Cipla

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Amlopres-10 (Amlodipine Besylate Tablets USP 10mg)

COMPOSITION
Each uncoated tablet contains:
Amlodipine Besylate USP equivalent to Amlodipine……..10mg

DOSAGE FORM
Tablets

DESCRIPTION
White to off white, round tablets with ‘’10’’ debossed on one side and plain on other side.

PHARMACOLOGY

Pharmacodynamics
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 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 ischaemic 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 ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

Amlodipine provides significant 24 hour blood pressure reduction in hypertensive patients. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

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Amlodipine has been shown to increase exercise time, time to angina onset, and time to 1 mm ST segment depression, and decrease both angina attack frequency and glyceryl trinitrate tablet consumption in patients with angina.

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.

Use in Patients with Heart Failure: Amlodipine does not lead to clinical deterioration or increased mortality in heart failure patients.

Amlodipine has been shown to reduce blood pressure in hypertensive children. The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood has also not been established.

Pharmacokinetics

Absorption, distribution, plasma protein binding: 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 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.

Use in the 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.

INDICATIONS

Amlodipine is indicated for the first line treatment of hypertension and can be used as the sole agent to control blood pressure in majority of patient.

Patients not adequately controlled on a single antihypertensive agent may benefit from the addition of amlodipine, which has been used in combination with a thiazide diuretic, alpha blockers, beta adrenoceptor blocking agent, or an angiotensin-covering enzyme inhibitor.

Amlodipine is indicated for the first line treatment of myocardial ischemia, whether due to fixed obstruction (stable angina) and/or vasospasm/vasoconstriction (Prinzmetal’s or variant angina) of coronary vasculature.

Amlodipine may be used where the clinical presentation suggests a possible vasopastic/vasoconstrictive component but where vasospasm/vasoconstriction has not been confirmed.

Amlodipine may be used alone, as monotherapy, or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta blockers.

DOSAGE AND METHOD OF ADMINISTRATION

In 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. No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin converting enzyme inhibitors.

Use in children: Not recommended.

Use in the elderly: Amlodipine, used at similar doses in elderly or younger patients, is equally well tolerated. Therefore normal dosage regimens are recommended.

Patients with hepatic impairment: See section *Warnings and Precautions for use*.

Patients with 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.

Route of administration

Oral

CONTRAINDICATIONS

- Amlodipine is contra-indicated in patients with a known sensitivity to dihydropyridines, amlodipine or any of the excipients
- Amlodipine should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmetal's angina)
- Pregnancy and lactation.

WARNINGS AND PRECAUTIONS

Use in patients with Heart Failure: Amlodipine has been associated with pulmonary oedema in heart failure patients. See section “Pharmacodynamic Properties”.

Use in patients with impaired hepatic function: As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. The drug should therefore be administered with caution in these patients.

There are no data to support the use of amlodipine alone, during or within one month of a myocardial infarction.

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

DRUG INTERACTIONS

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

In vitro data from studies with human plasma indicate that amlodipine has no effect on protein binding of digoxin, phenytoin, warfarin or indomethacin.

Special Studies: Effect of other agents on amlodipine

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

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

Sildenafil: When amlodipine and sildenafil were 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 of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

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

Warfarin: In healthy male volunteers, the co-administration of amlodipine does not significantly alter the effect of warfarin on prothrombin response time. Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.
Cyclosporin: Pharmacokinetic studies with cyclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporin.

Drug/Laboratory test Interactions: None known.

PREGNANCY AND LACTATION

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in pregnancy or lactation. Accordingly, amlodipine should not be administered during pregnancy, or lactation, or to women of childbearing potential unless effective contraception is used.

UNDESIRABLE EFFECTS

Adverse events that have been reported in amlodipine trials are categorised below, according to system organ class and frequency.

Blood and the Lymphatic System Disorders	thrombocytopenia	Very Rare
Immune System Disorders	allergic reaction	Very Rare
Metabolism and Nutrition Disorders	hyperglycaemia	Very Rare
Psychiatric Disorders	insomnia, mood changes	Uncommon
Nervous System Disorders	somnolence, dizziness, headache	Common
	tremor, taste perversion, syncope, hypoaesthesia, paraesthesia	Uncommon
	peripheral neuropathy	Very Rare
Eye Disorders	visual disturbances	Uncommon
Ear and Labyrinth Disorders	Tinnitus	Uncommon

Cardiac Disorders	palpitations	Common
	myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation)	Very Rare
Vascular Disorders	flushing	Common
	hypotension	Uncommon
	vasculitis	Very Rare
Respiratory, Thoracic and Mediastinal Disorders	dyspnoea, rhinitis	Uncommon
	coughing	Very Rare
Gastrointestinal Disorders	abdominal pain, nausea	Common
	vomiting, dyspepsia, altered bowel habits, dry mouth	Uncommon
	pancreatitis, gastritis, gingival hyperplasia	Very Rare
Hepato-biliary Disorders	hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis)	Very Rare
Skin and Subcutaneous Tissue Disorders	alopecia, purpura, skin discolouration, increased sweating, pruritus, rash	Uncommon
	angioedema, erythema multiforme, urticaria	Very Rare
Musculoskeletal and Connective Tissue Disorders	arthralgia, myalgia, muscle cramps, back pain	Uncommon

Renal and Urinary Disorders	micturition disorder, nocturia, increased urinary frequency	Uncommon
Reproductive System and Breast Disorders	impotence, gynaecomastia	Uncommon
General Disorders and Administration Site Conditions	oedema, fatigue	Common
	chest pain, asthenia, pain, malaise	Uncommon
Investigations	weight increase, weight decrease	Uncommon

OVERDOSE

Available data suggest that gross 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.

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, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

SHELF-LIFE

24 months

STORAGE AND HANDLING INSTRUCTIONS

Store below 30^{O}C.

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PACK SIZE

Carton containing 10 blisters of 10 tablets.

REGISTRATION HOLDER IN MALYASIA

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DATE OF REVISION

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