

SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Amlo 2,5 mg, 5 mg and 10 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Each tablet contains: Amlodipinum INN, besylate, equivalent to Amlodipinum INN 2.5 mg, 5 mg or 10 mg

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension.
Stable angina pectoris.

4.2 Posology and method of administration

Dosage for adults:

Dosages are subjective. The initial dose and the usual maintenance dose is 5 mg once daily. The dose may be increased to a maximum of 10 mg once daily. Therapeutic result should be evaluated after at least four weeks of treatment. If satisfactory results have not been gained after 4 weeks, additional treatment or other treatment resources should be considered.

Dosages do not have to be changed when used concomitantly with thiazide, beta-blockers or ACE inhibitors.

Impaired hepatic function: Dosages need to be reduced when hepatic function is impaired.

Dosage for children: The drug is not recommended for children.

4.3 Contra-indications

- Hypersensitivity to amlodipine or to any of the excipients.
- See section 4.6 Pregnancy and lactation.

4.4 Special warnings and special precautions for use

Special caution should be used if the patient has:

- Impaired hepatic function.
- Aortic stenosis.
- Heart failure caused by an acute myocardial infarction.
- Untreated heart failure.

4.5 Interaction with other medical products and other forms of interaction

Amlodipine can be safely administered concomitantly with thiazide, alpha-blockers, beta-blockers, ACE inhibitors, long-acting nitrates, sublingual glyceryl trinitrate, NSAIDs, antibiotics and oral antidiabetics.

In-vitro testing indicate that amlodipine does not affect protein binding of the drugs tested (digoxin, phenytoin, warfarin and indometacin).

Special studies: Effect of other agents on amlodipine.

CIMETIDINE: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

GRAPEFRUIT JUICE: Co-administration of 240 ml of grape juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

AL/MAGNESIUM (antacids): Co-administration of al/magnesium antacids with a single oral dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

SILDENAFIL: A single 100 mg dose of sildenafil in patients with primary hypertension did not affect the pharmacokinetics of amlodipine. In co-administration of sildenafil and amlodipine, each agent independently exerted its own antihypertensive effect.

Special studies: Effect of amlodipine on other agents.

ATORVASTATIN: Co-administration of multiple 10 mg doses of amlodipine with 80 mg atorvastatin resulted in no significant change in the pharmacokinetics of atorvastatin at steady state plasma concentration.

DIGOXIN: Co-administration of amlodipine with digoxin did neither change serum digoxin levels nor digoxin renal clearance in healthy volunteers.

ETHANOL (alcohol): Neither single nor multiple 10 mg amlodipine doses had significant effect on the pharmacokinetics of ethanol.

WARFARIN: Co-administration of amlodipine with warfarin doesn't alter prothrombin response time.

CYCLOSPORIN: Pharmacokinetics studies with cyclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporin.

Drug/Laboratory test Interactions: None known.

4.6 Pregnancy and lactation

Effect on pregnancy:

Calcium channel blockers can prevent early uterus contraction but it is uncertain if the contraction inhibiting effects can occur in the final stages of pregnancy. Anoxia in the foetus is possible if the mother has hypotension. The blood flow to the uterus can then be reduced because of an increased blood flow to peripheral areas (caused by increased peripheral vasodilatation).

In tests on various animal species, calcium channel blockers have had foetotoxic and/or teratogenic effect. Therefore, Amlo should not be administered during pregnancy unless clearly necessary and after the benefit for the mother has been evaluated against the possible risk of damage to the foetus.

Effect on lactation:

No information is available on whether amlodipine is excreted in breast milk.

4.7 Effects on ability to drive and use machines

The effect of amlodipine on the ability to drive or use machines is not considered plausible.

4.8 Undesirable effects

The most common side effect of the drug is a dose-related ankle oedema (3% at 5 mg/daily and 11% at 10 mg/daily), which is caused by dilation of the smallest aortas. In clinical studies 1% of patients have ceased using the drugs because of ankle oedema.

Common (>1%):

General: Ankle oedema, headache, facial flush and heat, fatigue, asthenia.

Heart and vessels: Palpitations, dizziness.

Digestive system: Nausea, indigestion, stomach-ache.

Respiratory system: Shortness of breath.

Nervous system: Muscle cramps.

Rare (0.1-1%):

General: Back pain, malaise, dry mouth, increased sweating.

Blood: Leucopenia, thrombocytopenia.

Bloodstream: Hypotension, tachycardia, chest pain, angitis, fainting.

Endocrine glands: Gynaecomastia.

Digestive system: Gingival hyperplasia, constipation, diarrhoea.

Skin: Pruritus, rash, alopecia.

Liver: Pancreatitis.

Musculo-skeletal system: Arthralgia, myalgia.

Nervous system: Peripheral neuropathy.

Mental: Sleep disorders, agitation, depression.

Urinary and reproductive system: Increased urinary frequency, impotence.

Eye: Vision disturbances.

Very rare (<0.1%):

General: Vasculitis.

Heart: Extra systoles.

Skin: Urticaria.

Liver: Elevation of serum levels of hepatic enzymes, jaundice, hepatitis.

Metabolism: Hyperglycaemia.

Mental: Confusion.

In individual cases allergic reactions have occurred, including erythema multiforme. In individual cases ingravescant angina pectoris, myocardial infarction and arrhythmia have been reported but no connection to the use of amlodipine has been confirmed.

4.9 Overdose

Co-administration of beta-blockers can increase toxic effect.

Experience of overdose of amlodipine is limited. A dose of 140 mg taken by a 15 year old teenager proved lethal as did a dose of 70 mg amlodipine taken concomitantly with oxazepam by an adult. A 30 mg dose taken by a one and a half year old child that had gastric lavage, and 105 mg taken by an adult caused mild to medium toxicity.

In overdose of calcium channel blockers the main risk connects to the effect on blood stream.

Symptoms: Symptoms of overdose can be: nausea and vomiting. Headache, dizziness. Bradycardia (sometimes tachycardia), blood pressure drop. AV-block I-III, AV-dissociation, VES, atrial flutter, asystolia, impaired consciousness, coma, convulsions. Rubeosis, hypothermia. Dyspnoea, pulmonary edema and respiratory arrest. Perhaps ARDS. Acidosis, hypokalemia, hyperglycemia, perhaps hypocalcemia. Renal effect. Rhabdomyolysis, intestinal ischaemia.

Treatment: As needed: Activated charcoal, gastric lavage. Administer atropine before gastric lavage (adults 0,25-0,5 mg but children 10-20 microg/kg), to avoid vagus stimulation. Perhaps laxative. EKG-surveillance. Treatment in a respirator if necessary. Correction of acid-base and electrolyte

balance. For bradycardia and AV-blockage: Atropine administration (adult 0,5-1 mg, children 20-50 microg/kg) repeat if necessary or administer isoprenaline (beginning with 0,05 microg/kg/min which may be increased by 0,05 microg/kg/min if necessary at 10 min intervals). Artificial pacemaker quickly, in complicated cases.

For blood stream interference, administer as needed fluid iv, dobutamine and perhaps noradrenaline (start with 0,05 microg/kg/min. which may be increased by 0,05 microg/kg/min if necessary at 10 min intervals). Calciumglubionat, adults (9 mg Ca/ml) 20(-30) ml iv. in 5 min (children 3-5 mg Ca/kg) in the beginning and repeat if necessary or as an iv. In complicated cases glucagon administration can be tried (adults 10 mg, children 50-150 microg/kg) iv. in 2 min, perhaps followed with iv. and phosphodiesterase inhibitor (e.g. amrinone) as well as administration of *insulin-glucose*. In cases of haemostasis, resuscitative efforts for several hours can be justified. Diazepam can be used for convulsions. Other symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C 08 C A 01

Amlodipine is a dihydropyridine derivative and is an optically inactive mixture of optical active isomers. Amlodipine is a calcium channel blocker that reduces the flow of Ca-ions through ion channels (L-type) into myocardial cells and vascular smooth muscles. It reduces blood pressure due to direct relaxing effects on arterial smooth muscles. Animal testing of amlodipine indicate rather selective effect on vessels, i.e. the effect is significantly less in myocardial vessels compared to vascular smooth muscles. Amlodipine neither has negative effect on AV-conduction nor on heart contractility. Amlodipine reduces renal vessel resistance and increases renal plasma flow. Amlodipine may be administered to patients with treated heart failure. Studies on haemodynamics and endurance of patients with heart failure classes II-IV have shown that amlodipine does not cause any exacerbation considering endurance, ejection fraction or clinical symptoms. No changes occurred to the metabolism of e.g. plasma lipids or glucose.

Effects on blood pressure: Amlodipine reduces blood pressure due to direct relaxing effects on arterial smooth muscle. If Amlo is administered once a day the effects last for 24 hours. The blood pressure reduction follows normal blood pressure variations with very little changes over the day.

Maximum action is not reached until after at least four weeks of treatment. Amlodipine reduces blood pressure of lying and sitting position, standing position and while working. Since the pharmacodynamic effect appears gradually Amlo does not cause sudden hypotension or reflex heart beat. Treatment with amlodipine reduces left ventricular hypertrophy. Haemodynamic effects are unchanged in long term treatment. Amlo is either used solely or concomitantly with beta-blockers, diuretics, ACE-inhibitors or alfa- blockers.

Effect on angina pectoris: Amlodipine causes dilation in peripheral arterioles and reduces therefore peripheral afterload. As Amlo, despite this action, does not affect heart rate, the myocardium's need for oxygen and energy is reduced during treatment. Amlodipine probably causes dilation in coronary arteries, both at hypoxia and normal conditions. This dilation increases oxygen transport in the myocardium in patients with coronary convulsion (prinzmetals- or variant angina).

If a patient with stable angina pectoris takes amlodipine once a day, the drug causes increased endurance and longer intervals between seizures. Since the seizures decrease, the patient's need for nitro glycerine decreases as well. Amlodipine's duration of action against angina pectoris is at least 24 hours.

In treatment of angina pectoris Amlo is either used solely or concomitantly with beta-blockers or nitrates.

5.2 Pharmacokinetic properties

Absorption

After intake of therapeutic doses, amlodipine is well absorbed and the maximum plasma concentration is obtained after 6-12 hours. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg.

Food does not affect the absorption of amlodipine.

Biotransformation/elimination:

Plasma half-life is about 30-40 hours and a stable concentration is achieved in 7-8 days. Distribution volume is up to 21 l/kg. Plasma protein binding is high (98%). Plasma elimination is 7 ml/min/kg. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Amlodipine half-life will be extended for patients with impaired hepatic function.

The elderly:

The time to reach maximum plasma concentration is similar in elderly as in younger subjects.

Dose adjustment is not necessary for elderly patients or patients with impaired renal function, even though plasma clearance is a little slower in elderly patients.

Amlodipine plasma clearance tends to be decreased in elderly patients, resulting in an increased AUC and elimination half-life in elderly patients. Increase in AUC and elimination half-life in patients with heart failure where as expected for the patient age group studied.

5.3 Preclinical safety data

Carcinogenic effects

In rats and mice that were given amlodipine with food for two years in doses comparable to 0.5, 1.25 and 2.5 mg/kg/24h, no carcinogenic effects appeared. The highest dose (comparable to the maximum therapeutic dose for mice, but twice* as high as the maximum therapeutic dose for rats, i.e. 10 mg converted to mg/m²) was close to the highest therapeutic dose for mice but not for rats.

Mutagenic effects

Studies on mutagenic effects did not show drug dependent effect on neither genetic material nor chromosomes.

Effects on fertility

No effect on fertility arose in rats that received amlodipine (male for 64 days and female for 14 days prior to conception) in dosages up to 10 mg/kg/24h (eightfold* maximum therapeutic dose for humans i.e. 10 mg converted to mg/ m²).

* patient weight is assumed to be 50 kg.

Amlodipine half-life is longer in patients with impaired hepatic function.

Dose adjustment is not necessary for neither elderly patients nor patients with impaired renal function, even though plasma clearance is a little slower in elderly patients. A study showed a longer half-life and AUC in patients with heart failure, as expected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The following excipients were used in the manufacturing of Amlo: Microcrystalline cellulose, calcium hydrogen phosphate dihydrate., sodium starch glycolate and magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years in plastic bottles.

3 years in glass bottles.

6.4 Special precautions for storage

Store at room temperature (15-25°C) in closed containers.

Warning: Keep out of reach and sight of children.

6.5 Nature and contents of container

Tablet bottle made from coloured glass with a sealed plastic closure, containing:

Amlo 2.5 mg: 30 tablets and 100 tablets.

Amlo 5 mg: 30 tablets and 100 tablets.

Amlo 10 mg: 30 tablets and 100 tablets.

6.6 Instructions for use/handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Actavis hf
Reykjavíkurvegi 76-78,
220 Hafnarfirdi,
Iceland

8. MARKETING AUTHORISATION NUMBER

Amlo 2.5 mg: 960115 (IS)

Amlo 5 mg: 960116 (IS)

Amlo 10 mg: 960117 (IS)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Amlo 2.5 mg: 01.04.1998

Amlo 5 mg: 01.04.1998

Amlo 10 mg: 01.04.1998

Marketing authorisation renewal 4 February 2004

Duration of the marketing authorisation 4 February 2004 to 4 February 2009

10. DATE OF REVISION OF THE TEXT

13 July 2004