AMLIBON®

1. NAME OF THE MEDICINAL PRODUCT
AMLIBON 5 MG TABLETS
AMLIBON 10 MG TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Amlibon 5 mg tablets
Each tablet contains 5 mg amlodipine (as amlodipine besilate).

Amlibon 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.

Amlibon 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 score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. When the tablet has been divided, one part should be taken straight after the other.

Amlibon 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
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-blocker, beta adrenoceptor blocking agent, or an angiotensin-converting enzyme inhibitor.

Chronic Stable Angina
Amlodipine is indicated for the first line treatment of myocardial ischaemia, whether due to fixed obstruction (stable angina) and/or vasospasm/vasoconstriction (Prinzmetal's or variant angina) of coronary vasculature. Amlodipine may be used where the clinical presentation suggests a possible vasospastic/vasoconstrictive component but where vasospasm/vasoconstriction has not been confirmed. Amlodipine may be used alone, as monotherapy, or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or beta-blockers.

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. 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.

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

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.

Patients with renal impairment
The normal dose 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 dose 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 derivatives, amlodipine or to 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 (see section 5.1).

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.

Patients with hepatic impairment
The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dose 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.

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

Patients with renal impairment
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 dialysable.

4.5 Interaction with other medicinal products and other forms of interaction
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 resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly.

Clinical monitoring and dose adjustment may thus be required.

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
Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, *Hypericum perforatum*).

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailabilitymay

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 hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, 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.

Tacrolimus
There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. 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.

Ciclosporin
No drug interaction studies have been conducted with ciclosporin and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of ciclosporin were observed.
Consideration should be given for monitoring ciclosporin levels in renal transplant patients on amlodipine, and ciclosporin dose reductions should be made as necessary.

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.

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

4.6 Pregnancy and lactation
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.

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%, with 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.

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.

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.

Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

List of adverse reactions

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); veryrare (<1/10,000), not known (cannot be estimated from the available data).

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: 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, hypoaesthesia, paraesthesia
Very rare: Hypertonia, peripheral neuropathy
Not known: Extrapyramidal disorder

Eye disorders
Common: Visual disturbance (including diplopia)

Ear and labyrinth disorders
Uncommon: Tinnitus

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

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

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea
Uncommon: Cough, rhinitis

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

Hepatobiliary disorders
Very rare: Hepatitis, jaundice, hepatic enzymes increased*

Skin and subcutaneous tissue disorders
Uncommon: Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria
Very rare: Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
Not known: Toxic epidermal necrolysis

Musculoskeletal and connective tissue 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, gynaecomastia

General disorders and administration site conditions
Very Common: Oedema,
Common: Fatigue, asthenia
Uncommon: Chest pain, pain, malaise

Investigations
Uncommon: Weight increased, weight decreased

* mostly consistent with cholestasis

4.9 Overdose
In humans, experience with intentional overdose is limited.

Symptoms
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.

Treatment
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 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

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects, dihydropyridine derivatives
ATC code: C08CA01

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to outer carton.

6.4 Special precautions for storage

Store at a temperature below 30ºC in the original package.
Blister: Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

Blister (Al/Al).
Pack sizes: 20 and 30 tablets

Not all pack sizes or pack types may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. PRODUCT REGISTRATION HOLDER

Sandoz Products Malaysia Sdn. Bhd.
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Uptown 1, No. 1, Jalan SS21/ 58,
Damansara Uptown,
47400 Petaling Jaya Selangor, Malaysia

8. DATE OF REVISION OF THE TEXT

Mar 2024