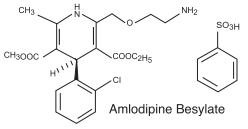
VELVET AM™

(USP Specification)
Amlodipine as Besylate + Valsartan
(USP Specification)
5mg/ 80mg, 5mg/160mg & 10mg/160mg
Film Coated Tablets

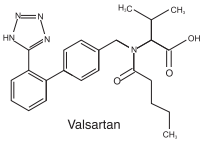
COMPOSITION:
Velvet-AM 5mg/ 80mg Tablets:
Each film coated tablet contains:
Amlodipine (as besylate) 5mg
Valsartan 80mg
(USP Specification)
Velvet-AM 5mg/ 160mg Tablets:
Each film coated tablet contains:
Amlodipine (as besylate) 5mg
Valsartan 160mg
(USP Specification)
Velvet-AM 10mg/ 160mg Tablets:
Each film coated tablet contains:
Amlodipine (as besylate) 10mg
Valsartan 160mg
(USP Specification)

DESCRIPTION:
VELVET-AM (Amlodipine + Valsartan) is a fixed combination of amlodipine and valsartan. **VELVET-AM** contains the besylate salt of amlodipine, a dihydropyridine calcium-channel blocker. The molecular formula is $C_{20}H_{25}ClN_2O_5 \bullet C_6H_6O_3S$ and the structural formula is:



Amlodipine Besylate

Valsartan is a nonpeptide, orally active and specific angiotensin II antagonist acting on the AT_1 receptor subtype. The molecular formula is $C_{24}H_{29}N_5O_3$ and the structural formula is:



Valsartan

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 AT^1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.
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.
Metabolism:
Amlodipine is extensively (approximately 90%) metabolized in the liver to inactive metabolites.
Excretion:
Amlodipine elimination from plasma is biphasic, with a terminal elimination halflife 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 hydroxy 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 half-life of valsartan is 6 hours.

THERAPEUTIC INDICATIONS
VELVET-AM (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.

DOSAGE AND ADMINISTRATION
The recommended dose of **VELVET-AM** (Amlodipine + Valsartan) is one tablet per day. **VELVET-AM** (Amlodipine + Valsartan) can be used with or without food and it is recommended to take **VELVET-AM** (Amlodipine + Valsartan) with some water.
VELVET-AM (Amlodipine + Valsartan) Tablets 5mg + 80mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5mg or valsartan 80mg alone.
VELVET-AM (Amlodipine + Valsartan) Tablets 5mg + 160mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5mg or valsartan 160mg alone.
VELVET-AM (Amlodipine + Valsartan) Tablets 10mg + 160mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 10mg or valsartan 160mg alone or with **VELVET-AM** (Amlodipine + Valsartan) Tablets 5mg + 160mg.
Individual dose titration with the components (i.e. amlodipine and valsartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.
The dosage can be increased after 1 to 2 weeks of therapy 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.
Special Population:
Renal impairment:
No dosage adjustment is required for patients with mild to moderate renal impairment. Monitoring of potassium levels and creatinine is advised in moderate renal impairment.
Hepatic impairment:
Caution should be exercised when administering **VELVET-AM** (Amlodipine + Valsartan) to patients with hepatic impairment or biliary obstructive disorders. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80mg valsartan. Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment. When switching eligible hypertensive patients with hepatic impairment to amlodipine or **VELVET-AM** (Amlodipine + Valsartan), the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.
Elderly (age 65 years or over):
In elderly patients, caution is required when increasing the dosage. When switching eligible elderly hypertensive patients to amlodipine or **VELVET-AM** (Amlodipine + Valsartan), the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.
Pediatric population:
The safety and efficacy of **VELVET-AM** (Amlodipine + Valsartan) in children aged below 18 years have not been established.

ADVERSE REACTIONS
Common:
Nasopharyngitis, influenza, hypokalemia, headache, asthenia, fatigue, facial edema, flushing, hot flush, edema, edema peripheral and pitting

edema.

Uncommon:

Anorexia, hypercalcemia, hyperlipidemia, hyperuricemia, hyponatremia, coordination abnormal, dizziness, dizziness postural, paraesthesia, somnolence, visual impairment, vertigo, palpitations, tachycardia, orthostatic hypotension, cough, pharyngolaryngeal pain, abdominal discomfort, abdominal pain upper, constipation, diarrhea, dry mouth, nausea, erythema, rash, arthralgia, back pain and joint swelling.

Rare:

Hypersensitivity, anxiety, visual disturbance, tinnitus, syncope, hypotension, exanthema, hyperhidrosis, pruritus, muscle spasm, sensation of heaviness, pollakiuria, polyuria and erectile dysfunction.

CONTRAINDICATIONS

The combination of amlodipine and valsartan is contraindicated in:

- Patients with known hypersensitivity to the active substances, to dihydropyridine derivatives or to any of the excipient of the product.
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) using concomitantly aliskiren-containing products.
- Second and third trimesters of pregnancy.
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high grade aortic stenosis).
- Hemodynamically unstable heart failure after acute myocardial infarction.

Nursing Mothers

The combination of amlodipine and valsartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

PRECAUTIONS

Hypertensive crisis:

The safety and efficacy of amlodipine in hypertensive crisis have not been established.

Pregnancy:

Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Sodium- and/or volume-depleted patients:

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 combination of amlodipine + valsartan or close medical supervision at the start of treatment is recommended.

Hyperkalemia:

Concomitant use 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 caution and with frequent monitoring of potassium levels.

Renal artery stenosis:

Combination of amlodipine + valsartan should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients.

Hepatic impairment:

Particular caution should be exercised when administering combination of amlodipine + valsartan to patients with mild to moderate hepatic impairment or biliary obstructive disorders. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80mg valsartan.

Primary hyperaldosteronism:

Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is affected by the primary disease.

DRUG INTERACTIONS

Other antihypertensive agents:

Commonly used antihypertensive agents and other medicinal products which may cause hypotensive adverse effects may increase the antihypertensive effect of the combination.

Grapefruit or grapefruit juice:

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

CYP3A4 inhibitors:

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers:

The concomitant use of CYP3A4 inducers (e.g. rifampicin, Hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Simvastatin:

Co-administration of multiple doses of 10mg amlodipine with 80mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20mg daily in patients on amlodipine.

OVERDOSAGE

Symptoms:

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 hemodialysis.

STORAGE

Store at 20°C - 25°C. Protect from light and moisture.
(excursions permitted to 15°C - 30°C)

HOW SUPPLIED

Velvet-AM 5mg/80mg Tablets: Pack of 14 film coated tablets.
Velvet-AM 5mg/160mg Tablets: Pack of 14 film coated tablets.
Velvet-AM 10mg/160mg Tablets: Pack of 14 film coated tablets.

TO BE SOLD AND USED ON THE PRESCRIPTION OF A REGISTERED MEDICAL PRACTITIONER ONLY.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

Lactose & Gluten Free

ویلوٹ اے ایم

(ایملوڈیپین + والسارٹن)

5 ملی گرام/80 ملی گرام، 5 ملی گرام/160 ملی گرام

اور 10 ملی گرام/160 ملی گرام

فلم کوٹڈ گولیاں

خوراک وہدایات

ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت کی جائے۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

دوا کو 25°C-20°C درجہ حرارت پر نمی اور روشنی سے محفوظ رکھیں۔

(درجہ حرارت کی حد 15°C سے 30°C ہے)

NEXT PHARMACEUTICAL

Manufactured by:
NEXT Pharmaceutical Products (Pvt.) Ltd.
Plot no. 44-A&B, Sunder Industrial Estate Lahore-Pakistan