Amlodar®

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Amlodipine Besilate

DESCRIPTION:
Amlodar® (amlodipine besilate) is a long-acting calcium channel blocker.
Inactive Ingredients: Maize starch, microcrystalline cellulose, magnesium stearate.

PHARMACOLOGY:
Pharmacodynamic properties:
SELECTIVE CALCIUM INHIBITOR WITH VASCULAR EEFECT
Amlodipine is a calcium antagonist belonging to the dihydropyridines group which acts on the calcium channel binding sites of both 1-4 dihydropyridine and diltiazem. It causes prolonged inhibition of the entry of calcium via slow calcium channels into smooth muscles and myocardial cells. As with the other dihydropyridines, amlopdipine has diuretic and natriuretic properties in the animal.
The mechanism of its hypertensive action is linked to a direct relaxant effect on vascular smooth muscle.
Single daily administration in hypertensive patients enables a significant lowering of blood pressure levels in supine or standing position throughout the 24-hour period, without any concomitant acceleration in heart rate. The progressive action of amlodipine avoids episodes of hypotension.
Amlodipine decreases total peripheral resistance (post-load) without causing reflex tachycardia. This is accompanied by a reduction in myocardial energy consumption and oxygen requirements. It causes vasodilatation of the coronary arteries and arterioles, thus increasing myocardial oxygen supply.
Administration of amlodipine in angina patients increases exercise tolerance, time to angina onset, ST segment depression and reduces both the frequency of angina attacks and nitroglycerin consumption.
As with the other calcium antagonists, amlodipine is metabolically neutral and has no effect on plasma lipid levels. It can be used in patients with diabetes or gout.
In hypertensive renal transplant recipients treated with cyclosporine, amlodipine at the usual doses decreases blood pressures, increases renal perfusion and glomerular filtration rate and lowers peripheral vascular resistance. The long term consequences of these modifications on the graft's function are not assessed.
Pharmacokinetic properties:
After oral administration at therapeutic doses, amlodipine is completely absorbed.
Amlodipine (absolute) bioavailability has been estimated to be between 64 and 80%.
Peak plasma concentration occurs late, approximately 6 to 12 hours after dosing.
The volume of distribution is 21 L/kg.
The terminal elimination half-life is 35 to 50 hours and enables single daily administration. Steady state concentrations are reached after 7 to 8 days of administration.
Amlodipine is almost entirely metabolized to inactive metabolites. 10% of the parent substance and 60% of metabolites are excreted in urine.
In vitro studies have shown that circulating amlodipine is 97.5% bound to plasma proteins.
Plasma concentrations of amlodipine in the elderly are higher than in younger patients this being unaccompanied by clinical manifestations, the terminal elimination half-life remaining unchanged.
An increase in half-life is observed in the presence of hepatic failure.
Renal failure patients: plasma amlodipine concentrations are not correlated with the degree of renal impairment.

INDICATIONS:
- Preventive treatment of angina: stable angina and spontaneous angina (including Prinzemetal's angina).
- Hypertension.

CONTRAINDICATIONS:
- This medicine must never be taken in case of hypersensitivity to dihydropyridines.
- This medicine is generally unadvised in case of combination with dantrolene (see "DRUG INTERACTIONS").

SIDE EFFECTS:
- Adverse reactions occurring most commonly are linked to the vasodilator action of the drug. These essentially involve headache, redness or feeling of heat of the face.
  These side effects occur most often during the initial weeks of the treatment and generally lessen as it continues.

In common with other dihydropyridines an ankle and/or facial edema could occur. This is more frequent at high doses.
- There have been rare reports of:
  - Cardiac effects: tachycardia, palpitations, syncope.
  - Cutaneomucous effects: alopecia, increased sweating, allergic reaction including pruritus, rash and angioedema. As with other dihydropyridines, slight gingival enlargement has been reported in patients with marked gingivitis/parodonitis. Such enlargement can be avoided or disappear by careful oral hygiene.
  - Digestive effects: abdominal pain, dyspepsia, dysgueusia, appetite loss, nausea, diarrhea, constipation, dry mouth.
  - Neuromuscular effects: muscular cramps, myalgia, arthralgia.
  - Liver effects: hepatitis, jaundice and hepatic enzyme elevations have been reported very rarely (mostly consistent with cholestasis) with a few cases severe enough to require hospitalization. They are recovered at the treatment withdrawal.
  - Lung effects: dyspnea.
  - Genito-urinary effects: pollakiuria, impotence as reported with other antihypertensive drugs, gynecomastia.
  - Neuropsychic effects: asthenia, giddiness, sleeping disorders, trembling, visual disturbances, depressive disorders.
  - General effect: malaise.
  - Hematopoietic effect: thrombocytopenia.
  - Vascular effect: vasculitis.
  - As with other calcium-channel blockers, the following events have been rarely reported: anginal pain, myocardial infraction, arrhythmia. They can be linked to the pathology pre-existent to the treatment, and must lead to discuss the continuation of the treatment.

WARNINGS AND PRECAUTIONS:
Special warnings:
Efficacy and safety has not been studied in children. It is unadvisable to use amlodipine in children.
When clinical signs (asthenia, anorexia, persistent nausea) are shown, it is recommended to perform liver enzymes assays. If increased and especially in case of jaundice, the treatment must be stopped.
Precautions for use:
- General: caution as with any other peripheral vasodilator, should be exercised when administering amlodipine, particularly in patients with severe aortic stenosis.
- Use in patients with congestive heart failure: in general, calcium channel blockers should be used with caution in patients with heart failure. Increase in AUC was observed in patients with moderate to severe heart failure.
- Use in patients with impaired hepatic function: amlodipine half-life is prolonged in patients with impaired liver function (see "*Pharmacokinetic properties*"). Dosage recommendations have not been established, so amlodipine should be administered with caution in these patients.
- Geriatric use: in general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
- Pregnancy and lactation:
  Pregnancy:
  Animal studies did not show any tetratogenic effects. Without teratogenic effect in animal, malformations in humans are not expected. To date, any substances responsible for malformations in humans have effectively been found to be teratogenic in animals in properly conducted studies on both species.
  Presently, there is no relevant or enough data to assess an eventual malformation or foetotoxic effect of amlodipine when administered during pregnancy.
  Consequently, as a precaution measure, it is preferable not to use amlodipine during pregnancy.
  Lactation:
  There is no data regarding the excretion of amlodipine in breast milk.
  However, as with other dihydropyridines, the quantities found in breast milk are low, and no undesirable effects were notified on the basis of isolated cases.
  As a precaution measure, it is advisable to avoid if possible, the administration of this medicine to the breast-feeding woman.
- Effects on ability to drive and use of machines: at the beginning of the treatment, a special caution will have to be observed by drivers or machines users, due to the risk of giddiness (see "SIDE EFFECTS").

DRUG INTERACTIONS:
Unadvisable combination (care measure):
Dantrolene (infusion): in animals, cases of fatal ventricular fibrillations are consistently observed when verapamil and dantrolene are administered by IV route. Thus, the combination of a calcium-channel blocker with dantrolene is potentially dangerous. However, a few patients have received the combination nifedipine and dantrolene without any trouble.
Combination needing precaution:
- Alpha-1 blockers (alfuzosin, prazosin): increase in the hypotensive effect. Risk of severe orthostatic hypotension. Clinical monitoring. Research of any orthostatic hypotension in the hours following the alpha-1 blocker drug administration (particularly at the beginning of the treatment).
- Baclofene: increase in the anti-hypertensive effect. Monitoring of the arterial pressure and posological adaptation of the anti-hypertensive drug if necessary.
- Rifampicin: described for verapamil, diltiazem and nifedipine. Decrease of the plasma levels of the calcium channel blocker due to an increase of its hepatic metabolism. Clinical monitoring and, eventually adjustment of the dose of the calcium channel blocker during the treatment with rifampicin and after its withdrawal.
- Itraconazole: extrapolated from nifedipine, felodipine and isradipine. Increased risk of oedema due to a decrease of the dihydropyridine hepatic metabolism. Clinical monitoring and, eventually adjustment of the dose of the dihydropyridine during the treatment with itraconazole and after its withdrawal.

Combination to be taken into account:
- Beta-blockers: hypotension, heart failure in patients with latent or un-controlled heart failure (in vitro negative inotropic effect of the dihydropyridines, more or less marked depending on the products and susceptible to add to the negative inotropic effect of beta-blockers). The presence of a beta-blocker treatment can moreover minimize the reflex sympathic reaction set into action in case of excessive hemodynamic repercussion.
- Imipramine antidepressants (tricyclics): antihypertensive effect and risk of orthostatic hypotension increased (additive effect).
- Corticosteroid, tetracosactid (general route): decrease in the antihypertensive effect (hydrosodic retention of the corticosteroids).
- Neuroleptics: antihypertensive effect and risk of orthostatic hypotension increased (additive effect).

Furthermore, amlodipine does not modify the plasma levels or the renal clearance of digoxin in the healthy volunteers.

DOSAGE AND ADMINISTRATION:
If you miss a dose, take it as soon as you remember. Do not take **Amlodar®** if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time.
- Adults: the usual initial antihypertensive oral dose of **Amlodar®** 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 **Amlodar®** 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.
- Children: the effective antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients.
- Use in renal failure: the treatment can be initiated at the usual recommended posology. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.
- 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.

OVERDOSAGE:
Massive overdose could cause notable peripheral vasodilation leading to marked and probably prolonged systemic hypotension. Any hypotension following acute poisoning requires, monitoring in a cardiology intensive unit. A vasoconstrictor could be used to restore vascular tone and blood pressure. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

PRESENTATIONS:
Amlodar® 5 Capsules: Packs of 28 capsules. Each capsule contains 5 mg Amlodipine (as amlodipine besilate).
Amlodar® 10 Capsules: Packs of 28 capsules. Each capsule contains 10 mg Amlodipine (as amlodipine besilate).

STORAGE CONDITIONS:
Store below 30°C.
Keep **Amlodar®** out of the light. Do not store in the bathroom.
Keep **Amlodar®** in a dry place.

This is a medicament.
- *Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.*
- *Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold you the medicament.*
- *The doctor and the pharmacist are experts in medicine, its benefits and its risks.*
- *Do not, by yourself, interrupt the period of treatment prescribed.*
- *Do not repeat the same prescription without consulting your doctor.*

Keep medicament out of reach of children

Manufactured by Dar Al Dawa, Na'ur - Jordan

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07/08