

New Zealand Data Sheet

Apo-Amlodipine

Amlodipine besylate tablets 2.5mg, 5mg and 10mg

Presentation

APO-AMLODIPINE 2.5mg are white to off-white, round unscored tablets, engraved "APO" on one side and "AML" over "2.5" on the other side. Each tablet typically weighs 45mg. Do not halve tablet.

APO-AMLODIPINE 5mg are white to off-white, round, flat faced beveled-edge scored tablets, engraved "APO" on one side and "AML" over scored "5" on the other side. Each tablet contains amlodipine besylate equivalent to 5 mg amlodipine and typically weighs 90mg

APO-AMLODIPINE 10mg are white to off-white, round flat faced beveled-edge unscored tablets, engraved "APO" on one side and "AML" over "10" on the other side. Each tablet contains amlodipine besylate equivalent to 10mg amlodipine and typically weighs 180mg.

Uses

Actions

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 exact mechanism of how amlodipine relieves angina has not been fully determined, but amlodipine reduces total ischaemic burden by the following two actions:

Amlodipine dilates the peripheral arterioles and therefore reduces the total peripheral resistance (afterload) against which the heart works. As the heart rate remains stable, the unloading of the heart reduces myocardial energy consumption and oxygen requirements.

The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. The dilatation increases the myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina) and blunts smoking induced coronary vasoconstriction.

Use in Patients with Heart Failure

Haemodynamic studies and exercise based controlled clinical trial in NYHA Class II-IV 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.

A placebo-controlled study (PRAISE) designed to evaluate patients with NYHA Class III-IV 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.

In a follow-up, long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA and III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis and diuretics, amlodipine has no effect on 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 as compared to placebo (refer to "Warnings and Precautions").

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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 between 6 to 12 hours post-dose. Oral administration of a single therapeutic dose gave a mean absolute bioavailability of 64% (range 52 to 88%). The volume of distribution is approximately 20L/kg. Amlodipine absorption is unaffected when taken with food. The terminal plasma elimination half-life is approximately 35 to 50 hours, which is consistent with once daily dosing. Steady state plasma levels are reached after 7 to 8 days of consecutive dosing. Amlodipine is metabolised by the liver to inactive metabolites, with 60% of the metabolites and 10% of the parent compound being excreted in the urine.

As shown by *in vitro* studies, approximately 97.5% of circulating amlodipine is bound to plasma proteins.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout a 24 hour period.

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 1mm ST segment depression, and decreases both angina attack frequency and nitroglycerine tablet consumption.

Amlodipine is not dialysable.

Indications

APO-AMLODIPINE is indicated for the first line treatment of hypertension and can be used as the sole agent to control blood pressure in the majority of patients. 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, beta adrenoceptor blocking agent, or an angiotensin-converting enzyme inhibitor.

APO-AMLODIPINE is indicated for the first line treatment of myocardial ischaemia, 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 vasospastic/vasoconstrictive component but where vasospasm/vasoconstriction has not been confirmed. APO-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 beta blockers.

Dosage and Administration

For both hypertension and angina, the usual initial dose of APO-AMLODIPINE is 5mg once daily. This may be increased to a maximum dose of 10mg per day depending on the individual patient's response.

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

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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.

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

Impaired Renal Function

Amlodipine is extensively metabolised to inactive metabolites with 10% excreted as unchanged drug in the urine. Changes in amlodipine plasma concentrations are not correlated with the degree of renal impairment. APO-AMLODIPINE may be used in such patients at normal doses.

Use in Elderly

Dose adjustment is not necessary in elderly patients.

Use in Children

APO-AMLODIPINE is not recommended for use in children.

Contraindications

APO-AMLODIPINE is contraindicated in patients with a known sensitivity to amlodipine, dihydropyridines or any of the components of this medicine.

Warnings and Precautions

In a long term placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischaemic etiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo (refer to "Actions – Use in patients with Heart Failure").

As with all calcium channel blockers, amlodipine half-life is prolonged in patients with impaired liver function and the dosage recommendations have not been established. The compound should therefore be administered with caution in these patients.

The safety and effectiveness of amlodipine in children has not been established.

Use in Pregnancy and Lactation

Category C

The safety of amlodipine during pregnancy has not been established. Amlodipine did not demonstrate and foetotoxic nor teratogenic potential in animal reproductive studies other than to delay parturition and prolong labour in rats at a dose level fifty times the maximum recommended dose in humans. No mutagenic activity has been found in tests for gene mutations of cytogenetic assays. Amlodipine should not be administered to pregnant women unless the expected benefits outweigh the potential risks.

The safety of amlodipine use during lactation has not been established, but as many drugs are excreted in human milk and because of the potential for serious adverse reactions for nursing

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infants from amlodipine, a decision should be made whether to discontinue nursing or to discontinue taking the drug, taking into account the importance of the drug to the mother.

Effects on ability to drive and use machines

APO-AMLODIPINE is presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery.

Adverse Effects

Amlodipine is well tolerated. In placebo controlled clinical trials involving patients with angina or hypertension, the most commonly observed adverse effects were: Abdominal pain, dizziness, fatigue, flushing, headache, nausea, oedema, palpitations and somnolence. In these trials there was no pattern of significant laboratory test abnormalities relating to amlodipine observed.

Less commonly observed side effects include:

Autonomic Nervous: Dry mouth and increased sweating.

Body as a Whole: Asthenia, back pain, malaise, pain and weight increase/decrease.

Cardiovascular (general): Hypotension and syncope.

Central and Peripheral Nervous: Hypertonia, hypoesthesia/paresthesia, peripheral neuropathy and tremor.

Endocrine: Gynaecomastia.

Gastrointestinal: Altered bowel habits, dyspepsia (including gastritis), gingival hyperplasia, pancreatitis and vomiting.

Metabolic / Nutritional: Hyperglycaemia.

Musculoskeletal: Arthralgia, muscle cramps and myalgia.

Platelet / Bleeding / Clotting: Purpura and thrombocytopenia.

Psychiatric: Impotence, insomnia and mood changes.

Respiratory: Coughing, dyspnoea and rhinitis.

Skin / Appendages: Alopecia, skin discolouration and urticaria.

Special senses: Taste perversion and tinnitus.

Urinary: Increased urinary frequency, micturition disorder and nocturia.

Vascular (extracardiac): Vasculitis.

Vision: Visual disturbances.

White Blood Cell / R.E.S.: Leucopenia.

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Rarely, allergic reactions such as, angioedema, erythema multiforme, pruritis and rash have been reported.

Very infrequently hepatic enzyme elevations, hepatitis and jaundice have been reported (mostly consistent with cholestasis). In some cases these were severe enough to cause hospitalisation, although, in many instances a causal association is uncertain.

As with other calcium channel blockers the following adverse effects have been reported rarely and cannot be distinguished from natural history of the underlying disease: Arrhythmia (including atrial fibrillation, bradycardia and ventricular tachycardia) chest pain and myocardial infarction.

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 hypoglycaemic agents, sublingual glyceryl trinitrate and thiazide diuretics.

In vitro data from studies with human plasma indicate that amlodipine has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin and indomethacin).

Special studies: Effect of other agents on amlodipine

Aluminium / Magnesium (antacid): Co-administration of a single dose of amlodipine with aluminium/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 10mg of amlodipine with 240ml of grapefruit juice in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: A single 100mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetics of amlodipine. 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 10mg doses of amlodipine with 80mg atorvastatin resulted in no significant changes in the steady state pharmacokinetic parameters of atorvastatin.

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

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 10mg 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.

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Overdosage

Data that is available suggests that gross overdosage could result in excessive peripheral vasodilation and possible 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 10mg of amlodipine has been shown to significantly decrease amlodipine absorption.

Gastric lavage may be worthwhile in some cases.

Clinically significant hypotension due to amlodipine overdose requires cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, 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 could be beneficial in reversing the effects of calcium channel blockade.

Dialysis is unlikely to be of benefit since amlodipine is highly protein-bound.

Pharmaceutical Precautions

Store at or below 25°C. Protect from heat light and moisture. Keep container tightly closed.

Shelf life: 36 months in bottles from date of manufacture for 2.5mg tablets, 36 months in bottles and blisters from the date of manufacture for 5mg and 10mg tablets.

Medicine Classification

Prescription Medicine

Package Quantities

Bottles of 100, 250 and 500 and blisters of 120 for 5mg and 10mg tablets

Bottles of 100 for 2.5mg tablets

Further Information

Contains Lactose

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