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INSTRUCTION
for medical use

SAMLOPIN®

Composition:
active substance: S(-) amlodipine besylate;
1 tablet contains S(-) amlodipine besylate equivalent to S(-) amlodipine 2,5 mg or 5 mg;
excipients: microcrystalline cellulose, calcium hydrogen phosphate dihydrate, ferric oxide yellow (E 172), silica colloidal anhydrous, sodium starch glycolate (type A), magnesium stearate.

Pharmaceutical form. Tablets.
Main physico-chemical properties: round flat faced, light yellow beveled tablets with «K» logo on one side.

Pharmacotherapeutic group. Selective calcium antagonists with a predominant effect on blood vessels.
ATC code C08C A01.

Pharmacological properties.
Pharmacodynamics.
Amlodipine is a racemic mixture of S(-) and R(+) isomers. S(-) amlodipine – is an active chiral form of amlodipine, calcium antagonist (dihydropyridine derivative), which blocks the influx of calcium ions to the myocardium and smooth muscle cells.
The mechanism of the hypotensive action of amlodipine is due to its direct relaxant effect on vascular smooth muscle. The precise mechanism of the antianginal effect of amlodipine is not fully determined, but its following effects have a certain role.
1. Amlodipine dilates peripheral arterioles and thus reduces the peripheral resistance (afterload). Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
2. The dilatation of major coronary arteries and coronary arterioles (normal and ischemic) may also play a role in the mechanism of amlodipine action. Such dilatation increases myocardial saturation with oxygen in patients with coronary artery spasm (Prinzmetal's angina or variant angina).
In patients with arterial hypertension, once daily dosing provides clinically significant reductions of blood pressure in both supine and standing positions throughout the 24 hour interval. Due to the slow onset of amlodipine action, acute arterial hypotension is not usually observed.
In patients with cardiac angina when using one daily dose of the drug, the total physical activity time, time to onset of angina and time to 1 mm ST-segment depression increases. The drug reduces the frequency of angina attacks and reduces the necessity of nitroglycerin administration.
Amlodipine has not been associated with any adverse metabolic effects or changes in blood plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Pharmacokinetics.
Absorption/distribution.
After oral administration of therapeutic doses amlodipine is gradually absorbed in blood plasma. The absorption of amlodipine is not influenced by concomitant intake of food. The absolute bioavailability of the unmodified molecule is about 64-80 %. The maximum plasma concentration is reached within 6-12 hours after administration. The volume of distribution is approximately 21 l/kg; the acid dissociation constant (pKa) of amlodipine is 8.6. *In vitro* studies have shown that approximately 97.5 % of amlodipine is bound to plasma proteins.
Metabolism/elimination.
The plasma elimination half-life is about 35-50 hours. The steady-state plasma concentration is reached after 7-8 days of continuous drug administration. Amlodipine is mainly metabolized to inactive metabolites. About 60 % of the administered dose is excreted in the urine, approximately 10 % of which is unchanged amlodipine.
Elderly patients.
The time to achieve steady-state plasma concentrations of amlodipine is similar in elderly patients and in younger patients. The clearance of amlodipine tends to be decreased, which leads to an increase in the area under the "concentration/time" curve (AUC) and elimination half-life of the drug in elderly patients.
Patients with renal impairment.
Amlodipine is extensively metabolized to inactive metabolites. 10 % of amlodipine is excreted unchanged in the urine. Changes in amlodipine plasma concentrations do not correlate with the degree of renal impairment. Amlodipine may be used at normal doses in patients with renal impairment. Amlodipine is not removed by dialysis.
Patients with hepatic impairment.
Information about amlodipine administration in patients with hepatic impairment is very limited. In patients with hepatic impairment, the clearance of amlodipine is decreased resulting in a longer half-life and an increase in AUC by about 40-60 %.

Clinical characteristics.
Indications.
– Arterial hypertension.
– Chronic stable angina.
– Vasospastic angina (Prinzmetal's angina).

Contraindications.
– Known hypersensitivity to dihydropyridines, amlodipine or any other excipient of the drug.
– Severe arterial hypotension.
– Shock (including cardiogenic shock).
– Left ventricular outflow tract obstruction (e.g. severe aortic stenosis).
– Hemodynamically unstable heart failure after acute myocardial infarction.

Interaction with other medicinal products and other forms of interaction.
Effects of other medicinal products on amlodipine.
There are data on the safe use of amlodipine with thiazide diuretics, alpha-blockers, beta-blockers, ACE inhibitors, prolonged-release nitrates, sublingual form of nitroglycerin, non-steroidal anti-inflammatory drugs, antibiotics, oral hypoglycemic drugs.
Data from *in vitro* human plasma studies indicate that amlodipine has no effect on protein binding of the investigated medicinal products (digoxin, phenytoin, warfarin or indomethacin).

CYP3A4 inhibitors.
The concomitant use of amlodipine and potent or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may lead to significant increase in amlodipine exposure, which may also lead to an increased risk of hypotension. The

clinical relevance of these variations may be more pronounced in elderly patients. Clinical monitoring and dose adjustment may thus be required.
It is not recommended to use amlodipine and grapefruit or grapefruit juice at the same time, since in some patients the bioavailability of amlodipine may increase, which leads to increased hypotensive effects.
CYP3A4 inducers.
The plasma concentration of amlodipine may change after the simultaneous use of known CYP3A4 inducers. Therefore, blood pressure monitoring and dose adjustment should be considered taking into account the co-administration of these drugs, both during and after concomitant treatment, especially with strong CYP3A4 inducers (e.g. rifampicin, St. John's wort).
Dantrolene (infusions).
In animals, lethal ventricular fibrillation and cardiovascular collapse were observed, which were associated with hyperkalemia after intravenous administration of verapamil and dantrolene. Due to risk of hyperkalemia, it is recommended to avoid administration of calcium channel blockers such as amlodipine in patients susceptible to malignant hyperthermia and during treatment of malignant hyperthermia.
Effect of amlodipine on other medicinal products.
The hypotensive effect of amlodipine potentiates the hypotensive effect of other antihypertensive drugs. Amlodipine does not affect the pharmacokinetics of atorvastatin, digoxin, warfarin.
Tacrolimus.
There is a risk of increased tacrolimus blood levels when concomitantly used with amlodipine, however, the pharmacokinetic mechanism of such interaction is not completely determined. Regular monitoring of tacrolimus blood levels and, if necessary, dosage adjustment are required to avoid the toxicity of tacrolimus when concomitantly using amlodipine.
mTOR inhibitors (mammalian target of rapamycin).
mTOR inhibitors, such as sirolimus, temsirolimus and everolimus, are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. When administered concurrently, amlodipine may increase the exposure of mTOR inhibitors.
Cyclosporine.
There have been no studies of interaction between cyclosporine and amlodipine in healthy volunteers or other groups, except for the use in renal transplant patients who demonstrated a transient increase of residual cyclosporine concentrations (on average by 0–40 %). For renal transplant patients who use amlodipine, the possibility of monitoring cyclosporine concentrations should be considered, and if required, the dose of cyclosporine should be decreased.
Simvastatin.
Co-administration of multiple doses of 10 mg amlodipine with 80 mg of simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin monotherapy. The dose of simvastatin in patients using amlodipine should be limited to 20 mg daily.
Sildenafil.
Single administration of 100 mg sildenafil in patients with essential hypertension did not affect the pharmacokinetics of amlodipine. When concomitantly using amlodipine and sildenafil as combined therapy, each drug showed a hypotensive effect independently of the other.
Other drugs.
Clinical studies of drug interaction have shown that amlodipine does not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.
Ethanol (alcohol).
Single and multiple administration of 10 mg amlodipine did not have a significant effect on the pharmacokinetics of ethanol.
Co-administration of amlodipine with cimetidine had no effect on the pharmacokinetics of amlodipine.
Co-administration of aluminum/magnesium (antacids) with a single dose of amlodipine did not have a significant effect on the pharmacokinetics of amlodipine.
Laboratory tests.
The effect on laboratory test values is unknown.

Administration details.

The safety and efficacy of amlodipine in hypertensive crisis have not been estimated.
Patients with heart failure.
Amlodipine should be used with caution in this category of patients. It has been shown that using amlodipine increases the incidence of pulmonary edema in patients with severe heart failure (class III and IV according to NYHA classification). Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of cardiovascular events and fatal events in the future.
Patients with hepatic impairment.
The half-life of amlodipine and AUC parameters are higher in patients with hepatic impairment; there are no recommendations for drug dosage. Therefore, drug administration should be started with the lowest dose in this category of patients. Caution should be exercised upon initiation of drug administration and when increasing the dose. Slow dose titration and careful monitoring of the patient's condition may be required in patients with severe hepatic impairment.
Elderly patients.
The drug dose should be increased with caution in this category of patients.
Patients with renal insufficiency.
Usual drug doses should be used in this category of patients. Changes in amlodipine plasma concentrations do not correlate with the degree of renal impairment.
Amlodipine is not removed by dialysis.
Amlodipine does not affect the results of laboratory tests.
It is not recommended to use amlodipine with grapefruit or grapefruit juice, since the bioavailability of amlodipine may be increased in some patients, resulting in increased hypotensive effects.
Sodium.
This medicinal product contains less than 1 mmol of sodium (23 mg) per tablet, therefore, it is essentially sodium-free.

Use during pregnancy or breast feeding.
The safety of amlodipine in pregnant women has not been established.
Use of amlodipine in pregnancy is only recommended when there is no safer alternative and the risk associated with the disease overweighs the possible harm of treatment for the mother and the fetus.
Animal studies have shown reproductive toxicity at high doses.
Breastfeeding.
Amlodipine is excreted in breast milk. The amount of amlodipine received by the infant from the mother's breast milk can range from 3-7 to 15 % of the dose used by mother. The effect of amlodipine on newborns is unknown. When deciding whether to continue breastfeeding or to use amlodipine, the benefits of breastfeeding for the child and the benefits of using the drug for the mother should be considered.
Fertility.
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility.

Effect on reaction rate when driving motor transport or using other mechanisms.
Amlodipine may have minor or moderate influence on the ability to drive motor transport or use other mechanisms.
The reaction rate may be reduced if there are symptoms such as dizziness, headache, confusion, or nausea.
Caution should be exercised, especially while initiating the treatment.

Dosage and administration.
Adults.

The usual starting dose of Samlopin® for the treatment of arterial hypertension and angina pectoris is 2.5 mg of S(-) amlodipine once daily. The dose can be increased to a maximum 5 mg of S(-) amlodipine once daily, depending on the individual response of the patient.
In patients with angina pectoris, amlodipine can be used as monotherapy or in combination with other antianginal medicinal products in a case of resistance to nitrates and/or adequate doses of beta-blockers.
There is experience of using the drug in combination with thiazide diuretics, alpha-blockers, beta-blockers or ACE inhibitors in patients with arterial hypertension.
No dose adjustment is required upon concomitant administration of thiazide diuretics, beta blockers, and ACE inhibitors
Elderly patients.
Dose adjustment is not required in this category of patients. The dose should be increased with caution.
Patients with renal impairment.
The normal dosage is recommended, because changes in amlodipine plasma concentration are not associated with the severity of renal impairment. Amlodipine is not removed by dialysis.
Use in patients with hepatic impairment.
Drug doses for use in patients with mild to moderate hepatic impairment have not been established, therefore, the dose should be titrated with caution and administration should be started with the lowest dose (see sections "Pharmacological properties", "Pharmacokinetics", and "Administration details").
The pharmacokinetics of amlodipine has not been studied in patients with severe hepatic impairment. The use of amlodipine should be initiated with the lowest dose and gradually increased in patients with severe hepatic impairment.
Samlopin® tablets 2.5 mg are not meant to be divided into halves to get a dose of 1.25 mg.
Samlopin® tablets 5 mg are not meant to be divided into halves to get a dose of 2.5 mg.

Children.
The safety of using S(-) amlodipine in children has not been established. The drug is contraindicated in this category of patients.

Overdose.
The experience of intentional overdose of amlodipine is limited.
Symptoms of overdose: available information suggests that a significant overdose of amlodipine will result in excessive peripheral vasodilation and, possibly, reflex tachycardia. Marked and possibly prolonged systemic hypotension, including lethal shock, has been reported.
Non-cardiogenic pulmonary edema due to amlodipine overdose, which may have a delayed onset (24–48 hours after administration) and require artificial lung ventilation, has been seldom reported. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors for non-cardiogenic pulmonary edema.
Treatment: clinically significant hypotension due to amlodipine overdose requires active support of the cardiovascular system, including frequent monitoring of cardiac and respiratory function, elevation of the lower extremities, monitoring of the volume of circulating fluid and urinary output.
Vasoconstrictive drugs can be used to restore vascular tone and blood pressure, provided that there are no contraindications to their use. Intravenous calcium gluconate may be useful for eliminating the effects of the calcium channel blockade.
Gastric lavage may be worthwhile in some cases. The use of activated charcoal in healthy volunteers up to 2 hours after administration of 10 mg amlodipine has been shown to significantly reduce the absorption rate of amlodipine.
Since amlodipine is highly protein-bound, the effect of dialysis is insignificant.

Adverse reactions.
The most frequently reported adverse reactions with amlodipine are as follows: somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, edema and increased fatigue
Adverse reactions observed with amlodipine are listed below according to organ systems and frequency: very common (≥ 1/10), common (from ≥ 1/100 to < 1/10), uncommon (from ≥ 1/1000 to ≤ 1/100), rare

(from ≥ 1/10000 to ≤ 1/1000), very rare (≤ 1/10000), unknown (cannot be estimated from the available data).
Blood and lymphatic system disorders: Very rare — leucopenia, thrombocytopenia. Unknown — purpura, anemia, agranulocytosis.
Immune system disorders: Very rare — allergic reactions.
Metabolic and nutrition disorders: Very rare — hyperglycemia. Unknown — thirst.
Psychiatric disorders: Uncommon — depression, mood changes (including anxiety), insomnia. Rare — confusion. Unknown — nervousness, loss of consciousness, sleep disturbances, depersonalization.
Nervous system disorders: Common — somnolence, dizziness, headache (especially at the beginning of treatment). Uncommon — tremor, dysgeusia, syncope, hypesthesia, paresthesia. Very rare — hypertonia, peripheral neuropathy. Unknown — extrapyramidal syndrome.
Eye disorders: Common — visual impairment (including diplopia). Unknown — conjunctivitis, eye pain.
Ear and labyrinth disorders: Uncommon — tinnitus. Unknown — sonitus.
Cardiac disorders: Common — palpitations. Uncommon — arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation). Very rare — myocardial infarction. Unknown — tachycardia, angina attacks, orthostatic (postural) hypotension, collapse, chest pain.
Vascular disorders: Common — flushing. Uncommon — arterial hypotension. Very rare — vasculitis. Unknown — peripheral ischemia.
Respiratory, thoracic and mediastinal disorders: Common — dyspnea. Uncommon — rhinitis, cough. Unknown — epistaxis.
Gastro-intestinal disorders: Common — abdominal pain, nausea, dyspepsia, intestinal dysperistalsis (including constipation and diarrhea). Uncommon — vomiting, dry mouth. Very rare — pancreatitis, gastritis, gingival hyperplasia. Unknown — anorexia, loss of appetite, epigastric discomfort, flatulence, bowel dysfunction, dysphagia, dysgeusia.
Hepatobiliary disorders: Very rare — hepatitis, including fulminant hepatitis, jaundice, increased liver enzymes (most often associated with cholestasis). Unknown — hyperbilirubinemia, hepatic impairment.
Skin and subcutaneous tissue disorders: Uncommon — alopecia, purpura, skin discoloration, hyperhidrosis, pruritus, rash, exanthema, urticaria. Very rare — angioedema, erythema multiforme, exfoliative dermatitis, Stevens — Johnson syndrome, Quincke's edema, photosensitivity. Unknown — skin depigmentation, erythematous rash, maculopapular rash, toxic epidermal necrolysis.
Musculo-skeletal system and connective tissue disorders: Common — ankle swelling, muscle cramps. Uncommon — arthralgia, myalgia, back pain. Unknown — muscle stiffness.
Renal and urinary disorders: Uncommon — urination disorder, nocturia, increased urinary frequency.
Reproductive system and breast disorders: Uncommon — impotence, gynecomastia. Unknown — sexual dysfunction.
General disorders and administration site conditions: Very common — edema. Common — increased fatigue, asthenia. Uncommon — retrosternal pain, pain, malaise.
Investigations: Uncommon — increase or decrease in body weight.
Exceptional cases of extrapyramidal syndrome have been reported.
Reporting of adverse reactions.
Reporting adverse reactions after the registration of the medicinal product is of great importance. It allows to monitor the correlation of the benefits and risks related to the use of the medicinal product. Healthcare and pharmaceutical professionals, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of efficacy of the medicinal product through the Automated pharmacovigilance information system available at: https://aisf.dec.gov.ua/.

Shelf-life.
3 years.

Storage conditions.
Store in the original package at a temperature not more than 25 °C.
Keep out of reach of children.

Package.
14 tablets are in blisters; 2 or 4, or 6 blisters are in a carton box.

Conditions of supply.
By prescription.

Manufacturer.
LLC “KUSUM PHARM”.
or
KUSUM HEALTHCARE PVT LTD.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Skryabina Str. 54.
or
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

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