

AMLODIPINE AND VALSARTAN - amlodipine 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 are the combination tablets 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 Tablets 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 Tablets were peripheral edema and vertigo. The adverse experiences that occurred in clinical trials ($\geq 2\%$ 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 1-866-

403-7592 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)
- Non-Steroidal Anti-Inflammatory Drug (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 level and lithium toxicity (7)

-----**USE IN SPECIFIC POPULATIONS**-----

Lactation: Breastfeeding is not recommended (8.2)
Geriatric Patients: Not recommended for initial therapy (8.5)
Hepatic Impairment: Not recommended for initial therapy (8.7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2023

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FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

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- **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 angiotensin II receptor blocker (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.

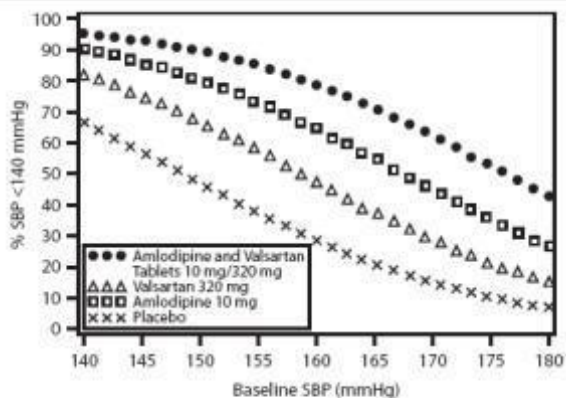


Figure 1: Probability of Achieving Systolic Blood Pressure <140 mmHg at Week 8

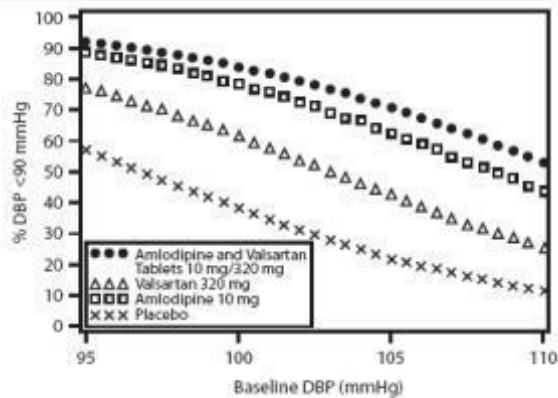


Figure 2: Probability of Achieving Diastolic Blood Pressure <90 mmHg at Week 8

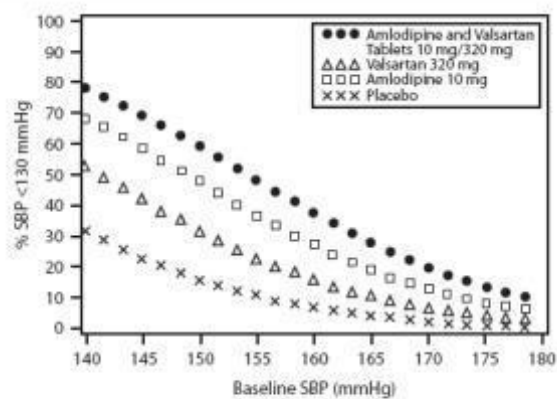


Figure 3: Probability of Achieving Systolic Blood Pressure <130 mmHg at Week 8

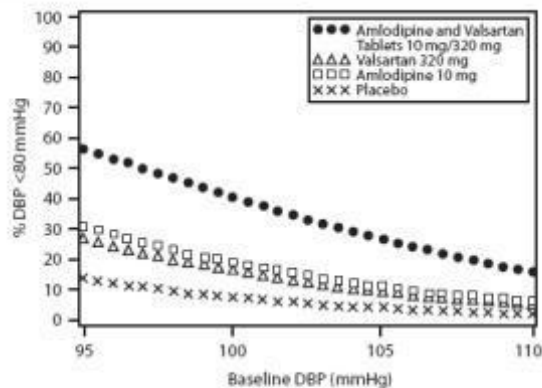


Figure 4: Probability of Achieving Diastolic Blood Pressure <80 mmHg at Week 8

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 10/320 mg 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 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 ARB) 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 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

Amlodipine and Valsartan Tablets are available as follows:

5/160 mg tablets, debossed "N 83" on one side and plain on the other

10/160 mg tablets, debossed "N 82" on one side and plain on the other

5/320 mg tablets, debossed "N 81" on one side and plain on the other

10/320 mg tablets, debossed "N 08" on one side and plain on the other

4 CONTRAINDICATIONS

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

Do not coadminister aliskiren with Amlodipine and Valsartan Tablets in patients with diabetes [see *Drug Interactions* (7)].

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Amlodipine and Valsartan Tablets can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. 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, place the patient in a supine position and, if necessary, give intravenous 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 have 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 3.0%), 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.

Studies with Valsartan:

Valsartan has been evaluated for safety in more than 4000 hypertensive patients in clinical trials. In trials in which valsartan was compared to an angiotensin-converting enzyme (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 ($p < 0.001$).

Clinical Lab Test Findings:

Creatinine: 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.

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 [see *Warnings and Precautions (5.4)*]

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

6.2 Postmarketing Experience

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

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:

Hypersensitivity: Angioedema has been reported. 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 reports of hepatitis

Musculoskeletal: Rhabdomyolysis

Renal: Impaired renal function, renal failure

Dermatologic: Alopecia, bullous dermatitis

Blood and Lymphatic: Thrombocytopenia

Vascular: Vasculitis

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

Coadministration 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 coadministered 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 coadministered with CYP3A inducers (e.g. rifampicin, St. John's Wort).

Sildenafil

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

Impact of Amlodipine on Other Drugs

Simvastatin

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

Immunosuppressants

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

Valsartan

Agents Increasing Serum 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.

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.

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 valsartan and other agents that affect the RAS.

Do not coadminister aliskiren with Amlodipine and Valsartan tablets in patients with diabetes. Avoid use of aliskiren with Amlodipine and Valsartan tablets 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. Monitor serum lithium levels during concomitant use.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Amlodipine and Valsartan Tablets can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. 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. Published reports include cases of anhydramnios and oligohydramnios in pregnant women treated with valsartan (*see Clinical Considerations*).

When pregnancy is detected, discontinue Amlodipine and Valsartan Tablets as soon as possible.

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

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal risk

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

Fetal/Neonatal Adverse Reactions

Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension and death.

Perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. If oligohydramnios is observed, consider alternative drug treatment. Closely observe neonates with histories of *in utero* exposure to Amlodipine and Valsartan Tablets for hypotension, oliguria, and hyperkalemia. In neonates with a history of *in utero* exposure to Amlodipine and Valsartan Tablets, if oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.

Data

Animal Data

In rats, administered 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. This corresponds to dose multiples of 9 and 19.5 times, respectively, the maximum recommended human dose (MRHD) of 10 mg/day for amlodipine and 320 mg/day for valsartan (based on body surface area and considering a 60 kg patient).

8.2 Lactation

Risk Summary

There is limited information regarding the presence of Amlodipine and Valsartan in human milk, the effects on the breastfed infant, or the effects on milk production. Valsartan is present in rat milk. Limited published studies report that amlodipine is present in human milk. Because of the potential for serious adverse reactions in breastfed infants, advise a nursing woman that breastfeeding is not recommended during treatment with Amlodipine and Valsartan Tablets.

Data

Valsartan was detected in the milk of lactating rats 15 minutes after oral administration of a 3 mg/kg dose.

8.4 Pediatric Use

Safety and effectiveness of Amlodipine and Valsartan Tablets in pediatric patients have not been established.

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 an 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 area under the curve (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 ($\text{CrCl} < 30 \text{ mL/min}$) have not been established. No dose adjustment is required in patients with mild ($\text{CrCl} 60 \text{ to } 90 \text{ mL/min}$) or moderate ($\text{CrCl} 30 \text{ to } 60 \text{ mL/min}$) 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 overdose 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, institute supportive treatment.

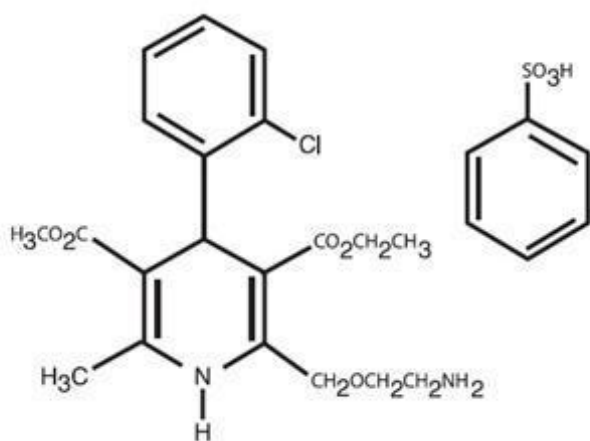
Valsartan is not removed from the plasma by hemodialysis.

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 MRHD on a mg/m² basis) (Calculations assume an oral dose of 320 mg/day and a 60 kg patient.)

11 DESCRIPTION

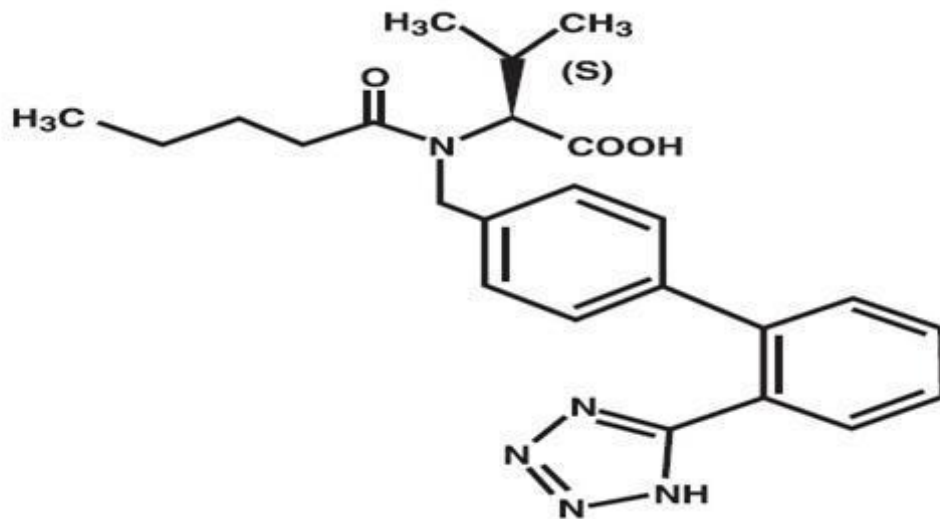
Amlodipine and Valsartan Tablets are a fixed combination of amlodipine and valsartan.

Amlodipine and Valsartan Tablets contains the besylate salt of amlodipine, a dihydropyridine calcium-channel blocker (CCB). Amlodipine besylate is a white to almost white 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 C₂₀H₂₅ClN₂O₅•C₆H₆O₃S 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 to off-white hygroscopic powder, soluble in ethanol and methanol and insoluble 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 C₂₄H₂₉N₅O₃ 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 (6.9 mg or 13.9 mg), equivalent to 5 mg or 10 mg of amlodipine respectively, 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, microcrystalline cellulose, mannitol and sodium starch glycolate.

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 (pK_a=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

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

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 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressure (+1/-2 mmHg).

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

As with other calcium channel blockers, hemodynamic measurements of cardiac

function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in 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 Amlodipine 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 Valsartan 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. Amlodipine and Valsartan Tablets may be administered with or without food.

Specific 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

Amlodipine

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

Coadministered 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

Coadministered amlodipine does not affect the exposure to atorvastatin, digoxin, ethanol and 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 [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)*].

Valsartan

No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered 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.

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

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.

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/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 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).

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.

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	-14.0	-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 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	-15.0	-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 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	-11.0	---	-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 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	-12.0	-3.9

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 Tablets 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 Tablets are available as biconvex, modified oval shaped tablets containing amlodipine besylate equivalent to 5 mg, or 10 mg of amlodipine respectively 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 and 90 count.

All strengths are packaged in bottles of 30 and 90 count.

5/160 mg Tablets – White to off white uncoated tablet, modified oval shaped, biconvex, debossed "N 83" on one side and plain on the other side.

Bottles of 30 NDC # 43386-083-03

Bottles of 90 NDC # 43386-083-09

10/160 mg Tablets - White to off white uncoated tablet, modified oval shaped, biconvex, debossed "N 82" on one side and plain on the other side.

Bottles of 30 NDC # 43386-082-03

Bottles of 90 NDC # 43386-082-09

5/320 mg Tablets – White to off white uncoated tablet, modified oval shaped, biconvex, debossed "N 81" on one side and plain on the other side.

Bottles of 30 NDC # 43386-081-03

Bottles of 90 NDC # 43386-081-09

10/320 mg Tablets – White to off white uncoated tablet, modified oval shaped, biconvex, debossed "N 08" on one side and plain on the other side.

Bottles of 30 NDC # 43386-080-03

Bottles of 90 NDC # 43386-080-09

Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [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: Advise female patients of childbearing age about the consequences of exposure to Amlodipine and Valsartan Tablets during pregnancy. Discuss treatment options with women planning to become pregnant. Ask patients to report pregnancies to their physicians as soon as possible [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1)*].

Lactation: Advise women not to breastfeed during treatment with Amlodipine and Valsartan Tablets [see *Use in Specific Populations (8.2)*].

Symptomatic Hypotension: Advise patients that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to their healthcare provider. Tell patients that if syncope occurs to discontinue Amlodipine and Valsartan Tablets until the physician has been consulted. Caution all patients that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope [see *Warnings and Precautions (5.2)*].

Hyperkalemia: Advise patients not to use salt substitutes without consulting their healthcare provider [see *Drug Interactions (7)*].

Manufactured by:

Novel Laboratories Inc.

Somerset, NJ 08873

Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, MD 21202

SAP Code: 270612

Rev. 06/2022

FDA-APPROVED PATIENT LABELING

PATIENT INFORMATION

Amlodipine (am loe' di peen) and Valsartan (val sar' tan) Tablets

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 contains 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 is present in human milk. It is not known whether Amlodipine and Valsartan affects your breastfed baby or milk production. 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:
 - are going to have surgery
 - 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:
 - take water pills
 - are on a low salt diet
 - get dialysis treatments
 - have heart problems
 - get sick with vomiting or diarrhea
 - 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 Amlodipine and Valsartan Tablets at room temperature between 59°F and 86°F (15°C and 30°C).
- 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 call 1-866-403-7592.

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,

crospovidone, magnesium stearate, microcrystalline cellulose, mannitol and sodium starch glycolate.

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.

Manufactured by:

Novel Laboratories Inc.

Somerset, NJ 08873

Manufactured For:

Lupin Pharmaceuticals, Inc.

Baltimore, MD 21202

SAP Code: 270612

Rev. 06//2022

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Amlodipine and Valsartan Tablets

5/160 mg

30 count



10/160 mg

90 count

NDC 43386-082-09 90 Tablets

Amlodipine and Valsartan

Tablets

10 mg/160 mg

Rx only



Each tablet contains:
 Amlodipine besylate..... 13.9 mg*
 Valsartan 160 mg
 *13.9 mg amlodipine besylate is equivalent to 10 mg of Amlodipine.

Usual Dosage: See package insert.
 Keep this and all drugs out of the reach of children.

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

Manufactured by: Novel Laboratories, Inc. Somerset, NJ 08873
 LA0820900201

Manufactured for: GAVIS Pharmaceuticals, LLC Somerset, NJ 08873
 Iss. 02/2015



N 3 43386-082-09 4

Lot No.:
Exp:

.5" Code Area

5/320 mg
30 count

NDC 43386-081-03 30 Tablets

Amlodipine and Valsartan

Tablets

5 mg/320 mg

Rx only



Each tablet contains:
 Amlodipine besylate..... 6.9 mg*
 Valsartan 320 mg
 *6.9 mg amlodipine besylate is equivalent to 5 mg of Amlodipine.

Usual Dosage: See package insert.
 Keep this and all drugs out of the reach of children.

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

Manufactured by: Novel Laboratories, Inc. Somerset, NJ 08873
 LA0810300201

Manufactured for: GAVIS Pharmaceuticals, LLC Somerset, NJ 08873
 Iss. 02/2015



N 3 43386-081-03 5

Lot No.:
Exp:

.5" Code Area

10/320 mg
90 count

NDC 43386-080-09 90 Tablets

Amlodipine and Valsartan
Tablets

10 mg/320 mg

Rx only

GAVIS
PHARMACEUTICALS

Each tablet contains:
Amlodipine besylate.....13.9 mg*
Valsartan.....320 mg
*13.9 mg amlodipine besylate is equivalent to 10 mg of Amlodipine.

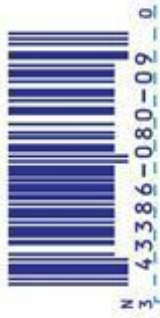
Usual Dosage: See package insert.

Keep this and all drugs out of the reach of children.

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

Manufactured by: Novel Laboratories, Inc. Somerset, NJ 08873 LA0800900201

Manufactured for: GAVIS Pharmaceuticals, LLC Somerset, NJ 08873 Iss. 02/2015



Lot No.: 3-43386-080-09-09
Exp: .5" Code Area

AMLODIPINE AND VALSARTAN

amlodipine and valsartan tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:43386-083
Route of Administration	ORAL		

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
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPVIDONE (UNII: 2S7830E561)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics

Color	WHITE	Score	no score
Shape	OVAL (modified oval, biconvex)	Size	15mm
Flavor		Imprint Code	N83
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date

1	NDC:43386-083-03	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/30/2015	
2	NDC:43386-083-09	90 in 1 BOTTLE; Type 0: Not a Combination Product	03/30/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202829	03/30/2015	

AMLODIPINE AND VALSARTAN

amlodipine and valsartan tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:43386-082
Route of Administration	ORAL		

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

Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPVIDONE (UNII: 2S7830E561)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics

Color	WHITE	Score	no score
Shape	OVAL (modified oval, biconvex)	Size	15mm
Flavor		Imprint Code	N82
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43386-082-03	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/30/2015	
2	NDC:43386-082-	90 in 1 BOTTLE; Type 0: Not a Combination	03/30/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202829	03/30/2015	

AMLODIPINE AND VALSARTAN

amlodipine and valsartan tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:43386-081
Route of Administration	ORAL		

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
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPVIDONE (UNII: 2S7830E561)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics

Color	WHITE	Score	no score
Shape	OVAL (modified oval, biconvex)	Size	18mm
Flavor		Imprint Code	N81
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43386-081-03	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/30/2015	
2	NDC:43386-081-09	90 in 1 BOTTLE; Type 0: Not a Combination Product	03/30/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202829	03/30/2015	

AMLODIPINE AND VALSARTAN

amlodipine and valsartan tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:43386-080
Route of Administration	ORAL		

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

Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPVIDONE (UNII: 2S7830E561)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics

Color	WHITE	Score	no score
Shape	OVAL (modified oval, biconvex)	Size	18mm
Flavor		Imprint Code	N08
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43386-080-03	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/30/2015	
2	NDC:43386-080-09	90 in 1 BOTTLE; Type 0: Not a Combination Product	03/30/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202829	03/30/2015	

Labeler - Lupin Pharmaceuticals, Inc. (089153071)

Registrant - Novel Laboratories, Inc. (793518643)

Establishment

Name	Address	ID/FEI	Business Operations
Novel Laboratories, Inc.		793518643	ANALYSIS(43386-080, 43386-081, 43386-082, 43386-083) , MANUFACTURE(43386-080, 43386-081, 43386-082, 43386-083) , PACK(43386-080, 43386-081, 43386-082, 43386-083)

Revised: 6/2022

Lupin Pharmaceuticals, Inc.