



Amlodipine 5 mg and 10 mg Tablet

Description

Amdocal[®] is a preparation of Amlodipine. Amlodipine is a dihydropyridine calcium antagonist, with a long duration of action, used for the treatment of hypertension and angina pectoris.

Mode of Action

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action 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 (afterload) 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 dilation increases myocardial oxygen delivery in patients with coronary artery spasm (prinzmetals or variant angina).

Indications

Hypertension

Amdocal[®] is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Stable angina

Amdocal[®] is indicated for the treatment of chronic stable angina. It may be used alone or in combination with other antianginal agents.

Vasospastic angina

Amdocal[®] is indicated for the treatment of confirmed or suspected vasospastic angina. The drug may be used as single therapy or in combination with other antianginal drugs.

Dosage and Administration

The dose should be individualized according to the goal of therapy and patient response.

Usual Adult Dose

The usual initial oral dose for stable or vasospastic angina and hypertension is 5 mg once daily with a maximum dose of 10 mg once daily.

Pediatric use

Children with hypertension from 6 years to 17 years of age

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

The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

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 dialysable.

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 (2.5 mg once daily) and titrated slowly in patients with severe hepatic impairment.

Contraindications

Amdocal[®] is contraindicated in patients with

- hypersensitivity to amlodipine, dihydropyridine derivatives or any of the excipients
- shock (including cardiogenic shock)
- obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis)
- unstable angina
- hemodynamically unstable heart failure after acute myocardial infarction (during the first 28 days)
- severe hypotension

Special Warnings and Precautions

Hypotension

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 the drug with any other peripheral vasodilator particularly in patients with severe aortic stenosis.

Cardiac failure

Patients with heart failure should be treated with caution. 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.

Beta blocker withdrawal

Amlodipine gives no protection against the danger of abrupt beta blocker withdrawal; any such withdrawal should be gradual reduction of the dose of beta blocker.

Hepatic failure

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

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. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers

There is no data available regarding the effect 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.

Grapefruit or grapefruit juice

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 hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the coadministration 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

Other antihypertensive agents.

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other antihypertensive agents.

Atorvastatin, digoxin, warfarin or ciclosporin

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

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.

Fertility, Pregnancy and Lactation

Pregnancy

Pregnancy Category C

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 fetus.

Lactation

It is not known whether amlodipine is excreted in breast milk. 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.

Side Effects

Peripheral edema may occasionally be severe but is fully reversible. As with other calcium antagonist drugs, peripheral edema and skin erythema occur in a proportion of patients (5-10%) and facial flushing in 2-5% of patients. Complaint of fatigue was also reported more frequently than in placebo-treated patients. There is evidence that these effects are more common in patients treated with doses greater than 10 mg daily.

Common or very common

Abdominal pain, dizziness, fatigue, flushing, headache, nausea, edema, palpitation, sleep disturbances.

Uncommon

Alopecia, arthralgia, asthenia, back pain, chest pain, dry mouth, dyspnoea, gastro-intestinal disturbances, gynaecomastia, hypotension, impotence, mood changes, muscle cramps, myalgia, paresthesia, pruritus, purpura, rashes, rhinitis, skin discolouration, sweating, syncope, taste disturbances, tinnitus, tremor, urinary disturbances, visual disturbances, weight changes.

Very rare

Angioedema, arrhythmias, cholestasis, coughing, gastritis, gingival hyperplasia, hepatitis, hyperglycaemia, jaundice, myocardial infarction, pancreatitis, peripheral neuropathy, tachycardia, thrombocytopenia, urticaria, vasculitis.

Frequency not known

Erythema multiforme.

Overdose

In humans, experience with intentional overdose is limited.

Symptoms

Available data suggest that large overdosage 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.

Management

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, 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 10mg has been shown to reduce the absorption rate of amlodipine. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

Pharmaceutical Precautions

Keep out of the reach of children. Store below 30°C. Keep in the original package in a cool & dry place in order to protect from light and moisture.

Commercial Pack

Amdocal® 5 Tablet: Box containing 100 tablets in 10 x 10's blister strips. Each tablet contains Amlodipine Besylate BP equivalent to Amlodipine 5 mg.

Amdocal® 10 Tablet: Box containing 60 tablets in 6 x 10's blister strips. Each tablet contains Amlodipine Besylate BP equivalent to Amlodipine 10 mg.



Manufactured by

BEXIMCO PHARMACEUTICALS LTD.

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