TENOX TABLETS 5 mg P I
TENOX TABLETS 10 mg P I

1. NAME OF THE MEDICINAL PRODUCT

Tenox 5 mg tablets
Tenox 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tenox 5 mg tablets:
Each tablet contains 5 mg amlodipine (as amlodipine besilate).

Tenox 10 mg tablets:
Each tablet contains 10 mg amlodipine (as amlodipine besilate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Tenox 5 mg:
The tablets are white, round (diameter 8 mm), slightly biconvex tablets with bevelled-edges, scored on one side. The tablet can be divided into equal halves.

Tenox 10 mg:
The tablets are white, round (diameter 10.5 mm), slightly biconvex tablets with bevelled-edges.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

Amlodipine is indicated for the first-line treatment of hypertension and can be used as the sole agent to control blood pressure in the majority of patients. Patients not adequately controlled on a single antihypertensive agent may benefit from the addition of amlodipine, which has been used in combination with a thiazide diuretic, alpha blockers, beta adrenoceptor blocking agent, or an angiotensin-converting enzyme (ACE) inhibitor.

Coronary Artery Disease

Chronic Stable Angina
Amlodipine is indicated for the symptomatic treatment of chronic stable angina. Amlodipine may be used alone or in combination with other antianginal drugs.

Vasospastic Angina (Prinzmetal's or Variant Angina)
Amlodipine is indicated for the treatment of confirmed or suspected vasospastic angina. Amlodipine may be used as monotherapy, or in combination with other antianginal drugs.

Angiographically Documented Coronary Artery Disease
In patients with recently documented coronary artery disease (CAD) by angiography and without heart

failure or an ejection fraction <40%, amlodipine is indicated to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure.

4.2 Posology and method of administration

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.

For patients with coronary artery disease, the recommended dosage range is 5 mg to 10 mg once daily. In clinical studies, the majority of patients required 10 mg once daily (see section 5.1. Pharmacodynamic properties - Use in Patients with Coronary Artery Disease).

No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, beta-blockers, and ACE inhibitors.

Use in the Elderly

Normal dosage regimens are recommended. Amlodipine, used at similar doses in the elderly or younger patients, is equally well-tolerated.

Use in Children

Safety and effectiveness of amlodipine in children have not been established.

Use in Patients with Impaired Hepatic Function

See section 4.4. Special warnings and precautions for use.

Use in Patients with Renal Failure

Amlodipine may be used at normal doses in patients with renal failure. Changes in amlodipine plasma concentrations are not correlated with the degree of renal impairment. Amlodipine is not dialyzable.

4.3 Contraindications

Amlodipine is contraindicated in patients with a known hypersensitivity to dihydropyridines* or any of the inert ingredients.

* Amlodipine is a dihydropyridine calcium channel blocker.

4.4 Special warnings and precautions for use

Use in Patients with Heart Failure

In a long-term placebo-controlled study (PRAISE-2) of amlodipine in patients with New York Heart Association (NYHA), class III and IV heart failure of non-ischemic etiology, amlodipine was associated with increased reports of pulmonary edema despite no significant differences in the incidence of worsening heart failure compared to placebo (see section 5.1. Pharmacodynamic properties).

Use in Patients with Impaired Hepatic Function

As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established in these patients. The drug should therefore be administered with caution in these patients.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Amlodipine has been safely administered with thiazide diuretics, alpha blockers, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

In vitro data from studies with human plasma indicate that amlodipine has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin, or indomethacin).

Simvastatin
Co-administration of multiple doses of 10 mg 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.

Grapefruit Juice
Grapefruit juice is known to inhibit the cytochrome P450 system, thereby affecting the pharmacokinetics of drugs such as calcium channel blockers. Co-administration of 240 mL grapefruit juice with a single oral dose of 10 mg amlodipine in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine. The study did not allow examination of the effect of genetic polymorphism in CYP3A4, the primary enzyme responsible for metabolism of amlodipine; therefore, 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.

CYP3A4 Inhibitors
Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients (69 to 87 years of age) resulted in a 57% increase in amlodipine systemic exposure. Co-administration of erythromycin in healthy volunteers (18 to 43 years of age) did not significantly change amlodipine systemic exposure (22% increase in area under the concentration versus time curve [AUC]). Although the clinical relevance of these findings is uncertain, pharmacokinetic variations may be more pronounced in the elderly.

Strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution when administered with CYP3A4 inhibitors.

Clarithromycin
Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co-administered with clarithromycin.

CYP3A4 Inducers
There is no data available regarding the effect of CYP3A4 inducers on amlodipine. Concomitant use of CYP3A4 inducers (e.g., rifampicin, Hypericum perforatum (St. John’s Wort)) may decrease the plasma concentrations of amlodipine. Amlodipine should be used with caution when administered with CYP3A4 inducers.

Special Studies: Effect of Other Agents on Amlodipine

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

Aluminum/Magnesium (Antacid)

Co-administration of aluminum/magnesium (antacid) with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil
A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering 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 steady-state pharmacokinetic parameters of atorvastatin.

Digoxin
Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in healthy volunteers.

Ethanol (Alcohol)
Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Warfarin
Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Cyclosporin
No drug interaction studies have been conducted with cyclosporin and amlodipine in healthy volunteers or other populations, with the exception of renal transplant patients. Various studies in renal transplant patients report that co-administration of amlodipine with cyclosporin affects the trough concentrations of cyclosporin, from no change up to an average increase of 40%. Consideration should be given for monitoring cyclosporin levels in renal transplant patients on amlodipine.

Tacrolimus
There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors
mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Drug/Laboratory Test Interactions

None known

4.6 Fertility, pregnancy and lactation

The safety of amlodipine in human pregnancy or lactation has not been established. Amlodipine does not demonstrate toxicity in animal reproductive studies other than delay in parturition and prolongation of labor in rats at a dose level 50 times the maximum recommended dose in humans. Accordingly, use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and fetus. There was no effect on the fertility of rats treated with amlodipine (see section 5.3. Preclinical safety data).

Experience in humans indicates that amlodipine is transferred into human breast milk. The median amlodipine concentration ratio of milk/plasma in 31 lactating women with pregnancy-induced hypertension was 0.85 following amlodipine administration at an initial dose of 5 mg once daily which was adjusted as needed (mean daily dose and body weight adjusted daily dose: 6 mg and 98.7 mcg/kg, respectively). The estimated daily dose of amlodipine in the infant via breast milk was 4.17 mcg/kg.

4.7 Effects on ability to drive and use machines

Clinical experience with amlodipine indicates that it is unlikely to impair a patient's ability to drive or use machinery.

4.8 Undesirable effects

Amlodipine is well tolerated. In placebo controlled clinical trials involving patients with hypertension or angina, the most commonly observed side effects were:

Vascular Disorders: Flushing

Nervous System Disorders: Dizziness, headaches, somnolence

Gastrointestinal Disorders: Abdominal pain, nausea

Cardiac Disorders: Palpitations

General Disorders and Administration Site Conditions: Fatigue, oedema

In these clinical trials no pattern of clinically significant laboratory test abnormalities related to amlodipine has been observed.

Less commonly observed side effects in marketing experience include:

General Disorders and Administrative Site Conditions: Asthenia, malaise, pain

Investigations: Weight increased/decreased

Nervous System Disorders: Hypertonia, hypoaesthesia/paraesthesia, peripheral neuropathy, syncope, dysgeusia, tremor, extrapyramidal disorder

Reproductive System and Breast Disorders: Gynaecomastia, erectile dysfunction

Gastrointestinal Disorders: Change in bowel habits, dry mouth, dyspepsia (including gastritis), gingival hyperplasia, pancreatitis, vomiting

Metabolism and Nutrition Disorders: Hyperglycemia

Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, muscle spasms, myalgia

Blood and Lymphatic System Disorders: Leukopenia, thrombocytopenia

Psychiatric Disorders: Insomnia, mood altered

Respiratory, Thoracic and Mediastinal Disorders: Coughing, dyspnoea, rhinitis

Skin and Subcutaneous Tissue Disorders: Alopecia, hyperhidrosis, purpura, skin discoloration, urticaria

Ear and Labyrinth Disorders: Tinnitus

Renal and Urinary Disorders: Pollakiuria, micturition disorder, nocturia

Vascular Disorders: Hypotension, vasculitis

Eye Disorders: Visual impairment

Rarely reported events were allergic reaction including pruritus, rash, angioedema, and erythema multiforme.

Hepatitis, jaundice and hepatic enzyme elevations have also been reported very infrequently (mostly consistent with cholestasis). Some cases severe enough to require hospitalization have been reported in association with use of amlodipine. In many instances, causal association is uncertain.

As with other calcium channel blockers the following adverse events have been rarely reported and cannot be distinguished from the natural history of the underlying disease: myocardial infarction (MI), arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) and chest pain.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 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.

Administration of activated charcoal to healthy volunteers immediately after or up to 2 hours after amlodipine 10 mg ingestion has been shown to significantly decrease amlodipine absorption. Gastric lavage may be worthwhile in some cases. Clinically significant hypotension due to amlodipine overdose 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 there is no contraindication to its use.
Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects, ATC code: C08CA01.

Amlodipine is a calcium ion influx inhibitor (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 ischemic 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 ischemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina) and blunts smoking-induced coronary vasoconstriction.

In patients with hypertension, once-daily dosing provides clinically significant reductions in blood pressure in both the supine and standing positions throughout the 24-hour 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 1 mm ST segment depression, and decreases both angina attack frequency and nitroglycerine 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.

Use in Patients with Coronary Artery Disease

The effects of amlodipine on cardiovascular morbidity and mortality, the progression of coronary atherosclerosis, and carotid atherosclerosis were studied in the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT). This multicenter, randomized, double-blind, placebo-controlled study followed 825 patients with angiographically defined CAD for 3 years. The population included patients with previous MI (45%), percutaneous transluminal coronary angioplasty (PTCA) at baseline (42%), or history of angina (69%). The severity of CAD ranged from 1-vessel disease (45%) to 3+ vessel disease (21%). Patients with uncontrolled hypertension (diastolic blood pressure [DBP] >95 mmHg) were excluded from the study. Major cardiovascular events were adjudicated by a blinded endpoint committee. Although there were no demonstrable effects on the rate of progression of coronary artery lesions, amlodipine arrested the progression of carotid intima-media thickening. A significant reduction (-31%) was observed in amlodipine-treated patients in the combined endpoint of cardiovascular death, MI, stroke, PTCA, coronary artery bypass graft (CABG), hospitalization for unstable angina, and worsening congestive heart failure (CHF).

A significant reduction (-42%) in revascularization procedures (PTCA and CABG) was also seen in amlodipine-treated patients. Fewer hospitalizations (-33%) were seen for unstable angina in amlodipine-treated patients than in the placebo group.

CAMELOT enrolled 1997 patients with CAD recently documented by angiography, without left main coronary disease and without heart failure or an ejection fraction <40%. Patients (76% males, 89% Caucasian, 93% enrolled at US sites, 89% with a history of angina, 52% without PCI, 4% with PCI and no stent, and 44% with a stent) were randomized to double-blind treatment with either amlodipine besylate tablets (5 mg to 10 mg once daily) or placebo in addition to standard care that included aspirin (89%), statins (83%), beta-blockers (74%), nitroglycerin (50%), anti-coagulants (40%), and diuretics (32%), but excluded other calcium channel blockers, for 2 years. The primary endpoint was the time to first occurrence of one of the following events: hospitalization for angina pectoris, coronary revascularization, MI, cardiovascular death, resuscitated cardiac arrest, hospitalization for heart failure, stroke/transient ischemic attack (TIA), or peripheral vascular disease (PVD).

The outcome of this study was largely derived from the prevention of hospitalizations for angina and the prevention of revascularization procedures (see Table 1). The other components of the primary endpoint including cardiovascular death, resuscitated cardiac arrest, MI, hospitalization for heart failure, stroke/TIA, or PVD did not demonstrate a significant difference between amlodipine besylate and placebo.

Table 1. Incidence of Significant Clinical Outcomes for CAMELOT

Clinical Outcomes N (%)	Amlodipine (n=663)	Placebo (n=655)	Risk Reduction (p-value)
Composite CV Endpoint*	110 (16.6)	151 (23.1)	31% (0.003)
Hospitalization for Angina	51 (7.7)	84 (12.8)	42% (0.002)
Coronary Revascularization	78 (11.8)	103 (15.7)	27% (0.033)

* 1) Defined in CAMELOT as cardiovascular death, non-fatal MI, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for CHF, fatal or non-fatal stroke or TIA, any diagnosis of PVD in a subject not previously diagnosed as having PVD or any admission for a procedure for the treatment of PVD.
2) The composite cardiovascular (CV) endpoint was the primary efficacy endpoint in CAMELOT.

Treatment to Prevent Heart Attack Trial (ALLHAT)

A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-lowering-treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5 mg/day to 10 mg/day (calcium channel blocker) or lisinopril 10 mg/day to 40 mg/day (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic chlorthalidone 12.5 mg/day to 25 mg/day in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed up for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including MI or stroke for >6 months or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), high-density lipoprotein-C (HDL-C) <35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), or current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal MI. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI [0.90-1.07], p=0.65. Among Secondary Endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52], p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.96 95% CI [0.89-1.02], p=0.20.

Use in Patients with Heart Failure

Hemodynamic studies and exercise-based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration, as measured by exercise tolerance, left ventricular ejection fraction, and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics, and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity in patients with heart failure.

In a follow-up, long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA class III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total or cardiovascular mortality. In this same population, amlodipine was associated with increased

reports of pulmonary edema despite no significant difference in the incidence of worsening heart failure compared to placebo.

5.2 Pharmacokinetic properties

Absorption

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6 and 12 hours post-dose. Absolute bioavailability has been estimated to be between 64% and 80%. The volume of distribution is approximately 21 L/kg. Absorption of amlodipine is unaffected by consumption of food.

In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Biotransformation/Elimination

The terminal plasma elimination half-life is about 35 to 50 hours and is consistent with once-daily dosing. Steady-state plasma levels are reached after 7 to 8 days of consecutive dosing. Amlodipine is extensively metabolized by the liver to inactive metabolites, with 10% of the parent compound and 60% of metabolites excreted in the urine.

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 CHF were as expected for the patient age group studied.

5.3 Preclinical safety data

Carcinogenesis

Rats and mice treated with amlodipine in the diet for 2 years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg, on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenesis

Mutagenicity studies revealed no drug-related effects at either the gene or chromosome levels.

Impairment of Fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg, on a mg/m^2 basis).

*Based on patient weight of 50 kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Starch, pregelatinised
Sodium starch glycolate (Type A)
Silica, colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package.

6.5 Nature and contents of container

Blister: 30 tablets, in a carton box.

MANUFACTURER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

DATE OF REVISION OF THE TEXT

March 2022