

Zeglopin-V

(Amlodipine Besylate U.S.P. + Valsartan U.S.P.) (ایملوڈیپین بےسیلیٹ یو ایس پی + ویلسارٹن یو ایس پی)

زیگلوپین وی

COMPOSITION

Each **Zeglopin-V** 5mg+80mg tablet contains Amlodipine Besylate eq. to Amlodipine 5mg and 80mg of Valsartan. Each **Zeglopin-V** 5mg+160mg tablet contains Amlodipine Besylate eq. to Amlodipine 5mg and 160mg of Valsartan. Each **Zeglopin-V** 10mg+160mg tablet contains Amlodipine Besylate eq. to Amlodipine 10mg and 160mg of Valsartan.

MECHANISM OF ACTION

Amlodipine Besylate: Amlodipine Besylate is a dihydropyridine calcium channel blocker that 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. Amlodipine Besylate 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: 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. Both Amlodipine Besylate and Valsartan lower blood pressure by reducing peripheral resistance, but calcium influx blockade and reduction of angiotensin II vasoconstriction are complementary mechanisms.

PHARMACOKINETICS

Amlodipine Besylate: Peak plasma concentrations of Amlodipine Besylate are reached in 6-12 hours after administration of Amlodipine Besylate alone. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of Amlodipine Besylate is not altered by the presence of food.

Approximately 93% of circulating Amlodipine Besylate is bound to plasma proteins in hypertensive patients. Amlodipine Besylate 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. Terminal elimination half-life is about 30-50 hours. Steady state plasma levels of Amlodipine Besylate are reached after 7-8 days of consecutive daily dosing.

Valsartan: Following oral administration of Valsartan alone peak plasma concentrations of Valsartan are reached in 2-4 hours.

Absolute bioavailability is about 25% (range 10%-35%). Food decreases the exposure (as measured by AUC) to Valsartan by about 40% and peak plasma concentration (Cmax) by about 50%.

Valsartan is highly bound to serum proteins (95%), mainly serum albumin. Valsartan is not transformed to a high extent as only about 20% of dose is recovered as metabolites. Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. The half-life of Valsartan is 6 hours.

Amlodipine Besylate + Valsartan

Following oral administration of Amlodipine Besylate + Valsartan in normal healthy adults, peak plasma concentrations of Valsartan and Amlodipine Besylate are reached in 3 and 6-8 hours, respectively. The rate and extent of absorption of Valsartan and Amlodipine Besylate from Amlodipine Besylate + Valsartan are the same as when administered as individual tablets. The bioavailabilities of Amlodipine Besylate and Valsartan are not altered by the co-administration of food.

Special Populations

Pediatric patients (age below 18 years): No pharmacokinetic data are available in the pediatric population.

Geriatric: Studies with Amlodipine Besylate: Elderly patients have decreased clearance of Amlodipine Besylate with a resulting increase in AUC of approximately 40%-60%; therefore a lower initial dose of Amlodipine Besylate may be required. Studies with Valsartan: Exposure (measured by AUC) to Valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary.

Renal Insufficiency: Studies with Amlodipine Besylate: The pharmacokinetics of Amlodipine Besylate is not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose. Studies with Valsartan: Dose adjustment is not required in patients with mild-to-moderate renal dysfunction. In the case of severe renal disease, exercise care with dosing of Valsartan.

Hepatic Insufficiency: Studies with Amlodipine Besylate: Patients with hepatic insufficiency have decreased clearance of Amlodipine Besylate with resulting increase in AUC of approximately 40%-60%; therefore, a lower initial dose of Amlodipine Besylate may be required.

Studies with Valsartan: No dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease.

INDICATIONS

Hypertension: **Zeglopin-V** (Amlodipine Besylate and Valsartan) is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

Zeglopin-V may be used in patients whose blood pressure is not adequately controlled on either monotherapy. **Zeglopin-V** may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

DOSAGE AND ADMINISTRATION

General Considerations: Amlodipine Besylate is an effective treatment of hypertension in once daily doses of 2.5 mg to 10 mg while Valsartan is effective in doses of 80 mg to 320 mg. In clinical trials with once daily **Zeglopin-V** (Amlodipine Besylate and Valsartan) using Amlodipine Besylate doses of 5 mg to 10 mg and Valsartan doses of 160 mg to 320 mg, the antihypertensive effects increased with increasing doses.

The majority of the antihypertensive effect is attained within 2 weeks after initiation of therapy or a change in dose. 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.

Zeglopin-V may be administered with or without food.

Zeglopin-V may be administered with other antihypertensive agents.

Elderly patients

Because of decreased clearance of Amlodipine Besylate, therapy should usually be initiated at 2.5 mg. **Renal Impairment:** No initial dosage adjustment is required for patients with mild or moderate renal impairment. Titrate slowly in patients with severe renal impairment.

Hepatic Impairment: No initial dosage adjustment is required for patients with mild or moderate liver insufficiency. Titrate slowly in patients with hepatic impairment.

Add-on Therapy: A patient whose blood pressure is not adequately controlled with Amlodipine Besylate (or another dihydropyridine calcium-channel blocker) alone or with Valsartan (or another angiotensin II receptor blocker) alone may be switched to combination therapy with **Zeglopin-V**.

A patient who experiences dose-limiting adverse reactions on either component alone may be switched to **Zeglopin-V** containing a lower dose of that component in combination with the other to achieve similar blood pressure reductions. **Replacement Therapy:** For convenience, patients receiving Amlodipine Besylate and Valsartan from separate tablets may instead wish to receive tablets of **Zeglopin-V** containing the same component doses.

Initial Therapy: A patient may be initiated on **Zeglopin-V** if it is unlikely that control of blood pressure would be achieved with a single agent. The usual starting dose is **Zeglopin-V** 5+160 mg once daily in patients who are not volume-depleted.

SIDE EFFECTS

The adverse reactions that occurred in placebo-controlled clinical trials in at least 2% of patients treated with Amlodipine Besylate + Valsartan but at a higher incidence in Amlodipine Besylate + Valsartan patients (n=1,437) than placebo (n=337) included peripheral edema (5.4% vs. 3.0%), nasopharyngitis (4.3% vs. 1.8%), upper respiratory tract infection (2.9% vs 2.1%) and dizziness (2.1% vs 0.9%).

Orthostatic events (orthostatic hypotension and postural dizziness) were seen in less than 1% of patients. Other adverse reactions that occurred in placebo-controlled clinical trials with Amlodipine Besylate + Valsartan ($\geq 0.2\%$) are listed below. It cannot be determined whether these events were causally related to Amlodipine Besylate + Valsartan.

Blood and Lymphatic System Disorders: Lymphadenopathy.

Cardiac Disorders: Palpitations, tachycardia.

Ear and Labyrinth Disorders: Ear pain.

Gastrointestinal Disorders: Diarrhea, nausea, constipation, dyspepsia, abdominal pain, upper abdominal pain, 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, sciatia, 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.

DRUG INTERACTIONS

No drug interaction studies have been conducted with Amlodipine Besylate + Valsartan and other drugs, although studies have been conducted with the individual Amlodipine Besylate and Valsartan components, as described below:

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

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

Sildenafil: When Amlodipine Besylate and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Atorvastatin: Co-administration resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

Simvastatin: Limit the dose of simvastatin in patients on Amlodipine Besylate to 20 mg daily.

Studies with Valsartan: No clinically significant pharmacokinetic interactions were observed when Valsartan was co-administered with Amlodipine Besylate, 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 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, co-administration 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.

CYP 450 Interactions: In vitro metabolism studies indicate that CYP 450 mediated drug interactions between Valsartan and coadministered drugs are unlikely because of low extent of metabolism. As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.

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. Co-administration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to Valsartan. **Clinical Laboratory Findings:** Liver Function Tests: Occasional elevations (greater than 150%) of liver chemistries occurred in **Zeglopin-V** treated patients.

PRECAUTIONS

Hypotension: Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with Amlodipine Besylate + Valsartan in placebo-controlled studies. Volume depletion should be corrected prior to administration of Amlodipine Besylate + Valsartan. Treatment with Amlodipine Besylate + Valsartan should start under close medical supervision. Initiate therapy cautiously in patients with heart failure or recent myocardial infarction and in patients undergoing surgery or dialysis.

Risk of Myocardial Infarction or Increased Angina: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Congestive Heart Failure

Studies with Amlodipine Besylate: In general, calcium channel blockers should be used with caution in patients with heart failure.

Studies with Valsartan: Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium on Valsartan. 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 the diuretic and/or Valsartan may be required.

Pregnancy: Pregnancy Category D. Amlodipine Besylate + Valsartan can cause fetal harm when administered to a pregnant woman.

Nursing Mothers: It is not known whether Amlodipine Besylate and Valsartan are excreted in human milk. Because many drugs are excreted into human milk and because of the potential for adverse reactions in nursing infants from Amlodipine Besylate + Valsartan, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of Amlodipine Besylate + Valsartan in pediatric patients have not been established.

OVERDOSE

Symptoms: The major symptom of overdose with Valsartan is possibly pronounced hypotension with dizziness. Overdose with Amlodipine Besylate may result in excessive peripheral vasodilation and, possibly, reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment: If ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of Amlodipine Besylate has been shown to significantly decrease Amlodipine Besylate absorption. Clinically significant hypotension due to Amlodipine Besylate + Valsartan overdose calls for active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Both Valsartan and Amlodipine Besylate are unlikely to be removed by haemodialysis.

CONTRAINDICATIONS

Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients.

Severe hepatic impairment, biliary cirrhosis or cholestasis.

Severe renal impairment (GFR <30 ml/min/1.73 m²) and patients undergoing dialysis.

Second and third trimesters of pregnancy.

PRESENTATION

Zeglopin-V 5mg+80mg Tablets: 14's/pack.

Zeglopin-V 5mg+160mg Tablets: 14's/pack.

Zeglopin-V 10mg+160mg Tablets: 14's/pack.

خوراک:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو سردی سے بچائی گئی ہے کہ دم درجہ حرارت پر رکھیں۔

دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔

DOSAGE
As directed by the physician.

INSTRUCTIONS

Store below 30°C.

Protect from sunlight and moisture.

Keep out of reach of children.

Detailed prescribing information is available on request.



Manufactured by:
AsianContinental (Pvt.) Ltd.
D-32, S.I.T.E. II, Super Highway,
Karachi-Pakistan.



An ISO Certified Company

LFT/052/00