AMLOCIAN 10
Amlodipine Besylate Tablets USP 10 mg

COMPOSITION:
Each uncoated tablet contains:

Amlodipine Besylate USP	
Eq. to Amlodipine	10 mg
Excipients	q.s.

DESCRIPTION:
AMLOCIAN 10 contains Amlodipine 10 mg. Amlodipine is indicated for the treatment of Hypertension, Chronic stable angina pectoris and Vasospastic (Prinzmetal's) angina pectoris.

THERAPEUTIC INDICATION:
- Hypertension
- Chronic stable angina pectoris.
- Vasospastic (Prinzmetal's) angina

PHARMACOKINETICS:
Absorption, distribution, plasma protein binding:
After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.
The bioavailability of amlodipine is not affected by food intake.
Biotransformation/elimination
The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.
Use in hepatic impairment
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.
Use in the elderly
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half life in elderly patients. Increases in AUC and elimination half life in patients with congestive heart failure were as expected for the patient age group studied.
Use in Children
A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females.

PHARMACODYNAMICS:
Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects
ATC code: C08CA01
Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.
The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:
1) Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. 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, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).
In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hours interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.
In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.
Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

POSOLOGY AND METHOD OF ADMINISTRATION :
Posology
Adults
For both hypertension and angina the usual initial dose is 5 mg Amlodipine once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response.
In hypertensive patients, Amlodipine has been used in combination with a thiazide diuretic, alpha blocker, beta blocker, or an angiotensin converting enzyme inhibitor. For angina, Amlodipine may be used as monotherapy or in combination with other antianginal medicinal products in patients with angina that is refractory to nitrates and/or to adequate doses of beta blockers.
No dose adjustment of Amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.
Special populations
Elderly
Amlodipine used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care.
Hepatic impairment
Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.
Renal impairment
Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.
Paediatric population
Children and adolescents with hypertension from 6 years to 17 years of age:
The recommended antihypertensive oral dose in paediatric patient age 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in paediatric patients.
Doses of amlodipine 2.5 mg are not possible with this medicinal product.
Children under 6 years old:
No data are available.
Method of administration
Tablet for oral administration.
The tablets should be taken with a glass of water independently from meals.

CONTRAINDICATION:
Amlodipine is contraindicated in patients with:
- Hypersensitivity to dihydropyridine derivatives, amlodipine or any of the excipients
- Severe hypotension
- Shock (including cardiogenic shock)
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- Haemodynamically unstable heart failure after acute myocardial infarction

SPECIAL WARNING AND PRECAUTION FOR USE:
The safety and efficacy of amlodipine in hypertensive crisis has not been established.
Patients with cardiac failure:
Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.
Use in patients with impaired hepatic function:
The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.
Use in elderly patients
In the elderly increase of the dosage should take place with care.
Use in renal failure
Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.

INTERACTION WITH OTHER MEDICINE AND CONCOMITANT USE:
Effects of other medicinal products on amlodipine
CYP3A4 inhibitors: Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.
CYP3A4 inducers: There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.
Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.
Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.
Effects of amlodipine on other medicinal products
The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.
In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or cyclosporin.
Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

FERTILITY, PREGNANCY AND LACTATION :
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.
Pregnancy
The safety of amlodipine in human pregnancy has not been established.
In animal studies, reproductive toxicity was observed at high doses.
Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.
Lactation
It is not known whether amlodipine is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

UNDESIRABLE EFFECTS:
The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.
The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Blood and lymphatic system disorders
Very Rare - Leukocytopenia, thrombocytopenia
Immune system disorders
Very Rare - Allergic reactions
Metabolism and nutrition disorders
Very Rare - Hyperglycaemia
Psychiatric disorders
Uncommon - Insomnia, mood changes (including anxiety), depression
Nervous system disorders
Common - Somnolence, dizziness, headache (especially at the beginning of the treatment)
Uncommon - Tremor, dysgeusia, syncope, hypoesthesia, paresthesia
Very Rare - Hypertonia, peripheral neuropathy
Eye disorders
Uncommon - Visual disturbance (including diplopia)
Ear and labyrinth disorders
Uncommon - Tinnitus
Cardiac disorders
Common – Palpitations
Uncommon – Hypotension
Vascular disorders
Common – Flushing
Uncommon – Hypotension
Respiratory, thoracic and mediastinal disorders
Uncommon - Dyspnoea, rhinitis
Very Rare - Cough
Gastrointestinal disorders
Common - Abdominal pain, nausea
Uncommon - Vomiting, dyspepsia, altered bowel habits (including diarrhoea and constipation), dry mouth
Very Rare - Pancreatitis, gastritis, gingival hyperplasia
Hepato-biliary disorders
Very Rare - Hepatitis, jaundice, hepatic enzymes increased
Skin and subcutaneous tissue disorders
Uncommon - Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema
Very Rare - Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-
Johnson syndrome, Quincke oedema, photosensitivity
Musculoskeletal and connective tissue disorders
Common - Ankle swelling
Renal and urinary disorders
Uncommon - Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders
Uncommon - Impotence, gynecomastia
General disorders and administration site conditions
Common - Oedema, fatigue
Uncommon - Chest pain, asthenia, pain, malaise

OVERDOSE:
In humans experience with intentional overdose is limited
Symptoms:
Overdosage 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 overdosage calls for active cardiovascular support including frequent 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.
Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 5 mg has been shown to reduce the absorption rate of amlodipine.
Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

INCOMPATIBILITIES :
Not applicable

SHELF LIFE:
36 Months

PACKAGING:
10 tablets are packed in Alu-Alu blister and such 10 blisters are packed in a printed carton along with insert.

STORAGE CONDITION:
Store in a dry place below 30°C. Keep out of reach of children.

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