SUMMARY OF THE PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amlodipine ratiopharm tablets 5 mg, tablets
Amlodipine ratiopharm tablets 10 mg, tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Amlodipine ratiopharm tablets 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 ratiopharm tablets 5 mg, tablets
White to off-white, round, one sided convex tablets, with “A” and “5” embossed on break line side.

Amlodipine ratiopharm tablets 10 mg, tablets
White to off-white, round, one sided convex tablets, with “A” and “10” embossed on break line 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) with or without food.

Adults
For the treatment of hypertension and angina pectoris, the starting dose is 5 mg once daily. If the desired therapeutic effect cannot be achieved within 2-4 weeks, the dose can be increased to a maximum 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 and adolescents (under 18 years of age)
The use of amlodipine is not recommended for children and adolescents (below 18 years of age) due to insufficient data on safety and efficacy.

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

Patients with renal impairment
The normal dosage is recommended (see section 5.2). Amlodipine is not dialyzable. Amlodipine should be administered with particular caution to patients undergoing dialysis (see section 4.4).

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 suffering from:
- hypersensitivity to amlodipine, other dihydropyridines or any of the excipients
- severe hypotension
- shock, including cardiogenic shock
- heart failure after acute myocardial infarction (during the first 28 days)
- high grade aortic stenosis
- unstable angina pectoris

4.4 Special warnings and special precautions for use
Amlodipine should be administered with caution to patients with cardiac failure. There are no data to support the use of amlodipine alone, during or within the first month of myocardial infarction. The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Use in children and adolescents (under 18 years of age)
Amlodipine should not be administered to children due to insufficient clinical experience.

Use in elderly patients
In elderly patients, caution is advised when the dosage is increased (see section 5.2).

Use in patients with renal impairment
Amlodipine is not dialyzable. Amlodipine should be administered with particular caution to patients undergoing dialysis.

Use in patients with impaired hepatic function
The terminal half-life of amlodipine is prolonged in patients with impaired hepatic function; dosage recommendations have not yet been established. Therefore, amlodipine should be administered with caution in these patients.
Use in patients with heart failure
Patients suffering from heart failure should be treated with caution. A long-term study of patients with severe heart failure (NYHA class III and IV) showed an increased incidence of pulmonary oedema in patients treated with amlodipine in comparison with the placebo group. However, this did not indicate a deterioration of the heart failure (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on amlodipine
CYP3A4 inhibitors: A study of elderly patients has shown that diltiazem inhibits metabolism of amlodipine, probably via CYP3A4, since the plasma concentration increases by approx. 50% and the effect of amlodipine is increased. It cannot be excluded that other inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, HIV-protease-inhibitors, clarithromycin, erythromycin, telithromycin and nefazodone) also increase the plasma concentration of amlodipine. In case of strong CYP3A4-inhibitors like ketoconazol, itraconazol or ritonavir the concentration of amlodipine may be increased even to a greater extent than by diltiazem. Caution should be exercised in combination of amlodipine and CYP3A4 inhibitors.

CYP3A4 inducing agents: There is no information available on the effect of CYP3A4 inducers (e.g. rifampicin, St. John’s wort, dexamethasone, phenobarbital, phenytoin, carbamazepine, nevirapine and rifabutin) on amlodipine. Co-administration may lead to reduced plasma concentration of amlodipine. Caution should be exercised in combination of amlodipine and CYP3A4 inducers.

Effects of amlodipine on other medicinal products
Amlodipine may potentiate the antihypertensive effect of other medicinal products that lower blood pressure (e.g. beta-adrenoceptor blocking agents, ACE-inhibitors, alpha-1-blockers and diuretics). In patients with an increased risk (for example after myocardial infarction), the combination of a calcium channel blocker with a beta-adrenoceptor blocking agent may lead to heart failure, to hypotension and to a (new) myocardial infarction.

In clinical interaction studies, amlodipine did not influence the pharmacokinetic properties of atorvastatin, digoxin, warfarin or cyclosporine.

Amlodipine does not influence laboratory parameters.

Grapefruit juice had no significant effect on the pharmacokinetics of amlodipine.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of amlodipine in pregnant women. Animal studies have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Amlodipine should not be used during pregnancy unless the therapeutic benefit clearly outweighs the potential risks of treatment.
**Lactation**
It is not known whether amlodipine is excreted in breast milk. It is advised to stop breastfeeding during treatment with amlodipine.

### 4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. In patients suffering from dizziness, headache, fatigue or nausea the ability to react may be impaired.

### 4.8 Undesirable effects

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>≥1/10</td>
</tr>
<tr>
<td>Common</td>
<td>≥1/100 and &lt;1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>≥1/1000 and &lt;1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>≥1/10 000 and &lt;1/1000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt;1/10 000, not known (cannot be estimated from the available data)</td>
</tr>
</tbody>
</table>

**Blood and lymphatic system disorders**
Very rare: Leukocytopenia, thrombocytopenia

**Endocrine disorders**
Uncommon: Gynaecomastia

**Metabolism and nutrition disorders**
Very rare: Hyperglycaemia

**Psychiatric disorders**
Uncommon: Sleep disturbances, irritability, depression
Rare: Confusion, mood changes including anxiety

**Nervous system disorders**
Common: Headache (especially at the beginning of the treatment), somnolence, dizziness, weakness
Uncommon: Malaise, dry mouth, tremor, paraesthesia, increased perspiration
Rare: Taste disorders
Very rare: Peripheral neuropathy

**Eye disorders**
Uncommon: Visual disturbances

**Ear and labyrinth disorders**
Uncommon: Tinnitus

**Cardiac disorders**
Common: Palpitations
Uncommon: Syncope, tachycardia, chest pain, aggravation of angina pectoris (may occur at the beginning of treatment).
Isolated cases of myocardial infarction and arrhythmias (including extrasystole, ventricular tachycardia, bradycardia and atrial arrhythmias) and angina pectoris have been reported in patients with coronary artery disease, but a clear association with amlodipine has not been established.

Vascular disorders
Uncommon: Hypotension, vasculitis

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, rhinitis
Very rare: Cough

Gastrointestinal disorders
Common: Nausea, dyspepsia, abdominal pain
Uncommon: Vomiting, diarrhoea, constipation, gingival hyperplasia
Very rare: Gastritis, pancreatitis

Hepatobiliary disorders
Rare: Elevated liver enzymes, jaundice, hepatitis

Skin and subcutaneous tissue disorders
Very common: Ankle oedema
Common: Facial flushing with heat sensation (especially at the beginning of the treatment)
Uncommon: Exanthema, pruritus, urticaria, alopecia, discoloration of the skin, purpura
Very rare: Angioedema.
Isolated cases of allergic reactions including erythema exsudativum multiforme, exfoliative dermatitis and Stevens-Johnson-Syndrome have been reported.

Musculoskeletal and connective tissue disorders
Uncommon: Muscle cramps, back pain, myalgia and arthralgia

Renal and urinary disorders
Uncommon: Increased micturition frequency

Reproductive system and breast disorders
Uncommon: Impotence

General disorders and administration site conditions
Uncommon: Gaining or losing weight

4.9 Overdose
In humans, there is little experience with deliberate overdose of amlodipine. The available data suggest that overdose (>100 mg) could result in excessive peripheral vasodilatation followed by a pronounced and probably prolonged systemic hypotension.
Clinically significant hypotension as a result of an overdose with amlodipine requires active cardiovascular support including frequent monitoring of the heart and lung function, the raising of arms and legs and the monitoring of the volume of the circulating fluids and the urine output. A vasoconstrictor could be useful to restore the vascular tonus and the blood pressure, providing it’s use is not contraindicated. Intravenous administration of calcium gluconate could be useful to reverse the effects of calcium channel blockage. Gastric lavage might be useful in some cases. In healthy volunteers, it was shown that the administration of activated charcoal within 2 hours after the administration of 10 mg amlodipine reduced the absorption rate of amlodipine. As amlodipine is strongly plasma protein bound, dialysis will probably have little effect.

5  PHARMACOLOGICAL PROPERTIES

5.1  Pharmacodynamic properties

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

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.

Haemodynamic studies in patients with heart failure and clinical studies based on exercise capacity in patients with heart failure class II-IV have demonstrated that amlodipine does not lead to clinical deterioration as measured by exercise capacity, left ventricular ejection fraction and clinical symptomatology.
A placebo controlled study (PRAISE) designed to evaluate heart failure patients in NYHA Class III-IV receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in the risk of mortality or a combined risk of mortality and morbidity in patients with heart failure.

A follow up study (PRAISE 2) showed that amlodipine had no effect on the total or cardiovascular mortality in patients with decompensatio cordis class III-IV without ischaemic origin. In this study, treatment with amlodipine was associated with an increase in pulmonary oedema, although this did not correlate to an increase in symptoms.

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.

Elderly patients
The time necessary to reach peak amlodipine plasma concentrations is the same as in younger patients.
The clearance tends to be decreased with resulting increases in ‘area under the curve’ (AUC) and terminal elimination half-life. The recommended dose for elderly patients remains the same, but caution is needed when a dose increase is required.

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
Microcrystalline cellulose (E460)
Calcium hydrogen phosphate (E341)
Sodium starch glycolate (Type A)
Magnesium stearate (E470b)

6.2 Incompatibilities
Not applicable

6.3 Shelf-life
3 years

6.4 Special precautions for storage
Store in the original package in order to protect from light.

6.5 Nature and content of container

<table>
<thead>
<tr>
<th>Amlodipine ratiopharm tablets 5 mg, tablets</th>
</tr>
</thead>
</table>
PVC/PVDC/Aluminium blister
10, 14, 20, 28, 30, 30x1, 50, 50x1, 56, 60, 90, 98, 100, 100x1, 200, 250 tablets
HDPE bottle
100 tablets, 250 tablets

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HDPE bottle
100 tablets, 250 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
7 MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8 MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10 DATE OF REVISION OF THE TEXT