AMICOR

Tablets

Composition

Each tablet contains Amlodipine besylate equivalent to 5 or 10 mg 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:

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'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
Amlodipine is well absorbed orally with peak blood levels occurring 6-12 hours post-dose. Oral administration of a single therapeutic dose gave a mean absolute bioavailability of 64% (range 52-88%). The volume of distribution is approximately 20 L/kg. The absorption of Amlodipine is unaffected by consumption of food. The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Steady state plasma levels reached after 7-8 days of consecutive 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. Approximately 97.5% of circulating Amlodipine is bound to plasma proteins. Amlodipine is not dialyzable.

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

Amicor is contraindicated in patients with known sensitivity to Amlodipine.

Warnings

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.

Precautions

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

There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 effects 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

Amlodipine has been safely administered with Alpha-blockers, angiotensin-converting enzyme inhibitors, antibiotics, beta-blockers, long-acting nitrates, non-steroidal anti-inflammatory agents, oral hypoglycemic agents, and sublingual glyceryl trinitrate and thiazide diuretics.

Special studies: Effect of other agents on Amlodipine
Aluminium / Magnesium (antacid): Co-administration of a single dose of Amlodipine with aluminum/magnesium antacid had no significant effect on the pharmacokinetics of Amlodipine.

Cimetidine: Co-administration of Amlodipine with cimetidine did not alter the pharmacokinetics of Amlodipine.

Grapefruit Juice: Co-administration of a single oral dose of 10 mg of Amlodipine with 240 ml of grapefruit juice in 20 healthy volunteers had no significant effect on the pharmacokinetics of Amlodipine.

Sildenafil: A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetics of Amlodipine. When Amlodipine and sildenafil are used in combination, each agent independently exerted its own blood pressure lowering effect.

Special studies: Effect of Amlodipine on other agents
Atorvastatin: Co-administration of multiple 10 mg doses of Amlodipine with 80 mg Atorvastatin resulted in no significant changes in the steady state pharmacokinetic parameters of Atorvastatin.

Cyclosporin: Pharmacokinetic studies with cyclosporine have demonstrated that Amlodipine does not significantly alter the pharmacokinetics of cyclosporine.

Digoxin: Co-administration of Amlodipine with digoxin did not alter serum digoxin levels or digoxin renal clearance in normal volunteers.

Ethanol (alcohol): Single and multiple 10 mg doses of Amlodipine had no significant effect on the pharmacokinetics of ethanol.

Warfarin: Co-administration of Amlodipine and warfarin did not alter the warfarin prothrombin response time.

Dosage and Administration

The usual initial antihypertensive oral dose of Amicor is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding Amlodipine to other antihypertensive therapy.

Dosage should be adjusted according to each patient's need. In general, Titration should proceed over 7 to 14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

The recommended dose for chronic stable or vasospastic angina is 5-10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect.

Co-administration with Other Antihypertensive and/or Antianginal Drugs: Amlodipine has been safely administered with thiazides, ACE inhibitors, beta-blockers, long-acting nitrates, and/or sublingual nitroglycerin.

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 significantly 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

Amicor 10 tablets
Box of 20 tablets