SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Amlodipine Sandoz 5 mg tablets
Amlodipine Sandoz 7.5 mg tablets
Amlodipine Sandoz 10 mg tablets

amlodipine besilate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Amlodipine 5 mg tablets
Each tablet contains 5 mg amlodipine (as amlodipine besilate)

Amlodipine 7.5 mg tablets
Each tablet contains 7.5 mg amlodipine (as amlodipine besilate)

Amlodipine 10 mg tablets
Each tablet contains 10 mg amlodipine (as amlodipine besilate)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Amlodipine 5 mg tablets
A white or almost white, oblong tablet with bevelled edges, score line on one side and marked with a "5" on the other side.
The tablet can be divided into equal halves.

Amlodipine 7.5 mg tablets
A white or almost white, oblong tablet with bevelled edges, double score line on one side and marked with a "7.5" on the other side.
The tablet can be divided into three equal parts.

Amlodipine 10 mg tablets
A white or almost white, oblong tablet with bevelled edges, score line on one side and marked with a "10" on the other side.
The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Essential hypertension.
Chronic stable and vasospastic angina pectoris.

4.2 Posology and method of administration

For oral use.
The tablets should be taken with a glass of liquid (e.g. a glass of water) independently from meals.

Simultaneous intake of grapefruit or grapefruit juice has no influence on the effect of amlodipine.

Adults
For the treatment of hypertension and angina pectoris, the usual dose is 5 mg amlodipine once daily. If the desired therapeutic effect cannot be achieved within 2-4 weeks, the dose can be increased to a maximum dose of 10 mg daily (given as a single dose) depending on the individual response of the patient. Amlodipine can be used as monotherapy or in combination with anti-anginal medication in patients suffering from angina pectoris.

Children with hypertension from 6 years to 17 years of age.
The recommended antihypertensive oral dose in paediatric patients ages 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 (see section 5.1 Pharmacodynamic Properties and section 5.2 Pharmacokinetic Properties). The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

Elderly patients
For elderly patients, the normal dose is recommended; however, caution is advised when the dose is increase (see section 5.2).

Patients with renal impairment
Amlodipine may be used in such patients at normal doses (see section 5.2). Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable
Patients with hepatic impairment
In patients with hepatic impairment, no dosage regimen has been defined, therefore amlodipine should be administered with caution (see section 4.4).

4.3 Contraindications

Amlodipine is contraindicated in patients with:
- hypersensitivity to dihydropyridine derivates, amlodipine or 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

4.4 Special warnings and precautions 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, but this was not associated with worsening of the heart failure (see section 5.1).

Use in patients with impaired hepatic function:
The half-life of amlodipine is prolonged in patients with impaired liver function; dosage recommendations have not been established. Amlodipine 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 section 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 medicinal products on amlodipine

CYP3A4 inhibitors:
With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively the plasma concentration of amlodipine increased by 22 % and 50 % respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.

CYP3A4 inducers:
There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (i.e. rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

In clinical interaction studies grapefruit juice, cimetidine, aluminium/magnesium (antacid) and sildenafil did not affect the pharmacokinetics of amlodipine.

Effects of amlodipine on other medicinal products
The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other antihypertensive agents.
In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, ethanol (alcohol), warfarin or cyclosporine.

There is no effect of amlodipine on laboratory parameters.

4.6 Pregnancy and lactation

Pregnancy
The safety of amlodipine in human pregnancy has not been established.
Reproductive studies in rats have shown no toxicity except for delayed date of delivery and prolonged duration of labour at dosages 50 times greater than the maximum recommended dosage for humans.

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.

4.7 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.

4.8 Undesirable effects

The following undesirable effects 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)
Not known (cannot be estimated from the available data)

System Organ Class	Frequency	Undesirable effects
Blood and the 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
	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	Uncommon	Visual disturbance (including diplopia)
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Uncommon	Palpitations
	Very Rare	Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
Vascular disorders	Common	Flushing
	Uncommon	Hypotension
	Very Rare	Vasculitis
Respiratory, thoracic and medicinal disorders	Uncommon	Dyspnoea, rhinitis
	Very Rare	Cough
Gastrointestinal disorders	Common	Abdominal pain, nausea
	Uncommon	Vomiting, dyspepsia, altered bowel habits (including diarrohea and constipation), dry mouth

	Very Rare	Pancreatitis, gastritis, gingival hypeplasia
Hepato-biliary disorders	Very Rare	Hepatitis, jaundice, hepatic enzymes increased*
Skin and subcutaneous tissue disorders	Uncommon	Alopecia, purpura, skin discolouration, hyperhydrosis, pruritus, rash, exanthema
	Very Rare	Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema
	Very rare	Photosensitivity
Musculoskeletal, connective tissue and bone disorders	Common	Ankle swelling
	Uncommon	Arthralgia, myalgia, muscle cramps, back pain
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
Investigations	Uncommon	Weight increase, weight decrease

*mostly consistent with cholestatis

4.9 Overdose

In humans experience with intentional overdose is limited.

Symptoms:
Available data suggest that gross 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 10 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.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Dihydropyridine derivatives
ATC code: C 08 CA 01

5.1 Pharmacodynamic properties

Amlodipine is a calcium antagonist that inhibits the influx of calcium ions into the cardiac and vascular smooth muscle. The mechanism of the antihypertensive action is the result of the direct relaxing effect on the arterial smooth muscle.

The mechanism that enables amlodipine to reduce angina pectoris has not been completely clarified; however, the two following mechanisms are involved:

1. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. This reduction of the heart load leads to a reduction of the energy consumption as well as of the oxygen requirements of the myocardium.
2. The dilatation of the main coronary vessels and coronary arterioles probably is involved in the mechanism of action of amlodipine. This dilatation increases the myocardial oxygen supply in patients suffering from Prinzmetal's angina pectoris.

In patients suffering from hypertension, once daily administration produces a clinically significant reduction in blood pressure (both in lying and standing position), lasting for 24 hours.

In patients suffering from angina pectoris, once daily administration increases total exercise time, the time to occurrence of angina and the time to a 1 mm ST segment depression. Amlodipine reduces both the frequency of anginal attacks and the use of glyceryl trinitrate tablets.

Use in Patients with Heart Failure
Haemodynamic 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 angiotensin-converting enzyme (ACE) inhibitors has shown that amlodipine did not lead to an increase in the risk of mortality or combined mortality and morbidity in patients with heart failure.

A follow up, long-term, placebo controlled study (PRAISE 2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic 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 oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Use in children
In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5mg dose, and 5.0mg 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

Absorption and distribution
After oral administration of therapeutic doses, amlodipine is slowly absorbed from the gastrointestinal tract. The bioavailability of amlodipine is not influenced by concomitant intake of food. The absolute bioavailability of the unchanged active substance is approximately 64-80%. Peak plasma concentrations are reached within 6-12 hours after administration. The volume of distribution is approximately 20 l/kg. The pKa of amlodipine is 8.6. In vitro plasma protein binding is approximately 98%.

Metabolism and elimination
The plasma half-life varies between 35 and 50 hours. Steady-state plasma concentration is reached after 7-8 days.

Amlodipine is extensively metabolised into inactive metabolites. Approximately 60% of the administered dose is excreted in the urine, 10% of which is in a non-metabolised form.

Use in children
A population PK study has been conducted in 74 hypertensive children aged from 12 months 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.

Use in 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 'area under the curve' (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 study (See Section 4.4).

Patients with impaired renal function
Amlodipine is extensively metabolised into inactive metabolites. 10% of the parent compound is excreted unchanged in the urine. The changes in the plasma concentration of amlodipine are not related to the degree of renal impairment. These patients can be treated with a normal dosage of amlodipine. Amlodipine is not dialyzable.

Patients with impaired hepatic function
The half-life of amlodipine is prolonged in patients with impaired hepatic function.

5.3 Preclinical safety data

Animal studies have shown no special risks for humans. This is based on information from pharmacological studies concerning safety and on information on repeat dose toxicity, genotoxicity and carcinogenicity. Reproductive studies in animals have shown a delayed parturition, difficult labour and an increased foetal and neonatal death at high dosages.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium starch glycollate (type A)
Calcium hydrogen phosphate, anhydrous
Cellulose, microcrystalline
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Blister: Keep the blister in the outer carton in order to protect from light.
Tablet container: Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blister (Al/PVC):
Pack sizes: 10, 14, 20, 28, 30, 50, 50 x 1, 60, 98 (only for DK/H/0960/001+003), 100 and 120 tablets

Blister (AL/OPA/Al/PVC):
Pack sizes 10, 14, 20, 28, 30, 50, 50 x 1, 60, 98 (only for DK/H/0960/001+003), 100 and 120 tablets

HDPE tablet containers and screw caps (tamper evident):
Pack sizes: 20, 30, 50, 60, 100, 120, 200 and 250 tablets.

Not all pack sizes or pack types may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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