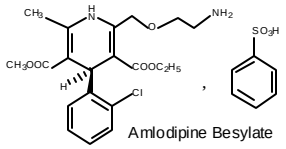
AMSTAN

[Amlodipine + Valsartan]

ایمسٹن

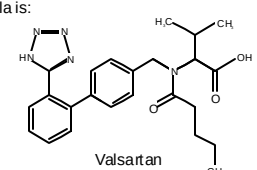
Tablets
5mg+80mg, 5mg+160mg & 10mg+160mg

DESCRIPTION
AMSTAN (Amlodipine + Valsartan) is a fixed combination of amlodipine and valsartan.
Amlodipine contains the besylate salt of amlodipine, a dihydropyridine calcium-channel blocker. Chemically, Amlodipine besylate is described as 3-Ethyl-5- methyl (4RS)-2-[(2-aminoethoxy) methyl] 4-(2-chlorophenyl)-6-methyl-1, 4-dihydropyridine-3,5-dicarboxylate benzenesulphonate. The molecular formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$. The structural formula is:



Amlodipine Besylate

Valsartan is a nonpeptide, orally active and specific angiotensin II antagonist acting on the AT1 receptor subtype. Its chemical name is N-(1-oxopentyl)-N-[[2[1]-(1H-tetrazol-5-yl) [1,1[1]-biphenyl]-4 yl]methyl]-L-valine. The molecular formula is $C_{24}H_{29}N_9O_3$ and the structural formula is:



Valsartan

QUALITATIVE & QUANTITATIVE COMPOSITION
AMSTAN (Amlodipine + Valsartan) is available for oral administration as:

1. AMSTAN Tablets 5mg + 80mg
   Each film-coated tablet contains:
   Amlodipine...5mg
   (as Amlodipine Besylate BP)
   Valsartan USP...80mg

2. AMSTAN Tablets 5mg + 160mg
   Each film-coated tablet contains:
   Amlodipine...5mg
   (as Amlodipine Besylate BP)
   Valsartan USP...160mg

3. AMSTAN Tablets 10mg + 160mg
   Each film-coated tablet contains:
   Amlodipine...10mg
   (as Amlodipine Besylate BP)
   Valsartan USP...160mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Amlodipine and Valsartan are antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine
Amlodipine inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions 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. Its action is therefore independent of the pathways for angiotensin II synthesis.

Pharmacokinetics
Combination of amlodipine and valsartan
Following oral administration of amlodipine and valsartan, peak plasma concentrations of amlodipine and valsartan are reached in 3 and 6 to 8 hours, respectively. The rate and extent of absorption of amlodipine and valsartan are equivalent to the bioavailability of amlodipine and valsartan when administered as individual tablets.

Amlodipine
Absorption
After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6 to12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution
Volume of distribution is approximately 21 L/kg. Approximately 97.5% of circulating drug is bound to plasma proteins in hypertensive patients.

Metabolism
Amlodipine is extensively (approximately 90%) metabolized in the liver to inactive metabolites.

Excretion
Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7 to 8 days. 10% of the parent compound and 60% of amlodipine metabolites are excreted in urine.

Valsartan
Absorption
Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2 to 4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%. However, this reduction in AUC is not accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given with or without food.

Distribution
Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Metabolism
Valsartan is not metabolized to a high extent as only about 20% of dose is recovered as metabolites. A hydroxyl metabolite has been identified in plasma at low concentration (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Excretion
Valsartan is primarily eliminated in feces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. The terminal elimination half-life is about 5 to 9 hours.

Special population
Elderly
Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in AUC and elimination half-life. Systemic exposure to valsartan is slightly elevated in the elderly as compared to the young, but this is of no clinical significance.

Renal Insufficiency
The pharmacokinetics of amlodipine is not significantly influenced by renal insufficiency. 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 insufficiency.

Hepatic Insufficiency
Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40% 60% in AUC. On average, patients administered with Valsartan for the treatment of mild to moderate chronic liver disease, AUC values were found to be doubled.

THERAPEUTIC INDICATIONS
AMSTAN (Amlodipine + Valsartan) is indicated for the treatment of:

- Hypertension.
- Patients whose blood pressure is not adequately controlled on either monotherapy.
- Patients who are likely to need multiple drugs to achieve their blood pressure goals.

210mm

135mm

DOSAGE & ADMINISTRATION

A patient whose blood pressure is not adequately controlled on monotherapy may be switched to combination therapy with AMSTAN (Amlodipine + Valsartan).

AMSTAN (Amlodipine + Valsartan) can be taken with or without food and is recommended to take it with water.

The recommended dose of AMSTAN (Amlodipine + Valsartan) is one tablet per day for the following strengths:

- AMSTAN Tablets 5mg + 80mg
- AMSTAN Tablets 5mg + 160mg
- AMSTAN Tablets 10mg + 160mg

The major 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 as needed to control blood pressure.

Elderly

Since both components of the combination are equally well tolerated when used at similar doses in elderly or younger patients, normal dosage regimens are recommended.

Renal and Hepatic Insufficiency

No initial dosage adjustment is required for patients with mild or moderate renal and liver insufficiency. Titrate slowly in patients with renal and liver insufficiency.

ADVERSE REACTIONS

Common

Headache, nasopharyngitis, influenza, edema (pitting edema, facial edema, edema peripheral), fatigue, flushing, asthenia, hot flush.

Uncommon

Tachycardia, palpitations, dizziness, somnolence, dizziness postural, paraesthesia, vertigo, cough, pharyngolaryngeal pain, diarrhoea, nausea, abdominal pain, constipation, dry mouth, rash, erythema, joint swelling, back pain, arthralgia, orthostatic hypotension.

Rare

Syncope, visual disturbance, tinnitus, pollakisuria, polyuria, hyperhidrosis, exanthema, pruritus, muscle spasm, sensation of heaviness, hypotension, hypersensitivity, erectile dysfunction, anxiety.

The most common reasons for discontinuation of therapy with the combination of Amlodipine and Valsartan are peripheral edema and vertigo.

CONTRAINDICATIONS

The combination of Amlodipine and Valsartan is contraindicated;

- In patients who are hypersensitive to any components of this product.
- In patients with severe hepatic insufficiency, biliary cirrhosis, or cholestatis and severe renal insufficiency (GFR <30mL/min/1.73 m^2).
- In patients undergoing dialysis.

Pregnancy

The combination of amlodipine and valsartan is contraindicated in second and third trimesters of pregnancy. When pregnancy is detected it should be discontinued as soon as possible because it can cause injury and even death to the developing fetus.

Nursing Mothers

The combination of amlodipine and valsartan is not recommended during breast feeding and alternative treatments with better established safety profiles during breast-feeding are preferable.

PRECAUTIONS

- In patients with an activated renin-angiotensin system (such as volume- and/or salt-depleted patients receiving high doses of diuretics) who are receiving angiotensin receptor blockers, symptomatic hypotension may occur. Correction of this condition prior to administration of the combination of amlodipine and valsartan or close medical supervision at the start of treatment is recommended.
- Particular caution should be exercised when administering the combination of amlodipine and valsartan to patients with mild to moderate hepatic impairment or biliary obstructive disorders.
- In case of moderate renal impairment, monitoring of potassium levels and creatinine is advised.
- The combination of amlodipine and valsartan should be used with caution in patients with severe heart failure.
- As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Drug Interactions

CYP3A4 inhibitors

Co-administration of amlodipine with CYP3A4 inhibitors like diltiazem inhibits the metabolism of amlodipine, thereby increasing the plasma concentration of amlodipine by approximately 50% and the effect is also increased. The more potent inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem.

CYP3A4 inducers

Co-administration of amlodipine with CYP3A4 inducers like anticonvulsant agents (e.g., carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone), rifampicin, Hypericum perforatum may lead to reduced plasma concentrations of amlodipine.

Lithium

Concurrent use of ACE inhibitors with lithium causes reversible increases in serum lithium concentrations and toxicity.

Potassium supplements

Concomitant use of valsartan with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (heparin, etc.) should be undertaken with frequent monitoring of potassium levels.

Non-steroidal anti-inflammatory medicines (NSAIDs)

Concomitant administration of NSAIDs including selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day), and non-selective NSAIDs with angiotensin II antagonists may cause attenuation of antihypertensive effect. Furthermore, it may lead to an increased risk of worsening of renal function and an increase in serum potassium.

Other antihypertensive agents

Commonly used antihypertensive agents (e.g., alpha blockers, diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g., tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia) may increase the antihypertensive effect of the combination.

OVERDOSAGE

The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilation and, possibly, reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome may occur.

Treatment

If ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal immediately or up to two hours after ingestion of amlodipine can significantly decrease amlodipine absorption. Clinically significant hypotension due to the combination of Amlodipine and 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 are unlikely to be removed by haemodialysis.

STORAGE

Store at 25°C (Excursions permitted between 15°C to 30°C). Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

AMSTAN (Amlodipine + Valsartan) Tablets 5mg+ 80mg are available in blister pack of 14's.

AMSTAN (Amlodipine + Valsartan) Tablets 5mg+ 160mg are available in blister pack of 14's.

AMSTAN (Amlodipine + Valsartan) Tablets 10mg+ 160mg are available in blister pack of 14's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Getz Pharma (Pvt.) Limited, 29-30/27,
K.I.A., Karachi - 74900, Pakistan.

Marketed by:

SCILIFE

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Karachi - 75350, Pakistan.

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