AMLIZEKT

Instructions for the medicinal product

Trade name: Amlizekt.
International Nonproprietary Name: Amlodipine + Lisinopril.
Dosage Form: Uncoated tablets.
Composition:
Amlizekt 5 mg + 5 mg: Each uncoated tablet contains:
Amlodipine Besilate BP equivalent to Amoldipine 5 mg;
Lisinopril USP equivalent to Anhydrous Lisinopril 5 mg.

Amlizekt 5 mg + 10 mg: Each uncoated tablet contains:
Amlodipine Besilate BP equivalent to Amoldipine 5 mg;
Lisinopril USP equivalent to Anhydrous Lisinopril 10 mg.
Pharmacotherapeutic group: ACE inhibitors in combination with other drugs. ACE inhibitors in combination with blockers "slow" calcium channels.
ATC Code: C09BB.
Pharmacological properties:
Pharmacodynamics:
The beneficial effects of *lisinopril* in hypertension appear to result primarily from suppression of the renin-angiotensin-aldosterone system (RAAS). Inhibition of ACE results in decreased plasma angiotensin II which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. ACE is identical to kininase, an enzyme that degrades bradykinin.
Administration of lisinopril to patients with hypertension results in a reduction of supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is usually not observed, although it can occur and should be anticipated in volume and/or salt- depleted patients. When given together with thiazide-type diuretics, the blood pressure lowering effects of the two drugs are approximately additive.
Onset of antihypertensive activity at one hour after oral administration of an individual dose of lisinopril, with peak reduction of blood pressure achieves by 6 hours. The mean antihypertensive effect was substantially smaller 24 hours after dosing than it was six hours after dosing. In some patients, achievement of optimal blood pressure reduction may require two to four weeks of therapy.
In patients with renovascular hypertension, lisinopril well tolerated and effective in controlling blood pressure.
Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.
Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. Following administration of therapeutic doses to patients with hypertension, amlodipine besylate tablets produce vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.
With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. In hypertensive patients with normal renal function, therapeutic doses of amlodipine besylate tablets resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.
Pharmacokinetics:
Lisinopril:
Following oral administration of lisinopril, peak serum concentrations of lisinopril occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients.
Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with large intersubject variability (6-60%) at all doses tested (5-80 mg). Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract.
Impaired renal function decreases elimination of lisinopril, which is excreted principally through the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 mL/min. Above this glomerular filtration rate, the elimination half-life is changed little. With greater impairment, however, peak and trough lisinopril levels increase, time to peak concentration increases and time to attain steady state is prolonged. Older patients, on average, have (approximately doubled) higher blood levels and AUC than younger patients. Lisinopril can be removed by hemodialysis.
Amlodipine:
After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of amlodipine is not altered by the presence of food.
Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism, with 10% of the parent compound and 60% of the metabolites excreted in the urine. Approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.
Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.
The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.
Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in the area under the plasma concentration time curve (AUC) of approximately 40-60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.
Indications for use:
- treatment of mild to moderate hypertension.

It is also indicated in hypertension not responding to monotherapy with ACE inhibitors or calcium antagonists. It may also be substituted for the titrated doses of the individual components.

Contra-indications:
- Hypersensitivity to lisinopril or other ACE inhibitors;
- Hypersensitivity to amlodipine or other dihydropyridine derivatives;
- Increased sensitivity to the auxiliary components of the drug;
- Marked hypotension;
- A history of angioedema during therapy with ACE inhibitors;
- Hereditary or idiopathic angioedema;
- Hemodynamically significant aortic stenosis, mitral stenosis, hypertrophic obstructive cardiomyopathy , cardiogenic shock;
- Heart failure after acute myocardial infarction (within 28 days);
- Unstable angina (except Prinzmetal angina);
- Children and adolescents under 18 years of age (because of insufficient data safety and efficacy).

Pregnancy and lactation:
When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment. Hence, the combination is contraindicated in pregnancy.
It is not known whether lisinopril or amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while the combination is administered.
Dosage and direction for use:
The usual initial dosage of Amlizekt is one tablet *(5 mg+5 mg or 5 mg +10 mg)* daily.
If blood pressure control is inadequate after a week or two, the dose may be increased to two tablets daily.
The dosage, however, should be individualized.
Side effects:
Common:
- dizziness, headache, drowsiness;
- dry cough, stops to remove the drug;
- weakness, diarrhea, nausea, vomiting, change in taste;
- orthostatic hypotension;
- itching, skin rash, swelling, redness of the skin.

Uncommon:
- pain in the chest, back, arthralgia, myalgia, muscle cramps tonic;
- mood changes, sleep disorders;
- hypersensitivity / angioneurotic edema of the face, extremities, lips, epiglottis and larynx;
- agranulocytosis, a slight decrease in hemoglobin and hematocrit long-term use of the drug;
- hyperkalemia;
- increase in serum creatinine, urea, residual nitrogen, elevated liver enzymes and bilirubin levels in the blood serum, especially if the disease is present in the history of kidney disease, diabetes, or renovascular hypertension;
- paresthesia, hyperesthesia, fatigue , asthenia, tremor;
- visual disturbances, ringing in the ears;
- cerebrovascular accident, Raynaud's phenomenon, syncope;
- bronchospasm, allergic alveolitis, dyspnea;
- Rhinitis;
- dyspepsia, increased bowel movements;
- an increase or decrease in body weight;
- nocturia, gynecomastia.

Rarely:
- tachycardia (probably due to excessive hypotension in patients with an increased risk of myocardial infarction and stroke, brain);
- indigestion, dry mouth, abdominal pain, pancreatitis, hepatocellular or cholestatic jaundice, hepatitis, hypertrophic gingivitis;
- swelling, sweating;
- itchy skin, psoriasis, urticaria, alopecia;
- renal dysfunction, poliguriya, anuria, acute renal failure, uremia, proteinuria, impotence;
- hyponatremia.

Very rare:
- suppression of bone marrow hematopoiesis: leukopenia, neutropenia, thrombocytopenia, hemolytic anemia, ESR increase, eosinophilia, leukocytosis, lymphadenopathy;
- hypoglycemia, hyperglycemia;
- autoimmune disorders;
- peripheral neuropathy;
- myocardial infarction, ventricular tachycardia, atrial fibrillation, cardiac arrhythmias , vasculitis;
- eosinophilic pneumonia, sinusitis;
- toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus vulgaris, photosensitivity;
- liver failure;
- raising the level of antinuclear antibodies.

Overdose:
The most likely manifestation of overdosage of lisinopril would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. Lisinopril can be removed by hemodialysis.
If massive overdose of amlodipine should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipne is highly protein bound, hemodialysis is not likely to be of benefit.
Drug interactions:
Lisinopril:
Agents Increasing Serum Potassium: Lisinopril attenuates potassium loss caused by thiazide-type diuretics (e.g. spironolactone, amiloride, triamterene). If concomitant use of these agents is indicated, they should be used with caution, and with frequent monitoring of serum potassium. Therefore, co-administration should be carefully justified and manufactured with the utmost care and regular monitoring as serum potassium and renal function. Potassium-sparing diuretics may be taken in conjunction with the preparation Amlizekt only under strict medical supervision.
Diuretics: Patients on diuretics may occasionally experience an excessive reduction of blood pressure after initiation of therapy with this combination. The possibility of hypotensive effects can be minimized by either discontinuing the combination or increasing the salt intake prior to initiation of treatment.
Other antihypertensive agents: concomitant use of these drugs may increase the hypotensive effect of Amlizekt. Simultaneous treatment with nitroglycerin or other nitrates or vasodilators may lead to a greater reduction in blood pressure.
Tricyclic antidepressants / antipsychotics / anesthetics / drugs: concomitant use of these medications with ACE inhibitors may result in a greater reduction in blood pressure.
Alcohol enhances the hypotensive effect Amlizekt.
Allopurinol, procainamide, systemic corticosteroids, cytotoxic drugs may cause an increased risk of leucopenia, with concomitant administration of ACE inhibitors.
Immunosuppressive drugs with concomitant administration with ACE inhibitors may lead to an increased risk of graft rejection.
Antacids: while receiving ACE inhibitors reduce the bioavailability of the latter.
Sympathomimetics: may reduce the antihypertensive effect of ACE inhibitors, should be closely monitoring the achievement of the desired effect.
Hypoglycemic agents: while receiving ACE inhibitors and hypoglycemic drugs (insulin and oral hypoglycemic agents) may increase the probability of reduction of blood glucose levels and the risk of hypoglycemia. Most often, this phenomenon is observed during the first week of combined treatment and in patients with renal insufficiency.
Nonsteroidal antiinflammatory drugs (NSAIDs): in some patients with compromised renal function who are being treated with NSAIDs, the co- administration of lisinopril may result in a further deterioration of renal function. These effects are usually reversible. NSAIDs blunt the antihypertensive effect of ACE inhibitors, including lisinopril, and this should be given consideration in patients taking NSAIDs concomitantly with Amlizekt. Indomethacin may reduce the antihypertensive efficacy of lisinopril.
Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium.
Amlizekt and lithium should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended.
Amlodipine Inhibitors CYP3A4: elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60% and a lower initial dose may be required. . It is impossible to exclude the possibility that more potent inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the level of serum amlodipine to a greater extent than diltiazem. Simultaneous with the appointment should be made with caution.
Inducers of CYP3A4: concomitant administration with anticonvulsants (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone), rifampicin, herbal preparations containing St. John's wort (Hypericum perforatum) may reduce the concentration of amlodipine in plasma. Shows the clinical management of a possible dose adjustment of amlodipine during the treatment with the inducer and after its withdrawal. The simultaneous use should be undertaken with caution.
Other: as monotherapy amlodipine is well combined with thiazide diuretics, beta-blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, sildenafil, antacids (aluminum hydroxide, magnesium hydroxide, simethicone), cimetidine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic agents. Please inform your doctor about taking the drug Amlizekt before will be made general or local anesthesia, because the latter is a risk factor for short-term drop in blood pressure.
Cautions:
Hypotension, symptomatic:
In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment.
In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with lisinopril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of lisinopril may be necessary.
Renal impairment:
In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Amlizekt therapy.
Angioedema:
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported uncommonly in patients treated with angiotensin converting-enzyme inhibitors, including lisinopril. This may occur at any time during therapy. In such cases, Amlizekt should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.
Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.
Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.
Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor.
Anaphylactic reactions in hemodialysis patients:
Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.
Anaphylactic responses in patients during apheresis low density lipoprotein (LDL):
Rarely, patients receiving ACE inhibitors during low-density lipoproteins (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.
Desensitization of wasp or bee venom:
Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.
Hepatotoxicity:
Very rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving Lisinopril who develop jaundice or marked elevations of hepatic enzymes should discontinue Amlizekt and receive appropriate medical follow-up.
Hematologic toxicity:
In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Amlizekt should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If Amlizekt is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.
Surgical intervention / general anesthesia:
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.
Elderly patients:
Elderly patients with impaired renal function should be to adjust the dose Amlizekt.
Hyperkalemia:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including Lisinopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.
Diabetic patients:
In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor.
Lithium:
The combination of lithium and Amlizekt is generally not recommended.
Effects on ability to drive and use machines:
Amlizekt may affect the ability to drive a car and operate machinery, especially at the beginning of treatment, when the risk of hypotension is more likely. The dose and dosing regimen in which you can control the car and perform tasks associated with an increased risk of injury, set individually.
Presentation:
Amlizekt 5 mg+5 mg or 5 mg +10 mg: 3x10 alu alu Blister in a monocarton with instruction for use.
Storage:
Keep in dry place protected from light at temperature below 25°C. Keep out of reach of children.
Shelf life:
Labeled. Do not use after expiry date.
Distribution condition:
Prescribed medicine.

BELINDA
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