SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VAZKOR 10 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Amlodipine besilate 13.869 mg (equivalent to 10 mg amlodipine)

Excipients:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White, homogenous, slightly biconvex, round tablets embossed with a central notch on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Essential Hypertension:
It may be used alone or in combination with other antihypertensives to control blood pressure.

2. Coronary Artery Disease:

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

Vasospastic Angina or Prinzmetal's Angina:
It is indicated for the treatment of angina attacks due to vasospasm in coronary arteries. It may be used as monotherapy or in combination with other antianginal drugs.

4.2 Posology and method of administration

Posology/frequency and duration of administration
For hypertension and angina, the usual initial dose is 5 mg VAZKOR once daily and, depending on the patient's individual response, the dose may be increased to a maximum of 10 mg.

VAZKOR has been used in combination with thiazide diuretics, alpha blockers, beta blockers or an angiotensin-converting enzyme inhibitor. VAZKOR may be used as monotherapy or in combination with other anti-anginal medicinal products in patients with angina that is refractory to nitrates and/or to adequate doses of beta blockers.

No dose adjustment of VAZKOR is required upon concomitant administration of thiazide diuretics, beta blockers and angiotensin-converting enzyme inhibitors.

Method of administration
For oral administration.
Additional information on special populations:

Hepatic impairment:
Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be done with caution and should start at the lower end of the dosing range (see sections 4.4 and 5.2). The pharmacokinetics of amlodipine has not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and in patients with severe hepatic impairment, the dose should be increased gradually.

Renal impairment:
VAZKOR can be used in such patients at normal doses. Changes in amlodipine plasma concentration are not correlated with degree of renal impairment. Amlodipine is not dialyzable.

Pediatric population:
The recommended antihypertensive oral dose in pediatric patients aged 6-17 years is 2.5-5 mg once daily. The dose may be increased to 5 mg daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in pediatric patients (see sections 5.1 and 5.2). It is not possible to administer amlodipine at a dose of 2.5 mg with this medicine.

Effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

Geriatric population:
VAZKOR used at similar doses in elderly or younger hypertensive patients is equally well tolerated. Therefore, normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care (see sections 4.4 and 5.2).

4.3 Contraindications
VAZKOR is contraindicated in patients with the following diseases:
- Sensitivity to dihydropyridine derivatives (amlodipine is a dihydropyridine calcium channel blocker), amlodipine or any of the excipients in the composition of the drug
- Severe hypotension
- Shock (including cardiogenic shock)
- Obstruction of the outflow of the left ventricle (e.g. high-grade aortic stenosis)
- Hemodynamically unstable heart failure after myocardial infarction

4.4 Special warnings and precautions for use

General
The vasodilator effect of VAZKOR starts slowly. For this reason, rare cases of acute hypotension have been reported after oral use of VAZKOR. VAZKOR, like other peripheral vasodilators, should be used with caution, especially in patients with severe aortic stenosis.

Use in 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 (New York Heart Association-NYHA class III and IV) the

reported incidence of pulmonary edema was higher in the amlodipine treated group than in the placebo group (see section 5.1 Pharmacodynamic properties).

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
As with all other calcium channel antagonists, the half-life of VAZKOR is prolonged in patients with impaired liver function and dosage recommendations have not been established in these patients. VAZKOR should therefore be administered with caution in these patients.

Use in elderly patients
In the elderly, increase of the dosage should take place with care (see sections 4.2 and 5.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other agents on amlodipine

CYP3A4 inhibitors:
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole group antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may significantly increase plasma concentrations of amlodipine and increase the risk of hypotension.

The clinical significance of these pharmacokinetic changes may be more prominent in the elderly. Therefore, clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers: Co-administration of known inducers of CYP3A4 may alter the plasma concentration of amlodipine. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, St. John's Wort).

Grapefruit juice: 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 with hyperkalemia after administration of verapamil and dantrolene IV. 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 treatment of malignant hyperthermia.

Effects of amlodipine on other agents
The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicines with antihypertensive properties.

Tacrolimus: Although the exact pharmacokinetic mechanism is not known, there is a risk of increased blood levels of tacrolimus when tacrolimus and amlodipine are used concomitantly. 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 needed.

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.

Cyclosporine: No drug interaction studies have been conducted between cyclosporine and amlodipine in healthy volunteers or any other populations with the exception of renal transplant patients, whom unstable increases (average 0%-40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made if necessary.

Simvastatin: Co-administration of repeated doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. In patients receiving amlodipine treatment, the dose of simvastatin should be limited to 20 mg daily.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

Additional information on special populations

Hepatic/renal impairment:
No interaction studies have been conducted.

Pediatric population:
No interaction studies have been conducted.

4.6 Pregnancy and lactation

General recommendation:
Pregnancy category is C.

Women of child-bearing potential/Birth control (Contraception)
Women of child bearing potential should ensure that they use effective contraception.

Pregnancy
The safety of amlodipine in human pregnancy has not been established. Therefore, 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.

Animal studies are insufficient with respect to effects on pregnancy/and-or/embryonal/fetal development/and-or/parturition/and-or/postnatal development (see section 5.3 Preclinical safety data). The potential risk for humans is unknown.

Breast-feeding
Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3-7%, and a maximum of 15%. The effect of amlodipine on infants is unknown. 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.

Reproductive ability/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. In one rat study, adverse effects were found on male fertility (see section 5.3 Preclinical safety data).

4.7. Effects on ability to drive and use machinery
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.

4.8. Undesirable effects

Summary of the safety profile
The most commonly observed adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing in face, abdominal pain, nausea, ankle edema (swelling) and fatigue.

Tabular list of side effects:
The following side effects were observed 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) and unknown (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Blood and the lymphatic system disorders
Very rare: Leucopoenia, thrombocytopenia

Immune system disorders
Very rare: Allergic reaction

Metabolism and nutrition disorders
Very rare: Hyperglycemia

Psychiatric disorders
Uncommon: Depression, mood changes (including anxiety), insomnia
Rare: Confusion

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
Common: Visual disturbance (including diplopia)

Ear and inner ear disorders
Uncommon: Tinnitus

Cardiac disorders
Common: Palpitation
Uncommon: Arrhythmia (including bradycardia, ventricular tachycardia, atrial fibrillation)
Very rare: Myocardial infarction

Vascular disorders
Common: Flushing in face
Uncommon: Hypotension
Very rare: Vasculitis

Respiratory, thoracic diseases and mediastinal disorders
Common: Dyspnea
Uncommon: Cough, rhinitis

Gastrointestinal disorders
Common: Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhea and constipation)
Uncommon: Vomiting, dry mouth
Very rare: Pancreatitis, gastritis, gingival hyperplasia

Hepatobiliary disorders
Very rare: Hepatitis, jaundice and raising in hepatic enzymes (mostly consistent with cholestasis)

Skin and subcutaneous tissue disorders
Uncommon: Alopecia, purpura, skin discoloration, hyperhydrosis, itching (pruritus), rash, exanthema, urticaria
Very rare: Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke edema, photosensitivity
Unknown: Toxic epidermal necrosis

Musculoskeletal diseases, connective tissue and bone disorders
Common: Ankle swelling, muscle cramps
Uncommon: Arthralgia, myalgia, back pain

Renal and urinary disorders
Uncommon: Micturition disorder, nocturia, increased urinary frequency

Reproductive system and breast disorders
Uncommon: Impotence, gynecomasty

General disorders and administration site conditions
Very common: Edema
Common: Fatigue, asthenia

Uncommon: Chest pain, pain, malaise

Investigations
Uncommon: Weight increase/decrease
Exceptional cases of extrapyramidal syndrome have been observed.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in accordance with local requirements.

4.9. Overdose and treatment
In humans experience with intentional overdose is limited.

Symptom:
Available data suggest that overdosage of large amounts could result in excessive peripheral vasodilatation and possibly reflex tachycardia. A few cases have also been reported, starting with marked and possibly prolonged systemic hypotension and progressing to shock resulting in death.

Treatment:
Clinically significant hypotension due to amlodipine overdose requires active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, control of circulating fluid volume and volume of urine excreted. 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. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption.
Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Cardiovascular system, selective calcium channel blocker with mainly vascular effects, dihydropyridine derivatives
ATC code: C08CA01

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the entry of calcium ion across the cell membrane and into the cell in 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 (after load) 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 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 hour interval. Due to the slow onset of action, acute hypotension is not seen with amlodipine.

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.

No metabolic adverse effects or changes in plasma lipids have occurred with amlodipine and is suitable for use in patients with asthma, diabetes, and gout.

The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-centre, randomized, double-blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study. Of these patients, 663 were treated with amlodipine 5-10 mg, 673 patients were treated with enalapril 10-20 mg, and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization attempts in patients with CAD.

Table 1 – Incidence of Significant Clinical Outcomes for CAMELOT

	Cardiovascular event rates No. (%)			**Amlodipine vs. placebo**	
Clinical Outcomes	**Amlodipine**	**Placebo**	**Enalapril**	**Hazard Ratio (95% Confidence Interval -CI)**	***P* value**
Primary Endpoint					
Adverse cardiovascular events	110 (16.6)	151 (23.1)	136 (20.2)	0.69 (0.54-0.88)	0.003
Individual Components					
Coronary revascularization	78 (11.8)	103 (15.7)	95 (14.1)	0.73 (0.54-0.98)	0.03
Hospitalization caused of angina	51 (7.7)	84 (12.8)	86 (12.8)	0.58 (0.41-0.82)	0.002
Nonfatal myocardial infarction	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0.37-1.46)	0.37
Stroke or transient ischemic attack	6 (0.9)	12 (1.8)	8 (1.2)	0.50 (0.19-1.32)	0.15
Cardiovascular death	5 (0.8)	2 (0.3)	5 (0.7)	2.46 (0.48-12.7)	0.27
Hospitalization for congestive heart failure	3 (0.5)	5 (0.8)	4 (0.6)	0.59 (0.14-2.47)	0.46
Resuscitated cardiac arrest	0	4 (0.6)	1 (0.1)	NA	0.04
New-onset peripheral vascular disease	5 (0.8)	2 (0.3)	8 (1.2)	2.6 (0.5-13.4)	0.24

Use in Patients with Heart Failure

Hemodynamic 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 measurements and clinical symptomatology.

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

In a long-term, placebo-controlled follow-up study (PRAISE - 2) in patients with NYHA III and IV heart failure of non-ischemic etiology receiving stable doses of ACE inhibitors, digitalis and diuretics, amlodipine had no effect on total or cardiovascular mortality. In this same population there were increased reports of pulmonary edema with amlodipine use, despite no significant difference in the incidence of worsening heart failure as compared to placebo.

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 (2.5-10 mg/day) (calcium channel blocker) and lisinopril (10-40 mg/day) (angiotensin-converting-enzyme inhibitor (ACE) inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone (12.5-25 mg/day) in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one of the risk factors additionally, myocardial infarction or stroke >6 months ago or other documented cardiovascular disease (total 51.5%), type 2 diabetes (36.1%), HDL-C <35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), and smoking (21.9%).
The primary endpoint was a composite of fatal CHD and non-fatal myocardial infarction. 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 pediatric patients (ages between 6 -17 years)
In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5 mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced systolic blood pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

5.2. Pharmacokinetic properties

General properties
Absorption:

After oral administration of therapeutic doses, amlodipine is well absorbed and forms peak blood levels between 6 - 12 hours post-dose. Absolute bioavailability has been calculated to be between 64 and 80%.

The absorption of amlodipine is not affected by intake with food.

Distribution:
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.

Biotransformation:
Steady state plasma levels are reached after 7–8 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.

Elimination:
The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing.

Linearity/Non-linearity:
Data is not available.

Characteristics in patients
Use in the elderly patients:
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 under the curve (AUC) and elimination half-life in elderly patients. Increases in area under the curve (AUC) and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Use in patients with impaired hepatic function:
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 pediatric patients:
A population pharmacokinetic study has been conducted in 74 hypertensive children aged from 1 year 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. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

5.3. Preclinical safety data
Reproductive toxicology
Reproductive studies in rat and mice have shown delayed date of delivery, prolonged duration of labor pains and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Carcinogenesis

No evidence of carcinogenesis was obtained in mice and rats given amlodipine at concentrations corresponding to dose levels of 0.5, 1.25 and 2.5 mg/kg per day for two years. The highest dose (in mg/m2, similar to the human maximum recommended clinical dose of 10 mg for mice and twice the human maximum recommended clinical dose of 10 mg for rats*) is 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 level.

Impairment of fertility
There was no effect on the fertility in rats treated (males for 64 days and females 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). In another 30-day rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.
*Based on patient weight of 50 kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose (pH 102)
Calcium phosphate dibasic anhydrous
Sodium starch glycolate
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
48 months

6.4 Special precautions for storage
Store at room temperature below 30°C. Protect from light.

6.5 Nature and contents of container
Blisters consisting of printed aluminum foil on one side and opaque PVC on the other side. Packs of 20, 30 or 90 tablets.

6.6. Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

185/32

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 05.12.1997
Date of latest renewal :

10. DATE OF REVISION OF THE TEXT