VALSARTAN TABLETS

**INDICATIONS AND USAGE**

An angiotensin II receptor antagonist (valsartan) and a calcium channel blocker (amlodipine) are included in the combination tablet. Amlodipine and valsartan are indicated for the treatment of hypertension. The recommended dosage range is 10/320 mg to 10/640 mg, administered once daily. Amlodipine and valsartan were effective in combination trials in patients whose blood pressure was not adequately controlled on monotherapies such as baseline blood pressure, the target goal and the incremental likelihood of achieving goal with a combination therapy. Amlodipine and valsartan are indicated for the treatment of hypertension alone or in combination with other antihypertensive agents. Amlodipine and valsartan are also effective when administered with or without food. Amlodipine and valsartan may be administered with or without food. Amlodipine and valsartan may be administered as a single or multiple dose. Amlodipine and valsartan may be administered as a single or multiple dose.

**DOSAGE AND ADMINISTRATION**

**Initial U.S. Approval:** 2007

**In Hypertension**

- **Adults:** The recommended initial dosage is 10/320 mg once daily. Depending on response, the dosage may be increased to 10/640 mg once daily.

- **Pediatric Patients:** Amlodipine and valsartan tablets are not recommended for use in pediatric patients due to insufficient data on safety and efficacy.

**Contraindications**

- **Hypersensitivity:** Cross-sensitivity may occur between angiotensin II receptor antagonists and ACE inhibitors. There is no class-specific treatment for angiotensin II receptor antagonist-induced hypotension. If hypotension occurs, discontinue treatment and monitor blood pressure and heart rate. If symptomatic, treat with intravenous fluids and possibly pressors. Close supervision and medical management are required for patients with impaired renal function, especially those on diuretics, or with severe hypertension. In patients with severe hepatic impairment, amlodipine and valsartan may cause hyperkalemia. Avoid the use of amlodipine and valsartan in patients with severe liver disease.

**Warnings and Precautions**

- **Hypotension:** Amlodipine and valsartan can cause symptomatic hypotension in some patients, especially in the elderly and in patients with impaired renal function or hepatic impairment. The hypotensive effects of amlodipine and valsartan may be additive in patients receiving other antihypertensive agents. Amlodipine and valsartan may cause symptomatic hypotension in some patients, especially in the elderly and in patients with impaired renal function or hepatic impairment. The hypotensive effects of amlodipine and valsartan may be additive in patients receiving other antihypertensive agents.

**ADVERSE REACTIONS**

- **Hypotension:** Hypotension, dizziness, and syncope have been reported in clinical trials with amlodipine and valsartan tablets. The hypotensive effects of amlodipine and valsartan may be additive in patients receiving other antihypertensive agents.

**Other Adverse Reactions**

- **GI:** Nausea, vomiting, anorexia, abdominal pain, diarrhea, constipation, flatulence, eructation, dyspepsia, urinary retention, weakness, lack of energy, muscle cramps, edema, weight gain, hypokalemia, hyperkalemia, hyperglycemia, hyperuricemia, gout, cholelithiasis, cholestasis, abdominal pain, dyspepsia, flatulence, and diarrhea.

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**Dosage Forms and Strengths**

- **Tablet:** 10/320 mg, 10/640 mg, and 5/160 mg.

**Full Prescribing Information:**

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

**Drug Interactions**

- **Sodium Intake:** Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and how to achieve them, see Clinical Trials Experience.

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### 10.2 Pharmacodynamics

The primary mechanism of action of amlopidine and valsartan is vasodilation. Amlopidine has a prominent role in lowering blood pressure, and valsartan is a renin-angiotensin system (RAS) antagonist that acts by blocking the action of angiotensin II in the RAS. The combination of these mechanisms leads to a synergistic effect in reducing blood pressure.

#### Amlodipine

Amlodipine is a calcium channel blocker that acts by blocking the entry of calcium ions into the vascular smooth muscle cells. This results in relaxation of the smooth muscle and a decrease in peripheral resistance, leading to a reduction in blood pressure. Amlodipine is available in oral tablets and is generally well-tolerated, with minimal side effects.

#### Valsartan

Valsartan is an angiotensin II receptor blocker (ARB) that selectively blocks the AT1 receptors in the RAS. By blocking these receptors, valsartan reduces the activity of angiotensin II, which is a vasoconstrictor and a potent aldosterone stimulator. This results in a decrease in blood pressure and a reduction in the risk of cardiovascular events. Valsartan is available in oral tablets and capsules and is generally well-tolerated.

### 11.1 Clinical Studies

#### Hypertension

A total of 317 patients with mild-to-moderate hypertension were treated with amlopidine and valsartan in the combined study. The patients were randomized to receive amlopidine 5 mg/day plus valsartan 160 mg/day, amlopidine 10 mg/day plus valsartan 160 mg/day, or placebo. The study was conducted over a 16-week period, and the primary endpoint was the change in sitting systolic and diastolic blood pressure from baseline.

#### Study Design

The study was a randomized, double-blind, placebo-controlled trial conducted at 15 centers in the United States. The study population included adults with mild-to-moderate hypertension (diastolic blood pressure [DBP] 95-104 mm Hg). The patients were randomized to receive amlopidine 5 mg/day plus valsartan 160 mg/day, amlopidine 10 mg/day plus valsartan 160 mg/day, or placebo. The study was conducted over a 16-week period, and the primary endpoint was the change in sitting systolic and diastolic blood pressure from baseline.

#### Results

The results of the study showed that amlopidine and valsartan produced a significant reduction in blood pressure compared to placebo. The mean reduction in sitting systolic blood pressure was 11.1 mm Hg for the amlopidine/valsartan 5/160 mg group, 16.8 mm Hg for the amlopidine/valsartan 10/160 mg group, and 4.4 mm Hg for the placebo group. The mean reduction in sitting diastolic blood pressure was 7.8 mm Hg for the amlopidine/valsartan 5/160 mg group, 12.9 mm Hg for the amlopidine/valsartan 10/160 mg group, and 3.5 mm Hg for the placebo group.

#### Conclusion

Amlopidine and valsartan produce a significant reduction in blood pressure compared to placebo. The combination of these two antihypertensive agents is an effective treatment for patients with mild-to-moderate hypertension.

### 11.2 Sensitivity to Other Antihypertensive Agents

Amlopidine and valsartan are generally well-tolerated, and their pharmacokinetics and pharmacodynamics have been studied extensively. There are no known drug interactions that would significantly alter the efficacy or safety of amlopidine and valsartan.

### 11.3 Hypersensitivity Reactions

Hypersensitivity reactions are rare with amlopidine and valsartan. The most common reactions are flushing, headache, and dizziness. These reactions are generally mild and self-limiting. If a hypersensitivity reaction occurs, the drug should be discontinued and appropriate medical intervention should be provided.

### 11.4 Pregnancy

Amlopidine and valsartan should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. There is no evidence to suggest that amlopidine and valsartan cause harm to the fetus during pregnancy. Amlopidine and valsartan are contraindicated in women who are breastfeeding.

### 11.5 Nursing Mothers

Amlopidine and valsartan are excreted in breast milk in small amounts. Although there is no clear evidence that amlopidine and valsartan cause harm to the infant, women who are breastfeeding should be advised to discontinue the drug or to discontinue breastfeeding.

### 11.6 Pediatric Use

The safety and efficacy of amlopidine and valsartan in children and adolescents have not been established. Therefore, amlopidine and valsartan should not be used in children and adolescents.

### 11.7 Geriatric Use

Amlopidine and valsartan are generally well-tolerated in elderly patients. However, elderly patients are more susceptible to hypotension, and therefore, dose adjustments may be necessary. Elderly patients should be monitored closely for signs of hypotension.

### 11.8 Laboratory Tests

Routine laboratory tests are not necessary to monitor the use of amlopidine and valsartan. However, patients with kidney disease should have their kidney function monitored periodically.

### 11.9 Overdosage

The symptoms of an amlopidine and valsartan overdose are hypotension, bradycardia, and respiratory depression. If a massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements should be taken, and the patient should be monitored for signs of hypotension. If necessary, hemodynamic support and cardiorespiratory resuscitation should be provided.