitting Diastolic/Systolic Blood Pressure

Treatment Group	Diastolic BP		Systolic BP	
	Mean change*	Treatment Difference†	Mean change*	Treatment Difference†
Amlodipine and valsartan tablets 10/160 mg	-11.4	-4.8	-13.9	-5.7
Amlodipine and valsartan tablets 5/160 mg	-9.6	-3.1	-12	-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 tablets and the control group (Valsartan 160 mg)

In a double-blind, active-controlled study, a total of 944 patients with mild to moderate hypertension who were not adequately controlled on amlodipine 10 mg received a combination of amlodipine and valsartan (10/160 mg) or amlodipine alone (10 mg). At week 8, the combination treatment was statistically significantly superior to the monotherapy component in reduction of diastolic and systolic blood pressures.

Table 6: Effect of Amlodipine and Valsartan Tablets on Sitting Diastolic/Systolic Blood Pressure

Treatment Group	Diastolic BP		Systolic BP	
	Mean change*	Treatment Difference†	Mean change*	Treatment Difference†
Amlodipine and valsartan tablets 10/160 mg	-11.8	-1.8	-12.7	-1.9
Amlodipine 10 mg	-10	---	-10.8	---

* Mean Change from Baseline at Week 8 in Sitting Diastolic/Systolic Blood Pressure. Mean baseline BP was 147.0/95.1 (systolic/ diastolic) mmHg

† Treatment Difference = difference in mean BP reduction between amlodipine and valsartan tablets and the control group (Amlodipine 10 mg)

Amlodipine and valsartan tablets was also evaluated for safety in a 6-week, double-blind, active-controlled trial of 130 hypertensive patients with severe hypertension (mean baseline BP of 171/113 mmHg). Adverse events were similar in patients with severe hypertension and mild/moderate hypertension treated with amlodipine and valsartan tablets.

A wide age range of the adult population, including the elderly was studied (range 19 to 92 years, mean 54.7 years). Women comprised almost half of the studied population (47.3%). Of the patients in the

studied amlodipine and valsartan tablets group, 87.6% were Caucasian. Black and Asian patients each represented approximately 4% of the population in the studied amlodipine and valsartan tablets group.

Two additional double-blind, active-controlled studies were conducted in which amlodipine and valsartan tablets was administered as initial therapy. In 1 study, a total of 572 black patients with moderate to severe hypertension were randomized to receive either combination amlodipine/valsartan or amlodipine monotherapy for 12 weeks. The initial dose of amlodipine/valsartan was 5/160 mg for 2 weeks with forced titration to 10/160 mg for 2 weeks, followed by optional titration to 10/320 mg for 4 weeks and optional addition of HCTZ 12.5 mg for 4 weeks. The initial dose of amlodipine was 5 mg for 2 weeks with forced titration to 10 mg for 2 weeks, followed by optional titration to 10 mg for 4 weeks and optional addition of HCTZ 12.5 mg for 4 weeks. At the primary endpoint of 8 weeks, the treatment difference between amlodipine/valsartan and amlodipine was 6.7/2.8 mmHg.

In the other study of similar design, a total of 646 patients with moderate to severe hypertension (MSSBP of ≥160 mmHg and <200 mmHg) were randomized to receive either combination amlodipine/valsartan or amlodipine monotherapy for 8 weeks. The initial dose of amlodipine/valsartan was 5/160 mg for 2 weeks with forced titration to 10/160 mg for 2 weeks, followed by the optional addition of HCTZ 12.5 mg for 4 weeks. The initial dose of amlodipine was 5 mg for 2 weeks with forced titration to 10 mg for 2 weeks, followed by the optional addition of HCTZ 12.5 mg for 4 weeks. At the primary endpoint of 4 weeks, the treatment difference between amlodipine/valsartan and amlodipine was 6.6/3.9 mmHg.

There are no trials of the amlodipine and valsartan combination tablet demonstrating reductions in cardiovascular risk in patients with hypertension, but the amlodipine component and several ARBs, which are the same pharmacological class as the valsartan component, have demonstrated such benefits.

16 HOW SUPPLIED/STORAGE AND HANDLING

Amlodipine and Valsartan is available as tablets containing amlodipine besylate equivalent to 5 mg, or 10 mg of amlodipine free-base with valsartan 160 mg or 320 mg, providing for the following available combinations: 5/160 mg, 10/160 mg, 5/320 mg, and 10/320 mg.

All strengths are packaged in bottles of 30, 90 and 500 count, and unit dose blister packages.

5/160 mg Tablets – Mustard coloured, capsule shaped, film coated, biconvex tablets debossed 'LU' on one side and 'Q12' on the other side.

Bottles of 30	NDC # 68180-764-06
Bottles of 90	NDC # 68180-764-09
Bottles of 500	NDC # 68180-764-02

Unit Dose 100 tablets (10 x 10 tablets blister cards) NDC # 68180-764-13

10/160 mg Tablets - Yellow, capsule shaped, film coated, biconvex tablets debossed 'LU' on one side and 'Q14' on the other side.

Bottles of 30	NDC # 68180-765-06
Bottles of 90	NDC # 68180-765-09
Bottles of 500	NDC # 68180-765-02

Unit Dose 100 tablets (10 x 10 tablets blister cards) NDC # 68180-765-13

5/320 mg Tablets - Mustard coloured, capsule shaped, film coated, biconvex tablets debossed 'LU' on one side and 'Q13' on the other side.

Bottles of 30	NDC # 68180-766-06
Bottles of 90	NDC # 68180-766-09
Bottles of 500	NDC # 68180-766-02

Unit Dose 100 tablets (10 x 10 tablets blister cards) NDC # 68180-766-13

10/320 mg Tablets - Yellow, capsule shaped, film coated, biconvex tablets debossed 'LU' on one side and 'Q15' on the other side

Bottles of 30	NDC # 68180-767-06
Bottles of 90	NDC # 68180-767-09
Bottles of 500	NDC # 68180-767-02

Unit Dose 100 tablets (10 x 10 tablets blister cards) NDC # 68180-767-13

Store at 25^0C (77^0F); excursions permitted to 15 to 30^0C (59 to 86^0F). [See USP Controlled Room Temperature.] Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Information for Patients

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

Pregnancy

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

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Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States

Manufactured by:

Lupin Limited

Goa - 403722

India

Revised: October 2015 ID#: 242870

FDA-APPROVED PATIENT LABELING

PATIENT INFORMATION

Amlodipine (am-LOE-di-peen) and Valsartan (val-SAR-tan) Tablets

Rx only

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

What is the most important information I should know about amlodipine and valsartan tablets?

- Amlodipine and valsartan tablets 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 amlodipine and valsartan tablets, tell your doctor right away.

What are amlodipine and valsartan tablets?

Amlodipine and valsartan tablets contain 2 prescription medicines:

1. amlodipine, a calcium channel blocker

2. valsartan, an angiotensin receptor blocker (ARB).

Amlodipine and valsartan tablets may be used to lower high blood pressure (hypertension) in adults

- when 1 medicine to lower your high blood pressure is not enough
- as the first medicine to lower high blood pressure if your doctor decides you are likely to need more than 1 medicine.

Amlodipine and valsartan tablets have not been studied in children under 18 years of age.

What should I tell my doctor before taking amlodipine and valsartan tablets?

Tell your doctor about all of your medical conditions, including if you:

- **are pregnant or plan to become pregnant.** See "What is the most important information I should know about amlodipine and valsartan tablets?"
- **are breastfeeding or plan to breastfeed.** Amlodipine and valsartan tablets may pass into your milk. Do not breastfeed while you are taking amlodipine and valsartan tablets.
- have heart problems
- have liver problems
- have kidney problems
- are vomiting or having a lot of diarrhea
- have ever had a reaction called angioedema, to another blood pressure medicine. Angioedema causes swelling of the face, lips, tongue, throat, and may cause difficulty breathing.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some of your other medicines and amlodipine and valsartan tablets could affect each other, causing serious side effects.

Especially tell your doctor if you take:

- simvastatin or other cholesterol-lowering medicine
- other medicines for high blood pressure or a heart problem
- water pills (diuretics)
- potassium supplements. Your doctor may check the amount of potassium in your blood periodically.
- a salt substitute. Your doctor may check the amount of potassium in your blood periodically.
- nonsteroidal anti-inflammatory drugs (like ibuprofen or naproxen)
- medicines used to prevent and treat fungal skin infections (such as ketoconazole, itraconazole)
- medicines used to treat bacterial infections (such as clarithromycin, telithromycin)
- certain antibiotics (rifamycin group), a drug used to protect against transplant rejection (cyclosporine) or an antiretroviral drug used to treat HIV/AIDS infection (ritonavir). These drugs may increase the effect of valsartan.
- lithium, a medicine used in some types of depression

Know the medicines you take. Keep a list of your medicines and show it to your doctor or pharmacist

when you get a new medicine. Talk to your doctor or pharmacist before you start taking any new medicine. Your doctor or pharmacist will know what medicines are safe to take together.

How should I take amlodipine and valsartan tablets?

- Take amlodipine and valsartan tablets exactly as your doctor tells you.
- Take amlodipine and valsartan tablets once each day.
- Amlodipine and valsartan tablets can be taken with or without food.
- If you miss a dose, 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 amlodipine and valsartan tablets, call your doctor or Poison Control Center, or go to the emergency room.
- Tell all your doctors or dentist you are taking amlodipine and valsartan tablets if you:

  o are going to have surgery

  o go for kidney dialysis

What should I avoid while taking amlodipine and valsartan tablets?

You should not take amlodipine and valsartan tablets during pregnancy. See "What is the most important information I should know about amlodipine and valsartan tablets."

What are the possible side effects of amlodipine and valsartan tablets?

Amlodipine and valsartan tablets may cause **serious side effects** including:

- **harm to an unborn baby causing injury and even death.** See "What is the most important information I should know about amlodipine and valsartan tablets?"
- **low blood pressure (hypotension).** Low blood pressure is most likely to happen if you:

  o take water pills

  o are on a low salt diet

  o get dialysis treatments

  o have heart problems

  o get sick with vomiting or diarrhea

  o drink alcohol

Lie down if you feel faint or dizzy. Call your doctor right away.

- **more heart attacks and chest pain (angina)** in people that already have severe heart problems. This may happen when you start amlodipine and valsartan tablets or when there is an increase in your dose of amlodipine and valsartan tablets. Get emergency help if you get worse chest pain or chest pain that does not go away.
- **kidney problems.** Kidney problems may become worse in people that already have kidney disease. Some people will have changes in blood tests for kidney function and may need a lower dose of amlodipine and valsartan tablets. Call your doctor if you have swelling in your feet, ankles, or hands or unexplained weight gain. If you have heart failure, your doctor should check your kidney function before prescribing amlodipine and valsartan tablets.
- **laboratory blood test changes in people with heart failure**. Some people with heart failure who take valsartan, 1 of the medicines in amlodipine and valsartan tablets, have changes in blood tests including increased potassium and decreased kidney function.

The most common side effects of amlodipine and valsartan tablets include:

- swelling (edema) of the hands, ankles, or feet
- nasal congestion, sore throat, and discomfort when swallowing
- upper respiratory tract infection (head or chest cold)
- dizziness

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of amlodipine and valsartan tablets. 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 should I store amlodipine and valsartan tablets?

- Store at 25ºC (77ºF); excursions permitted to 15 to 30ºC (59 to 86ºF).
- Keep amlodipine and valsartan tablets dry (protect it from moisture).

Keep amlodipine and valsartan tablets and all medicines out of the reach of children.

General Information about amlodipine and valsartan tablets

Medicines are sometimes prescribed for conditions that are not mentioned in the patient information leaflet. Do not use amlodipine and valsartan tablets for a condition for which it was not prescribed. Do not give amlodipine and valsartan tablets to other people, even if they have the same symptoms that you have. It may harm them.

This patient information leaflet summarizes the most important information about amlodipine and valsartan tablets. If you would like more information about amlodipine and valsartan tablets, talk with your doctor. You can ask your doctor or pharmacist for information about amlodipine and valsartan tablets that is written for health professionals. For more information go to www.lupinpharmaceuticals.com or call 1-800-399-2561.

What are the ingredients in amlodipine and valsartan tablets?

Active ingredients: Amlodipine besylate and valsartan

The inactive ingredients of all strengths of the tablets are colloidal silicon dioxide, croscarmellose sodium, crospovidone, magnesium stearate and microcrystalline cellulose. The film coating contains hypromellose, polyethylene glycol, iron oxide yellow and titanium dioxide. Additionally, the 5/160 mg and 5/320 mg strengths contain iron oxide red.

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. Amlodipine and valsartan tablets can help your blood vessels relax so your blood pressure is lower. Medicines that lower blood pressure lower your chance of having a stroke or heart attack.

High blood pressure makes the heart work harder to pump blood throughout the body and causes damage to blood vessels. If high blood pressure is not treated, it can lead to stroke, heart attack, heart failure, kidney failure, and vision problems.

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Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States

Manufactured by:

Lupin Limited

Goa - 403722

India

Revised: October 2015 ID#: 242871

Strength: 5/160 mg Tablets

Container Label: 30s Pack

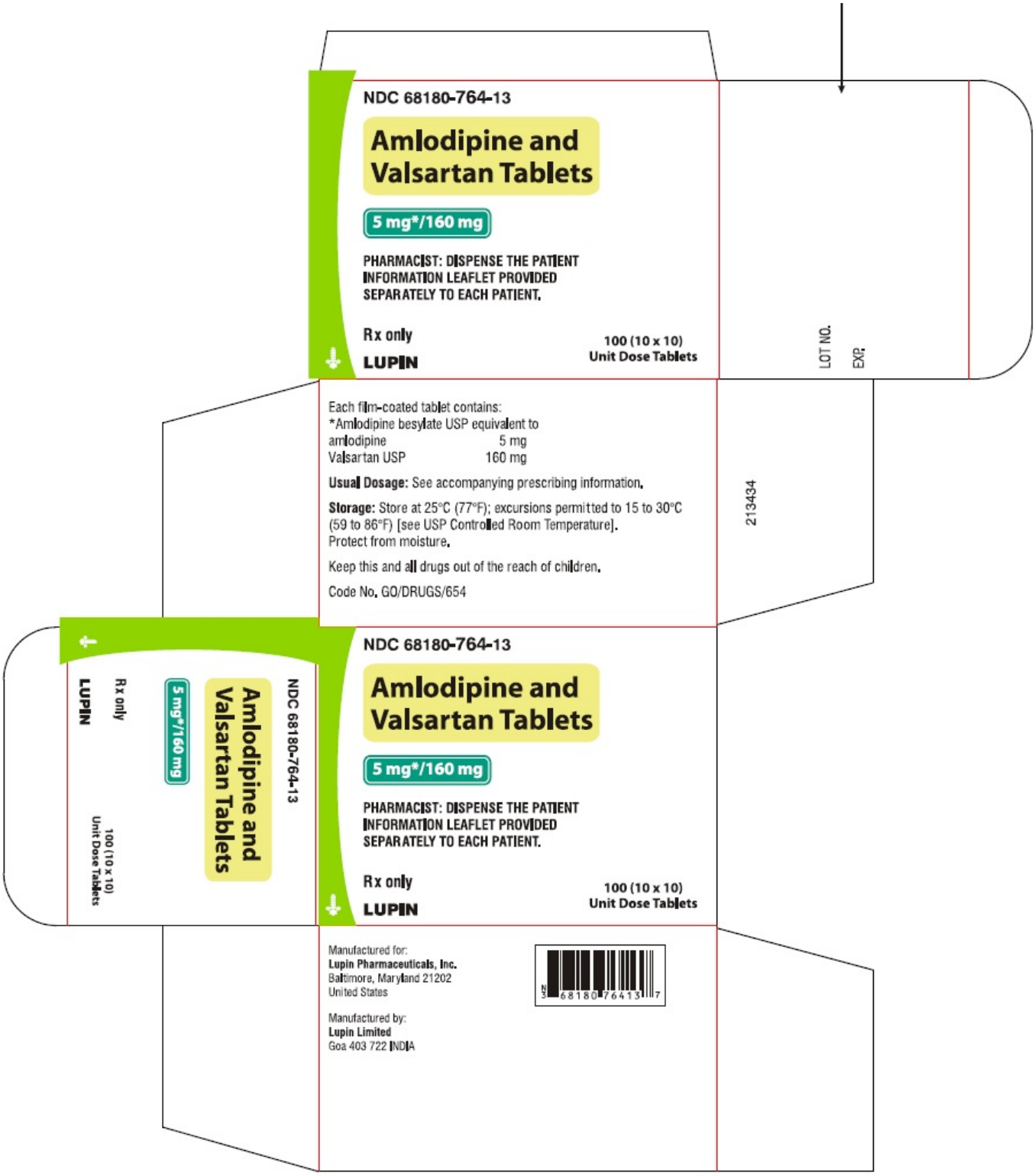
NDC 68180-764-06

5mg-160mg-30s-container

Strength: 5/160 mg Tablets

Carton Label: 100 Tablets

NDC 68180-764-13

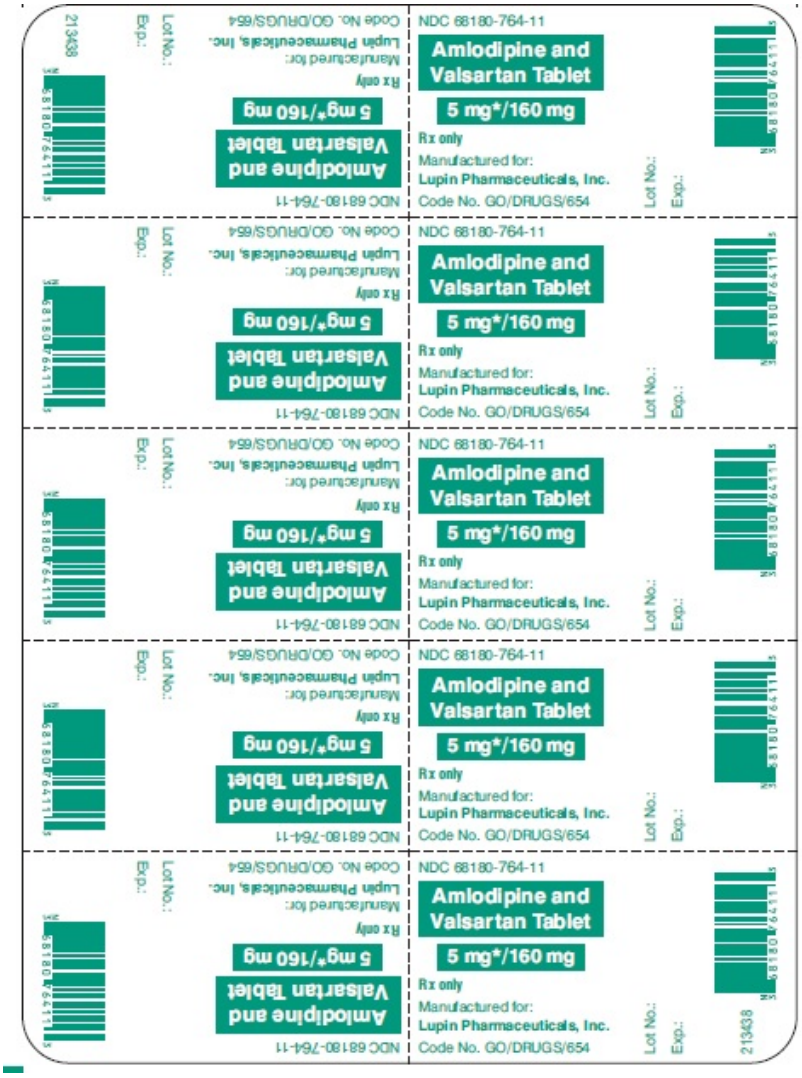


5mg-160mg-carton

Strength: 5/160 mg Tablets

NDC 68180-764-11

Blister strip of 10's

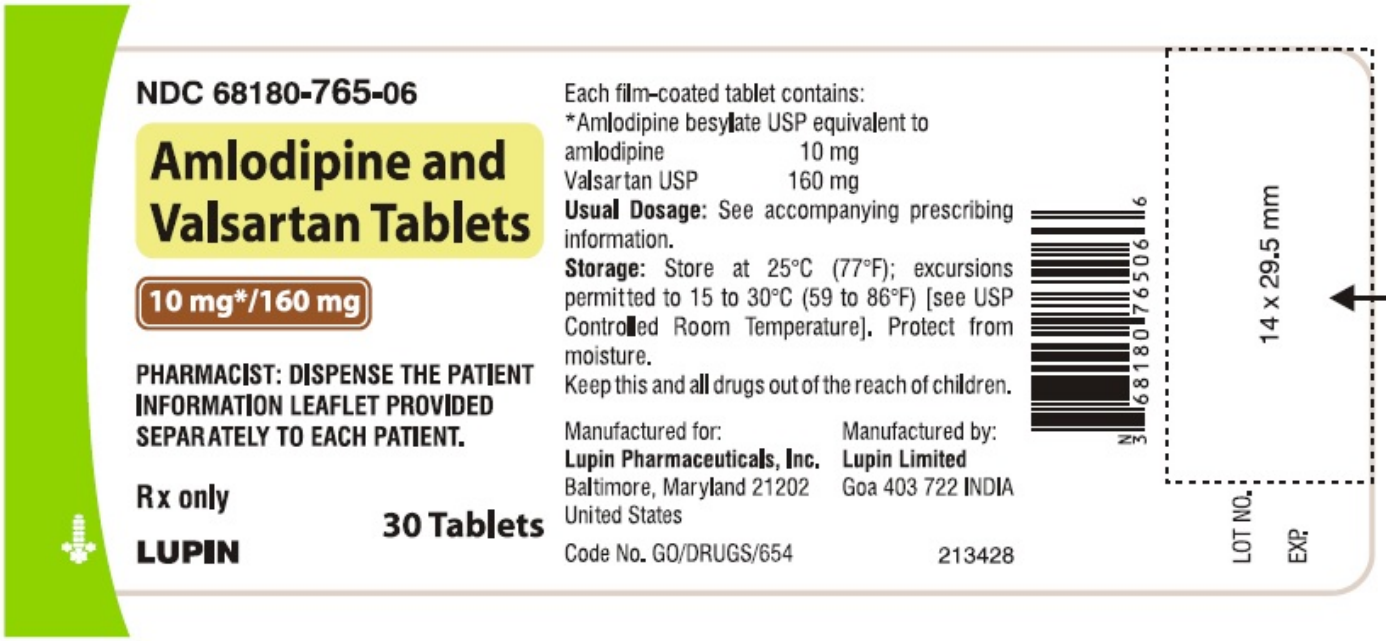


5mg-160mg-foil

Strength: 10/160 mg Tablets

Container Label: 30s Pack

NDC 68180-765-06

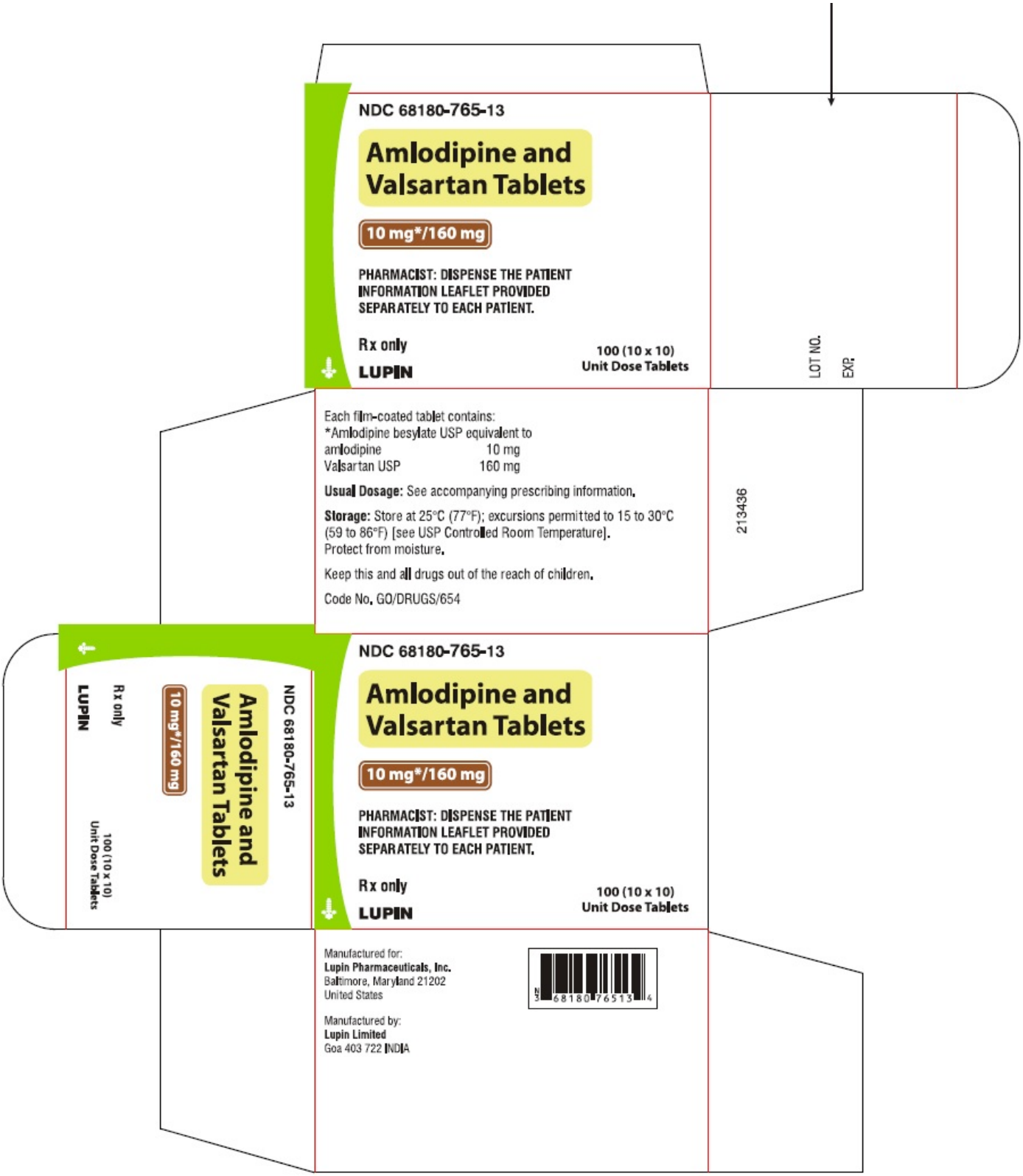


10mg-160mg-30s-container

Strength: 10/160 mg Tablets

Carton Label: 100 Tablets

NDC 68180-765-13

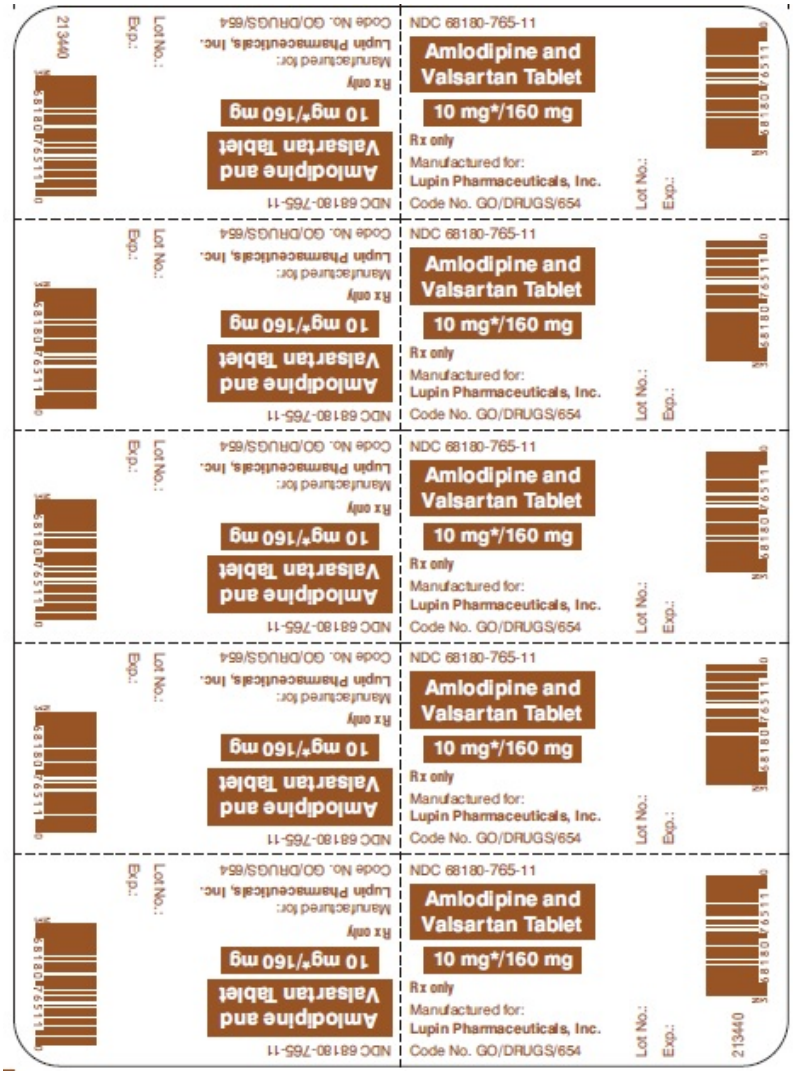


10mg-160mg-carton

Strength: 10/160 mg Tablets

NDC 68180-765-11

Blister strip of 10's

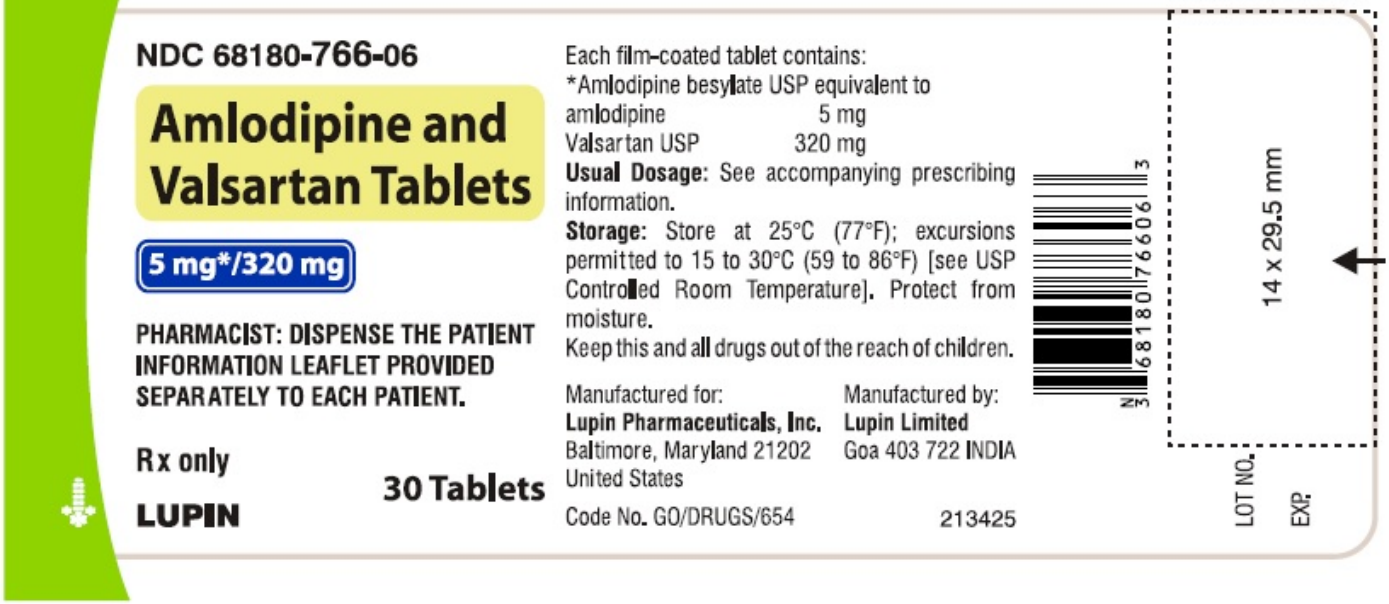


10mg-160mg-foil

Strength: 5/320 mg Tablets

Container Label: 30s Pack

NDC 68180-766-06

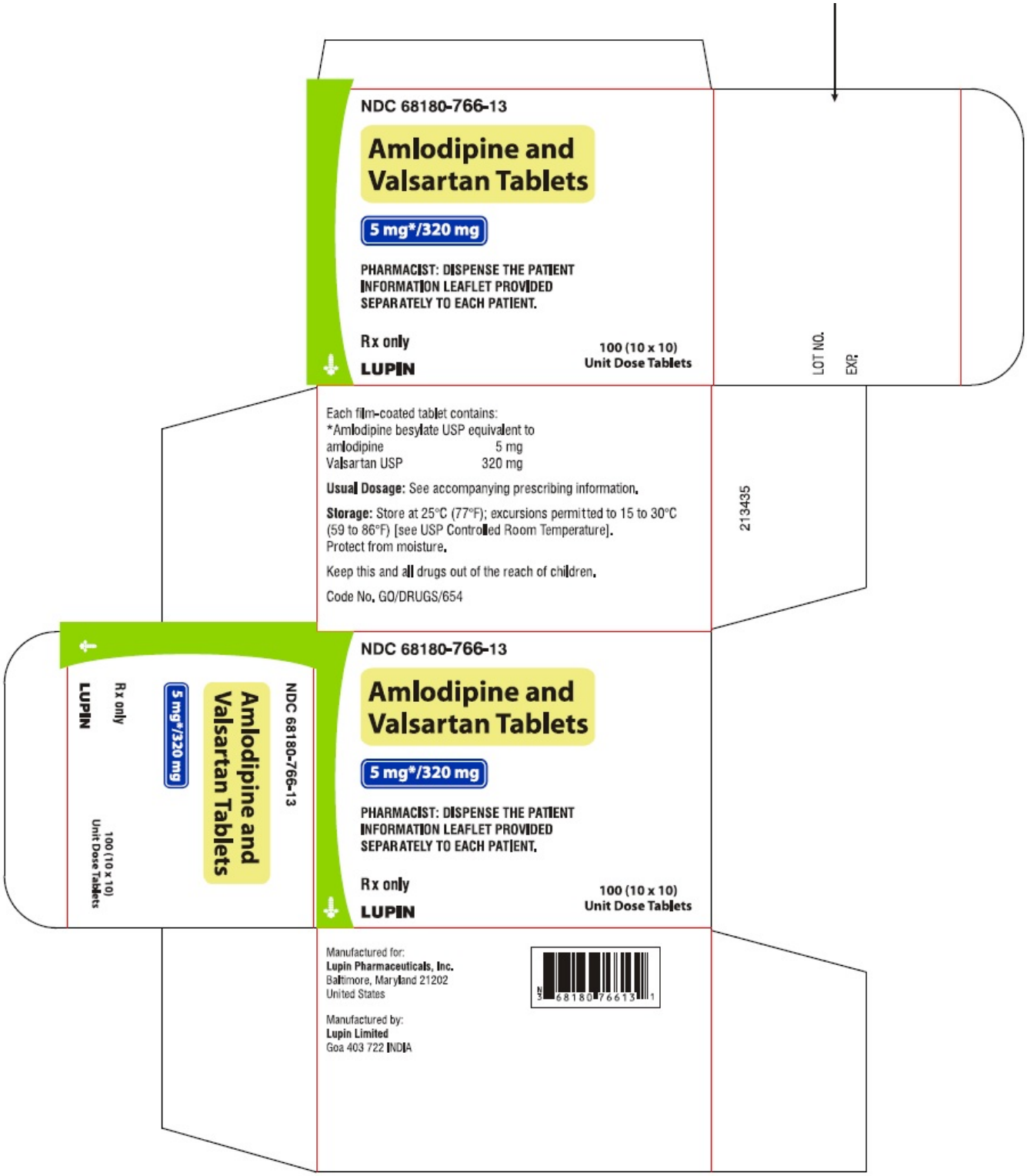


5mg-320mg-30s-container

Strength: 5/320 mg Tablets

Carton Label: 100 Tablets

NDC 68180-766-13

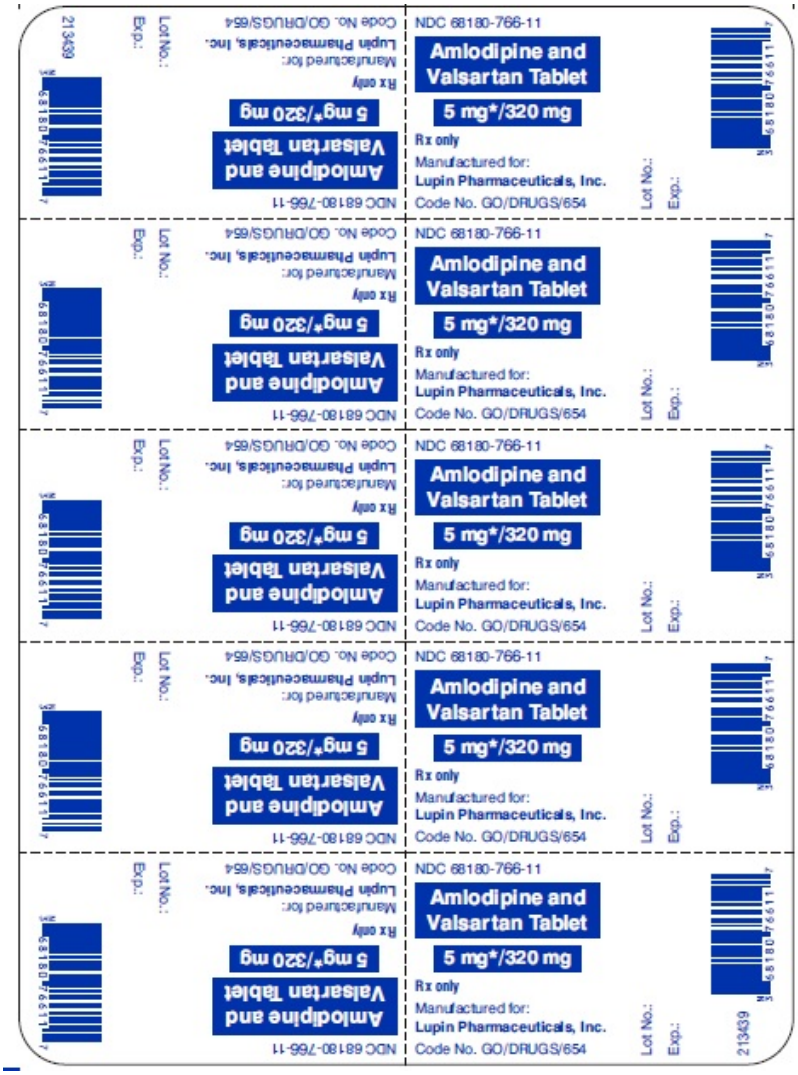


5mg-320mg-carton

Strength: 5/320 mg Tablets

NDC 68180-766-11

Blister strip of 10's

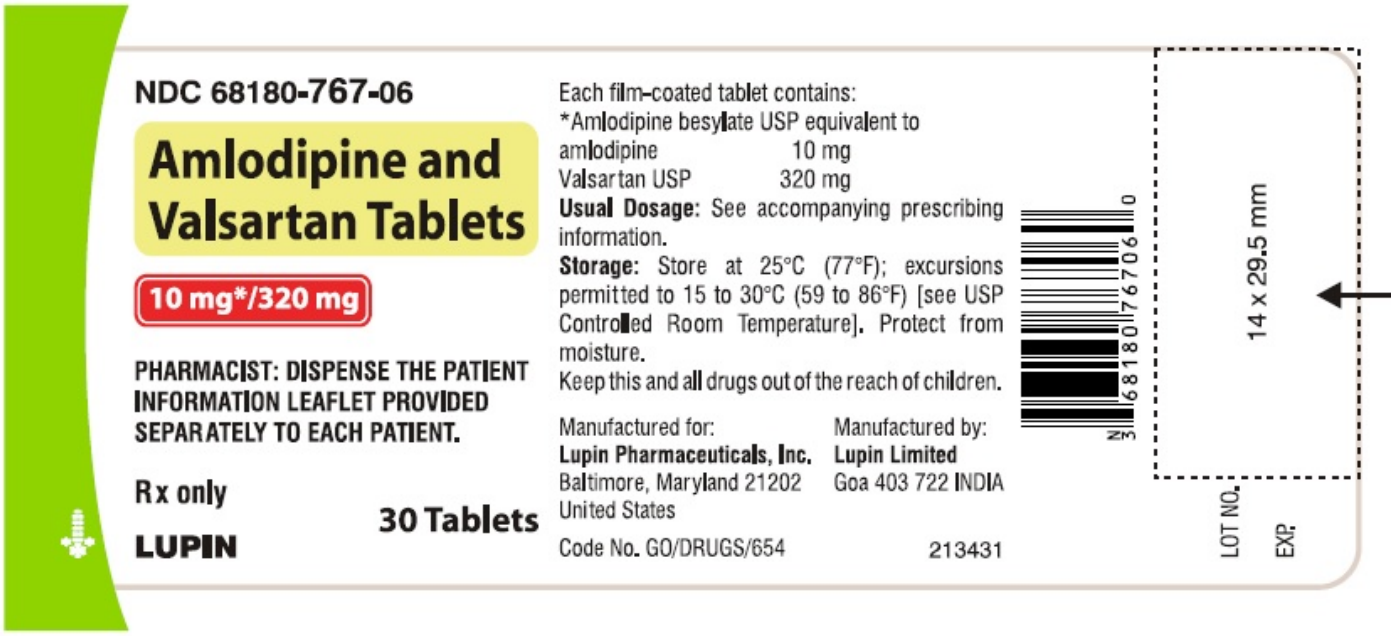


5mg-320mg-foil

Strength: 10/320 mg Tablets

Container Label: 30s Pack

NDC 68180-767-06

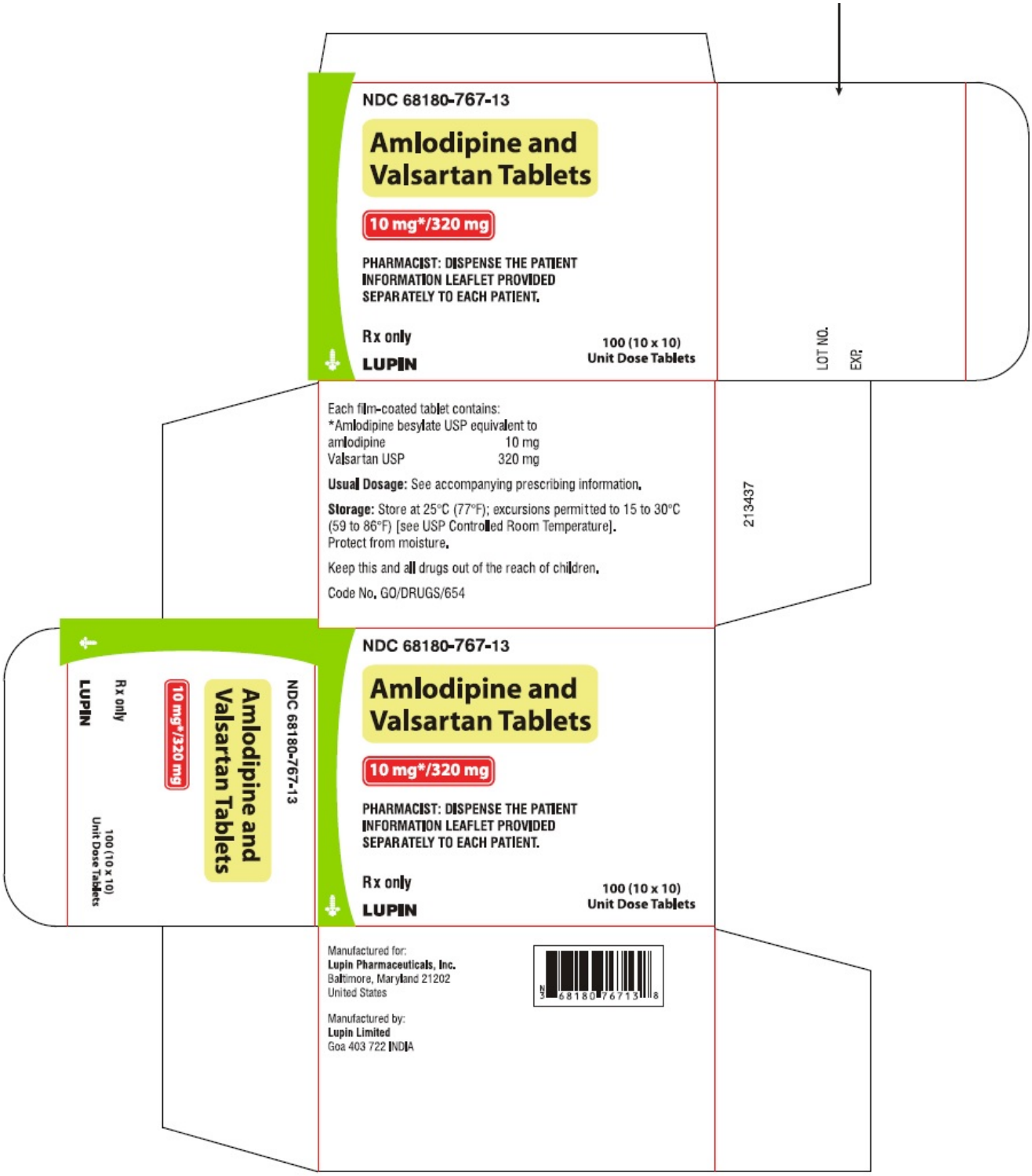


10mg-320mg-30s-container

Strength: 10/320 mg Tablets

Carton Label: 100 Tablets

NDC 68180-767-13



10mg-320mg-carton

Strength: 10/320 mg Tablets

NDC 68180-767-11

Blister strip of 10's

10mg-320mg-foil

AMLODIPINE AND VALSARTAN

amlodipine and valsartan tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68180-764
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (UNII: 864V2Q084H) (AMLODIPINE - UNII:1J444QC288)	AMLODIPINE	5 mg
VALSARTAN (UNII: 80M03YXJ7I) (VALSARTAN - UNII:80M03YXJ7I)	VALSARTAN	160 mg

Inactive Ingredients

Ingredient Name	Strength
FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics			
Color	YELLOW (Mustard)	**Score**	no score
Shape	CAPSULE (capsule)	**Size**	16mm
Flavor		**Imprint Code**	LU;Q12
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68180-764-02	500 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:68180-764-11	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		
3	NDC:68180-764-09	90 in 1 BOTTLE; Type 0: Not a Combination Product		
4	NDC:68180-764-06	30 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090245	03/30/2015	

AMLODIPINE AND VALSARTAN

amlodipine and valsartan tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68180-765
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
AMLODIPINE BESYLATE (UNII: 864V2Q084H) (AMLODIPINE - UNII:1J444QC288)	AMLODIPINE	10 mg
VALSARTAN (UNII: 80M03YXJ7I) (VALSARTAN - UNII:80M03YXJ7I)	VALSARTAN	160 mg

Product Characteristics			
Color	YELLOW (Yellow)	**Score**	no score
Shape	CAPSULE (capsule)	**Size**	16mm
Flavor		**Imprint Code**	LU;Q14
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68180-765-09	90 in 1 BOTTLE; Type 0: Not a Combination Product		

2	NDC:68180-765-02	500 in 1 BOTTLE; Type 0: Not a Combination Product		
3	NDC:68180-765-11	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		
4	NDC:68180-765-06	30 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090245	03/30/2015	

AMLODIPINE AND VALSARTAN

amlodipine and valsartan tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68180-766
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (UNII: 864V2Q084H) (AMLODIPINE - UNII:1J444QC288)	AMLODIPINE	5 mg
VALSARTAN (UNII: 80M03YXJ7I) (VALSARTAN - UNII:80M03YXJ7I)	VALSARTAN	320 mg

Inactive Ingredients

Ingredient Name	Strength
FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics

Color	YELLOW (Mustard)	**Score**	no score
Shape	CAPSULE (capsule)	**Size**	21mm
Flavor		**Imprint Code**	LU;Q13
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68180-766-11	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		
2	NDC:68180-766-06	30 in 1 BOTTLE; Type 0: Not a Combination Product		
3	NDC:68180-766-09	90 in 1 BOTTLE; Type 0: Not a Combination Product		
4	NDC:68180-766-02	500 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090245	03/30/2015	

AMLODIPINE AND VALSARTAN

amlodipine and valsartan tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68180-767
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (UNII: 864V2Q084H) (AMLODIPINE - UNII:1J444QC288)	AMLODIPINE	10 mg
VALSARTAN (UNII: 80M03YXJ7I) (VALSARTAN - UNII:80M03YXJ7I)	VALSARTAN	320 mg

Product Characteristics

Color	YELLOW (Yellow)	**Score**	no score
Shape	CAPSULE (capsule)	**Size**	21mm
Flavor		**Imprint Code**	LU;Q15
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68180-767-02	500 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:68180-767-11	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		
3	NDC:68180-767-09	90 in 1 BOTTLE; Type 0: Not a Combination Product		
4	NDC:68180-767-06	30 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090245	03/30/2015	

Labeler - Lupin Pharmaceuticals, Inc. (089153071)