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 dehydrate, yellow ferric oxide (E 172), anhydrous colloidal silica, 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 predominant vascular influence on vessels.  
ATC code C08C A01.

Pharmacological properties.  
pharmacodynamics.  
Amlodipine is a racemic mixture of S (-) and R (+) isomers. S (-) amlodipine is active chiral form of amlodipine, calcium antagonist (dihydropyridine derivative), which blocks the flow of calcium ions to the myocardium and to smooth muscle cells.  
The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism of amlodipine antianginal effect 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 mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles (normal and ischemized). This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).  
In patients with arterial hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of amlodipine action, acute arterial hypotension is not observed.  
In patients suffering from angina pectoris, once daily administration increases total exercise time, the time to occurrence of angina and the time to a 1 mm ST segment depression. The drug reduces the frequency of angina attacks and 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 unmodified molecule is about 64-80%. Maximum blood plasma concentration is between 6-12 hours after administration. The volume of distribution is approximately 21 l/kg; acid dissociation constant (pKa) of amlodipine is 8.6. *In vitro* studies have shown that approximately 97.5% of amlodipine is bound to blood plasma proteins. The absorption of amlodipine is not influenced by concomitant intake of food.

**Metabolism/elimination.**

The blood plasma elimination half-life is about 35-50 hours. The steady state concentration in blood plasma is reached after 7-8 days of continuous drug administration. Amlodipine is mainly metabolized to form 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 reach peak blood plasma concentrations of amlodipine is similar in elderly patients and adults. Amlodipine clearance tends to be decreased with resulting increases in area under curve (AUC) and elimination half-life in elderly patients.

**Patients with renal impairment.**

Amlodipine is extensively biotransformed to inactive metabolites. 10% of amlodipine is excreted unchanged in the urine. Changes in amlodipine blood plasma concentration are not correlated with the degree of renal impairment. In patients with renal impairment amlodipine may be administered at the normal dosage. Amlodipine is not dialyzable.

**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 with a resulting increase half-life and AUC of approximately 40–60%.

**Clinical characteristics:**

**Indications.**

– Arterial hypertension.
– Chronic stable angina.
– Vasospastic angina pectoris (Prinzmetal's angina).

**Contraindications.**

– Known hypersensitivity to dihydropyridine, amlodipine and any other excipient of the drug.
– Severe arterial hypertension.
– 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.*

**CYP3A4 inhibitors.**

The concomitant use of amlodipine and strong 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 the 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.

Consumption of grapefruits or grapefruit juice should be avoided while taking amlodipine, because the bioavailability of amlodipine may be increased in some patients, which leads to increased hypotensive effect.

**CYP3A4 inducers.**
There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers with amlodipine (e.g., rifampicin, saint john's wort) may lead to lower blood plasma concentration of amlodipine, thus such combinations should be used with caution.

_Dantrolene_ (infusions).

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia, after administration of verapamil and dantrolene intravenous. Due to risk of hyperkalemia, it is recommended to avoid co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the treatment of malignant hyperthermia.

**Effect of amlodipine on other medicinal products.**

Hypotensive effect of amlodipine potentiates the hypotensive effect of other antihypertensive agents. Amlodipine has no effect on pharmacokinetics of atorvastatin, digoxin, warfarin.

_Tacroliimus._

There is a risk of increase in the blood levels of tacrolimus when concomitant use with amlodipine, however, pharmacokinetic mechanism of such interaction is not completely determined. To avoid toxicity of tacrolimus, when concomitantly using amlodipine, a regular monitoring of tacrolimus blood levels is necessary and dosage adjustment if required.

_Cyclosporine._

There have been no studies of interaction between cyclosporine and amlodipine in healthy volunteers or other groups, except for the use in patients with a transplanted kidney, which had a transient increase of residual concentration of cyclosporine (on average by 0–40%). For patients with a transplanted kidney using amlodipine, the possibility of monitoring of cyclosporine concentrations should be considered, and if required, the dose of cyclosporine should be decreased.

_Simvastatin._

Concomitant use of multiple doses of amlodipine 10 mg and simvastatin 80 mg increased exposure to simvastatin by 77% compared to using simvastatin only. For patients using amlodipine, simvastatin dose should be limited to 20 mg per day.

**Administration details.**

Safety and efficacy of amlodipine administration in hypertensive crisis have not been estimated.

_Patients with heart failure._

Samlopin® should be used with caution in this population. It has been shown that amlodipine increases the incidence of pulmonary edema in patients with severe heart failure (class III and IV according to the classification NYHA). In patients with congestive heart failure, calcium channel blockers, including amlodipine, should be used with caution because they may increase the risk of cardiovascular events and deaths in the future.

_Patients with hepatic impairment._

The half-life of amlodipine and parameters AUC higher in patients with hepatic impairment; there are no recommendations for drug dosage. Therefore, the drug should be started with the lowest dose in this population. Caution should be exercised when starting to administer the drug, and when increasing the dose. Slow dose titration and careful control may be required in patients with severe hepatic impairment.

_Elderly patients._

Caution should be exercised when increasing the drug dose in these patients.

_Patients with renal insufficiency._

Usual drug doses should be administered to these patients. Changes in the amlodipine blood plasma concentration do not correlate with the degree of renal dysfunctions.

Amlodipine is not dialyzable.

Amlodipine does not affect the results of laboratory tests.

Consumption of grapefruits or grapefruit juice should be avoided while taking amlodipine, because the bioavailability of amlodipine may be increased in some patients, which leads to increased hypotensive effect.

**Use during pregnancy or breast feeding.**

Safety of use of amlodipine in pregnant women is not determined.

Amlodipine should not be used during pregnancy only if there is no safer alternative and the risk, associated with the disease outweighs the possible harm of treatment for the mother and fetus.
Animal studies have shown reproductive toxicity at high doses.

**Breast feeding.**

It is not known whether amlodipine is excreted in breast milk. A decision on whether to continue breast-feeding or to continue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

**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.

**Ability to influence on reaction rate while driving a car or operating any other mechanisms.**

Amlodipine may have minor or moderate influence on the ability to drive a car or operate other machines. In patients suffering from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution should be exercised, especially while initiating the treatment.

**Administration and dosage.**

**Adults.**

For the treatment of hypertension and angina pectoris, the starting dose of Samlopin® is S(-) amlodipine 2.5 mg 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 suffering from angina pectoris, amlodipine can be used as monotherapy or in combination with anti-anginal 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 angiotensin-converting enzyme inhibitors in patients with arterial hypertension. There is no need to adjust the drug dosage when using concomitantly with thiazide diuretics, beta-blockers and angiotensin-converting enzyme inhibitors.

**Elderly patients.**

The dose adjustment is not required in these patients. Caution should be exercised when increasing the dose.

**Patients with renal impairment.**

The normal dosage is recommended. because changes in blood plasma amlodipine concentration are not associated with the severity of renal failure. Amlodipine is not dialyzable.

**Use in patients with hepatic impairment.**

The drug doses for patients with mild or moderate hepatic impairment are not determined, thus start to administer the lowest dose and be careful when adjusting the dose (see sect. “Administration details” and “Pharmacological properties. Pharmacokinetics”). Pharmacokinetic of amlodipine has not been studied in patients with severe hepatic impairment. In patients with severe hepatic impairment the use of amlodipine should be started with the lowest dose and gradually increased.

Samlopin® tablets 2.5 mg are not intended to be divided into halves to get a dose of 1.25 mg. Samlopin® tablets 5 mg are not intended to be divided into halves to get a dose of 2.5 mg.

**Children.**

The safety use of S(-) amlodipine in children is not proved. The drug is contraindicated to be administered in this category of patients.

**Overdose.**

The experience with intentional overdose of amlodipine is limited.

**Symptoms of overdose:** available data suggest that gross overdose could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

**Treatment:** clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and monitoring of circulating fluid volume and urine output.
Use vasoconstrictor agents, making sure there are no contraindications to their use, to restore vascular tone and blood pressure. The use of calcium gluconate intravenously may be beneficial to the leveling effects of calcium channel blockade. Gastric lavage may be useful in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine. Since amlodipine is highly protein-bound, the dialysis effect is negligible.

**Adverse reactions.**

**Blood and lymphatic system:** leukocytopenia, thrombocytopenia, purpura, anemia, agranulocytosis.

**Immune system:** allergic reactions.

**Metabolism and nutrition:** hyperglycemia, thirst.

**Psychiatric:** insomnia, nervousness, mood changes (including anxiety), depression, confusion, unconsciousness, insomnia, depersonalization.

**Nervous system:** drowsiness, dizziness, headache (especially at the beginning of treatment), tremor, dysgeusia, syncope, hypoesthesia, paresthesia, hypertonia, peripheral neuropathy, extrapyramidal syndrome.

**Visual organs:** visual disturbances (including diplopia), conjunctivitis, eye pain.

**Acoustic organs and labyrinth:** tinnitus, sonitus.

**Cardiac:** palpitation, tachycardia, myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), angina, orthostatic (postural) hypotension, collapse, chest pain.

**Vascular:** flushing, arterial hypotension, vasculitis, peripheral ischemia.

**Respiratory, thoracic and mediastinal disorders:** dyspnea, rhinitis, cough, epistaxis.

**Gastro-intestinal tract:** anorexia, loss of appetite, epigastric discomfort, abdominal pain, nausea, vomiting, dyspepsia, intestinal dysperistalsis (including constipation and diarrhea), flatulence, bowel dysfunction, dry mouth, dysphagia, pancreatitis, gastritis, gingival hyperplasia, changes in taste.

**Hepatobiliary system:** hepatitis, jaundice, increases in liver enzymes (which are often associated with cholestasis), hyperbilirubinemia, liver function abnormality.

**Skin and subcutaneous tissue:** alopecia, purpura, skin discoloration, skin depigmentation, increased sweating, itching, rash, eczema, angioedema, multiforme erythema, erythematous rash, maculopapular rash, urticaria, exfoliative dermatitis, Stevens-Johnson Syndrome, Quincke's edema, photosensitivity.

**Musculoskeletal and connective tissue:** swollen legs, arthralgia, myalgia, muscle cramps, back pain, muscle stiffness.

**Renal and urinary tract:** inappropriate urination, nycturia, increased frequency of urination.

**Reproductive system and breast:** impotence, gynecomastia, sexual dysfunction.

**General disorders and administration site:** swelling, increased fatigue, chest pain, asthenia, pain, malaise.

**Investigations:** increase or decrease in body weight.

**Shelf-life.**

3 years.

**Storage conditions.**

Store in the original pack at the temperature NMT 25°C. Keep it 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.** On prescription.

**Manufacturer.**

“KUSUM PHARM” LLC

**Address.**

Ukraine, 40020, Sumy, Skryabina Str., 54.
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