# Lotevan®

## Amlodipine / Valsartan Tablets

**Pregnancy:**
Due to the mechanism of action of angiotensin II antagonists, a risk to the fetus cannot be ruled out. Fetal injury and death have been reported during the second and third trimesters in pregnant women using ACE inhibitors (a specific class of drugs that acts on the renin-angiotensin-aldosterone system (RAAS)).
**Lotevan** must not be used during pregnancy or in women planning to become pregnant.
Healthcare professionals prescribing any medicinal products that act on the RAAS should inform women of childbearing potential about the potential risk of these products during pregnancy.
When pregnancy is detected, discontinue **Lotevan** as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.
**Lactation:**
It is not known whether valsartan and/or amlodipine are excreted in human milk. Valsartan was excreted in the milk of lactating rats. Use is therefore contraindicated in women who are breast-feeding.

### Composition:

**Lotevan 5 mg/160 mg:** Each film coated tablet contains: Valsartan 160 mg and Amlodipine besylate equivalent to 5 mg Amlodipine.
**Lotevan 10 mg/160 mg:** Each film coated tablet contains: Valsartan 160 mg and Amlodipine besylate equivalent to 10 mg Amlodipine.
**Lotevan 5 mg/320 mg:** Each film coated tablet contains: Valsartan 320 mg and Amlodipine besylate equivalent to 5 mg Amlodipine.
**Lotevan 10 mg/320 mg:** Each film coated tablet contains: Valsartan 320 mg and Amlodipine besylate equivalent to 10 mg Amlodipine.
Excipients: Cellulose microcrystalline, crospovidone, colloidal silicone dioxide, magnesium stearate, HPMC, PEG, titanium dioxide and ferric oxide yellow.

### Properties:

**Lotevan** combines two antihypertensive active substances with complementary mechanism to control blood pressure in patients with hypertension: Amlodipine belongs to the calcium channel blocker class, and valsartan to the angiotensin II antagonist class of medicines. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.
Valsartan and amlodipine exhibit linear pharmacokinetics.
**Absorption:**
Following oral administration of **Lotevan**, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6-8 hours, respectively. The rate and extent of absorption of **Lotevan** are equivalent to the bioavailability of valsartan and amlodipine when administered as separate tablets, (Amlodipine: Absolute bioavailability is 64% and 80%, Valsartan: Absolute bioavailability is 23% (range 23±7)).
**Distribution:**
**Amlodipine:**
The volume of distribution is approximately 21 litres/kg. In vitro studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins in hypertensive patients.
**Valsartan:**
Valsartan is extensively (94-97%) bound to serum proteins, primarily albumin. Steady-state is reached within 1 week. The volume of distribution at steady-state is approximately 17 litres. Plasma clearance is relatively slow (about 2 litres/hour) compared with hepatic blood flow (about 30 litres/hour).
**Elimination:**
**Amlodipine:**
Amlodipine elimination from the 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 7-8 days. 10% of original amlodipine and 60% of amlodipine metabolites are excreted in the urine.
**Valsartan:**
Valsartan displays multiexponential decay kinetics (primary, alpha half-life <1 hour; terminal, beta half-life approximately 9 hours). Approximately 70% of absorbed valsartan is excreted in the faeces and 30% in the urine, mainly as unchanged compound.

### Indications:

**Lotevan** is indicated for the treatment of essential hypertension.
**Lotevan** is indicated in patients whose blood pressure is not adequately controlled by monotherapy.

### Contraindications:

**Lotevan** is contraindicated for patients with known hypersensitivity to any of its components.
**Lotevan** is contraindicated in patients with hereditary angioedema or in those in whom angioedema developed during earlier treatment with an ACE inhibitor or an angiotensin II receptor antagonist.

### Precautions:

**Effects on ability to drive and use machines:**
Due to possible adverse effects, caution is required when using machines or driving.

### Interactions with other drugs:

**Amlodipine:**
Amlodipine may be concomitantly administered with thiazide diuretics, alpha-blockers, beta-blockers, ACE inhibitors, long-acting nitrates, sublingual glyceryl trinitrate (nitroglycerin), NSAIDs, antibiotics and oral antidiabetics.
**Valsartan:**
Valsartan is only metabolized to a slight extent, so no clinically relevant drug interactions-in the form of metabolic induction or inhibition of the cytochrome P450 system-are to be expected.
There is no experience with concomitant use of valsartan and lithium. Regular monitoring of serum lithium levels is therefore recommended in the event of concomitant administration of lithium and valsartan.
Concomitant administration 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. Caution is therefore indicated when such co-medication is given.

### Warnings:

**Sodium – and/or volume – depleted patients**
Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with **Lotevan** in placebo-controlled studies. Symptomatic hypotension may occur in patients with an activated renin-angiotensin system (such as volume - and/or salt-depleted patients receiving high doses of diuretics) who are given angiotensin II antagonists. Correction of this condition prior to administration of **Lotevan**, or close medical supervision at the start of treatment, is recommended.
If hypotension occurs with **Lotevan**, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilized.
**Hyperkalaemia**
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.
**Beta-blocker withdrawal**
Amlodipine is not a beta-blocker and therefore provides no protection against the risks of abrupt beta-blocker withdrawal. Any such withdrawal should be by gradual reduction of the dose of the beta-blocker.
**Kidney transplantation**
No data are currently available on the safe use of **Lotevan** in patients who have recently undergone kidney transplantation.
**Hepatic impairment**
Valsartan is mostly eliminated unchanged via the bile, whereas amlodipine is extensively metabolized by the liver. Particular caution is required when administering **Lotevan** to patients with hepatic impairment or biliary obstructive disorders.
**Renal impairment**
No dosage adjustment of **Lotevan** is required in patients with mild to moderate renal impairment. However, no data are available on severe renal impairment (creatinine clearance <10 ml/minute) and caution is therefore required.
**Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy**
As with all other vasodilators, special caution is required in patients with aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

### Dosage and Administration:

Patients whose blood pressure is not adequately controlled by monotherapy may be switched to combination therapy with **Lotevan**.
The recommended dose is one tablet per day (5 mg amlodipine and 160 mg valsartan, or 10 mg amlodipine and 160 mg valsartan, 5 mg amlodipine and 320 mg valsartan, or 10 mg amlodipine and 320 mg valsartan). When clinically appropriate, a direct switch from monotherapy to the fixed-dose combination may be considered.
Patients receiving valsartan and amlodipine separately may be switched to the corresponding dose of **Lotevan**.
Both amlodipine and valsartan monotherapy can be taken with or without food. It is recommended to take **Lotevan** with some water.
**Elderly patients**
Since both components of the combination were equally well tolerated when used at similar doses in elderly or younger patients, normal dosage regimens are recommended.
**Children and adolescents**
**Lotevan** is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

### Overdosage:

There is no experience to date of overdose with **Lotevan**. The major symptom of overdose with valsartan is probably 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, have been reported.
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, has been shown to significantly decrease amlodipine absorption. Clinically significant hypotension due to **Lotevan** overdose calls for active cardiovascular support, including close 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.

### Side Effects:

Adverse effects are listed according to their frequency.
**Frequency**
Very common (> 1/10), common (> 1/100 to < 1/10), uncommon (> 1/1000 to < 1/100), rare (> 1/10000 to < 1/1000), very rare (< 1/10000).
Within each frequency grouping, adverse effects are listed in the order of decreasing severity.
**Infections**
Common: Nasopharyngitis, influenza.
**Immune system disorders**
Rare: Hypersensitivity.
**Nervous system disorders**
Common: Headache.
Uncommon: Dizziness, drowsiness, postural dizziness, paraesthesia.
**Eye disorders**
Rare: Disturbed vision.
**Cardiac disorders**
Uncommon: Tachycardia, palpitations.
Rare: Syncope.
**Respiratory tract**
Uncommon: Cough, laryngeal pain.
**Gastrointestinal disorders**
Uncommon: Diarrhea, nausea, abdominal pain, constipation, dry mouth.
**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 post marketing experience with valsartan:
Blood and Lymphatic: There are very rare reports of thrombocytopenia.
Hypersensitivity: There are rare reports of angioedema.
Digestive: Elevated liver enzymes and very rare reports of hepatitis.
Renal: Impaired renal function.
Clinical Laboratory Tests: Hyperkalemia.
Dermatologic: Alopecia.
Vascular: Vasculitis.
Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.
Consult your Pharmacist or Physician if any side effect is observed.

### Pharmaceutical Precautions:

Keep at room temperature (15-30°C).
Do not use beyond the expiry date or if the product shows any sign of deterioration.

### Presentations:

**Lotevan 5 mg/160 mg:** Packs of 30 Film Coated Tablets.
**Lotevan 10 mg/160 mg:** Packs of 30 Film Coated Tablets.
**Lotevan 5 mg/320 mg:** Packs of 30 Film Coated Tablets.
**Lotevan 10 mg/320 mg:** Packs of 30 Film Coated Tablets.
Hospital packs are available.



**THIS IS A MEDICAMENT**
- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Strictly follow the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

**Keep medicament out of reach of children.**

Council of Arab Health Ministers & Union of Arab Pharmacists.

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