Pfizer

AMLOR*

(Amlodipine)

1. TRADE NAME OF THE MEDICINAL PRODUCT

AMLOR 5 mg
AMLOR 10 mg
amlodipine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AMLOR 5 mg

Amlodipine (besylate)	6.944 mg
equivalent to amlodipine	5.000 mg
Microcrystalline cellulose	72.556 mg
Dried maize starch	20.000 mg
Magnesium stearate	0.500 mg

for one capsule n° 3 of 100 mg

AMLOR 10 mg

Amlodipine (besylate)	13,889 mg
equivalent to amlodipine	10.000 mg
Microcrystalline cellulose	65,611 mg
Dried maize starch	20.000 mg
Magnesium stearate	0.500 mg

for one capsule n° 3 of 100 mg

composition of the capsule coat:
body : gelatin, titanium dioxide
cap : gelatin, titanium dioxide, yellow

3. PHARMACEUTICAL FORM

Amlor 5mg: Capsule (yellow / white): 30 capsules.
Amlor 10mg: Capsule (grey): 30 capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Preventive treatment of angina : stable angina and spontaneous angina (including Prinzmetal's angina)
- Hypertension

4.2 Posology and method of administration

- Hypertension : The starting dose is 1 capsule (5mg) once a day, which may be increased to a single daily dose of 10 mg, depending on the treatment response.
- Angina Pectosis : The starting dose is 1 capsule (5mg) once a day, which may be increased to a single daily dose of 10 mg, depending on the treatment response.

The maximum daily dose is 10 mg.
Except in case of recent myocardial infraction, amlodipine can be administered whatever the degree of left ventricular heart failure.

- *Use in the Elderly*

Amlodipine, used at similar doses in elderly or younger patients, is equally well tolerated.

- *Use in Renal Failure*

The treatment can be initiated at the usual recomended posology. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.
No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, beta- blockers or angiotensin-converting enzyme inhibitors.

4.3 Contra-indications

This medicine must never be taken in case of hypersensitivity to dihydropyridines.
This medicine is generally unadvised in case of combination with dantrolene (see section 4.5. « Interaction with other medicines »).

4.4 Special warnings and special precautions for use

Special warnings :

Efficacy and safety has not been studied in children. It is unadvisable to use amlodipine in children.
When clinical signs (asthenia, anorexia, persistant nausea), it is recommanded to perform liver enzymes assays. If increased and especially in case of jaundice, the treatment must be stopped.

Precaution for use :

- Use in patients with impaired hepatic function: Amlodipine half-life is prolonged in patients with impaired liver function (see. Section 5.2 « Pharmacokinetic properties »). Dosage recommandations have not been established, so amlodipine should be administered with caution in these patients.
- Pregnancy and lactation : (see. section 4.6).

4.5 Interaction with other medicines and other forms of interaction

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.
- **Rifampicine** : described for verapamil, diltiazem and nifedipin. 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 rifampicine 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 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 effects of beta-blockers). The presence of a beta-blocker treatment can moreover minimise 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 digoxine in the healthy volunteers.

4.6 Pregnancy and lactation

Pregnancy :

Animal studies did not show any teratogenic 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 mesure, 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 others dihydropyridines, the quantities found in breast milk are low, and no undesirable effects were notified on the basis of isolated cases.
As a precaution mesure, it is advisable to avoid if possible, the administration of this medicine to the breast-feeding woman.

4.7 Effects on ability to drive and use 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 section 4.8 « Undesirable effects »).

4.8 Undesirable 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 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 rarer 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/parodontitis. Such enlargement can be avoided or disappear by careful oral hygiene.
- Digestive effects : abdominal pain, dyspepsia, dysgueusia, appetite loss, nausea, diarrhoea, 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.
- Lungs effects : dyspnea.
- Genito-urinary effects : pollakiuria, impotence as reported with other anti-hypertensive drugs, gynecomastia.
- Neuropsychic effects : asthenia, giddiness, sleeping disorders, paresthesia, 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 infarction, arrythmiaThey can be linked to the pathology pre-existent to the treatment, and must lead to discuss the continuation of the treatment.

4.9 *Overdose*

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. Amlodipine is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

SELECTIVE CALCIUM INHIBITOR WITH VASCULAR EFFECT

Amlodipine is a calcium antagonist belonging to the dihydropyridines group wich 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 muscle and myocardial cells. As with the other dihydropyridines, amlodipine has diuretic and natriuretic properties in the animal.
The mechanism of its antihypertensive 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 exercice 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 pressure, increases renal perfusion and glomerular filtration rate and lowers peripheral vascular resistance. The long term consequences of these modifications on the graft's fonction are not assessed.

5.2 Pharmacokinetic properties

After oral administration at therapeutic doses, amlodipine is completely absorbed.

Amlodipine (absolute) biovailability 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 metabolised to inactive metabolites. Ten per cent 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.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf life

product should not be used after the expiry date printed on the outer carton

6.2 Special precautions for storage

store below 25° C

6.3 Nature and contents of container

30 capsules : heat-formed blister pack (PVC/Aluminium).

7. DATE OF APPROVAL/REVISION:

Aug. 8, 2001 PFIZER. FRANCE.

* Trade mark of Pfizer Inc., New York, U.S.A.