AMICOR

Tablets

Composition

Each tablet contains Amlodipine besylate equivalent to 5 Amlodipine.

Action

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 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:

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.

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 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 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.

Use in Patients with Heart Failure
Hemodynamic studies in 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. Studies in patients with heart failure receiving digoxin, diuretics, and angiotensin converting enzyme (ACE) inhibitors has shown that Amlodipine did not lead to an increase in risk mortality or combined mortality and morbidity in patients with heart failure.

Patients with heart failure without clinical symptoms or objective findings suggestive of underlying ischemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, Amlodipine has no effect on total 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 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.

Pharmacokinetics
Absorption
After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The bioavailability of amlodipine is not a ected by food intake.

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/elimination

The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Paediatric population
A population PK study has been conducted in 74 hypertensive children aged from 1 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.

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 congestive heart failure were as expected for the patient age group studied.

Hepatic impairment
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%.

Indications

- **Hypertension**
  Amicor is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.
- **Chronic Stable Angina**
  Amicor is indicated for the treatment of chronic stable angina. Amicor may be used alone or in combination with other antianginal agents.
- **Vasospastic Angina (Prinzmetal's or Variant Angina)**
  Amicor is indicated for the treatment of confirmed or suspected vasospastic angina. Amicor may be used as a monotherapy or in combination with other antianginal drugs.

Contraindications

- hypersensitivity to dihydropyridine derivatives, amlodipine.
- 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

Warnings & Precautions

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration, and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

General
Since the vasodilatation induced by Amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration of Amlodipine. Nonetheless, caution should be exercised when administering Amlodipine as with any other peripheral vasodilator particularly in patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure
Although hemodynamic studies and a controlled trial in NYHA Class II-III 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, studies have not been performed in patients with NYHA Class IV heart failure. In general, all calcium channel blockers should be used with caution in patients with heart failure.

Beta-Blocker Withdrawal
Amlodipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker

Patients with Hepatic Failure
Since the liver extensively metabolizes Amlodipine and the plasma elimination half-life (t 1/2) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering Amlodipine to patients with severe hepatic impairment.

Pregnancy
Category C
Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Nursing Mothers
It is not known whether Amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while Amlodipine is administered.

Pediatric Use
Safety and effectiveness of Amlodipine in children have not been established.

Adverse Reactions
In general, treatment with Amlodipine was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with Amlodipine were of mild or moderate severity. The most common side effects are headache and edema.

The following events occurred in <=1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship.

Cardiovascular
Arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension.

Central and Peripheral Nervous System
Hypoesthesia, paraesthesia, tremor, vertigo.

Gastrointestinal
Anorexia, constipation, dyspepsia" dysphagia. Diarrhea, flatteries vomiting. Gingival hyperplasia. General: asthenia, back pain**, hot flushes, malaise, pain, rigors, weight gain.

Muscolo-skeletal System
Arthralgia, arthrosis, muscle cramps, myalgia**.

Psychiatric
Sexual dysfunction (male**and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System
Dyspnea, epistaxis**.

Skin and Appendages
Pruritus, rash**, erythematous rash **, maculopapular rash.

*Based on patient weight of 50 kg.
**These events occurred in less than 1% in placebo controlled trials, but the incidence of these side e ects was between 1% and 2% in all multiple dose studies.

Special Senses
Abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System
Micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System
Dry mouth, increased sweating.

Metabolic and Nutritional
Thirst, Hemopoietic purpura.

The following events occurred in <= 0.1% of patients:

Cardiac failure, pulse irregularity, extra systoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, Polyuria, parosmia taste perversion (Parosmia is a distorted sense of olfaction, often resulting in phantom, non-existent, and mostly unpleasant, smells.), abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

In post marketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) in some cases severe enough to require hospitalization have been reported in association with use of Amlodipine.
Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

Drug Interactions

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:

There is no data available regarding the e ect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers. 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 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.
In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

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.

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.

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.

Dosage and Administration

Adults
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.
In hypertensive patients, Amlodipine has been used in combination with a thiazide diuretic, alpha blocker, beta blocker, or an angiotensin converting enzyme inhibitor. For angina, amlodipine 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 amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Pediatric population
Children and adolescents with hypertension from 6 years to 17 years of age.
The recommended antihypertensive oral dose in pediatric 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 pediatric patients .

Children under 6 years old
No data are available.

Elderly

Amlodipine used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care .

Renal impairment
Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialyzable.

Hepatic impairment
Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Method of administration
Tablet for oral administration.

Over Dosage

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension including shock with fatal outcome has been reported.

Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of Amlodipine 10 mg has been shown to signi cantly decrease Amlodipine absorption. Gastric lavage may be worthwhile in some cases. 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, if there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Dialysis is not likely to be of benefit since Amlodipine is highly protein-bound.

Presentation

Amicor 5 tablets
Box of 30 tablets