Covasc®

5mg & 10mg tablet

Amlodipine Besylate

DESCRIPTION & COMPOSITION

Covasc Tablet **5mg**

White to off white, shield shape tablet, marked "COV" on one side and scored on the other side.

Each tablet contains amlodipine besylate equivalent to 5 mg amlodipine.

Covasc Tablet **10mg**

White to off white, shield shape tablet, marked "COV" on one side and marked "10" with scored line on the other side.

Each tablet contains amlodipine besylate equivalent to 10 mg amlodipine.

PHARMACEUTICAL FORM

Tablets.

PHARMACODYNAMIC

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 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 ischemic burden by the following two actions.

• 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.

• 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 dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina) and blunts smoking induced coronary vasoconstriction.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. 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 1 mm ST segment depression, and decreases both angina attack frequency and nitroglycerine tablet consumption.

In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

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.

Hemodynamic studies and exercise based controlled clinical trials 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 in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity in patients with heart failure. In the same study, in a group of patients without clinical signs or symptoms suggestive of underlying ischemic disease, a clinically and statistically significant reduction in mortality and combined mortality and morbidity was observed with amlodipine.

PHARMACOKINETIC

Absorption

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours postdose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. Absorption of amlodipine is unaffected by consumption of food.

Biotransformation/Elimination

The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Steady state plasma levels are reached after 7-8 days of consecutive dosing. Amlodipine is extensively metabolized 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 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, alpha blockers, beta adrenoceptor blocking agent, or an angiotensin-converting 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 vasospastic/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 ADMINISTRATION

For both hypertension and angina the usual initial dose is 5mg amlodipine once daily which may be increased to a maximum dose of 10mg depending on the individual patient's response.

No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, betablockers, and angiotensin-converting enzyme inhibitors.

Use in the Elderly

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

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Use in Children
Safety and effectiveness of amlodipine in children have not been established.

Use in Patients with Impaired Hepatic Function
See Precautions / Warnings.

Use in Renal Failure
Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.

CONTRAINDICATIONS
Patients with known sensitivity to dihydropyridines, amlodipine, or any of the inert ingredients.

PRECAUTIONS / WARNINGS
Use In Patients wlth Impaired Hepatic Function
As with all calcium antagonists, amlodipine 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.

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

Studies have indicated that the co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers, and that co-administration of cimetidine did not alter the pharmacokinetics of amlodipine.

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

In healthy male volunteers, the co-administration of amlodipine does not significantly alter the effect of warfarin on prothrombin response time.

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

Pregnancy And Lactation
Safety of amlodipine in human pregnancy or lactation has not been established. Amlodipine does not demonstrate toxicity in animal reproductive studies other than to delay parturition and prolong labor in rats at a dose level fifty times the maximum recommended dose in humans. Accordingly, 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.

Effects on Ability to Drive and Use Machines
Clinical experience with amlodipine indicates that it is unlikely to impair a patient's ability to drive or use machinery.

Undesirable Effects
Amlodipine is well tolerated. In placebo controlled clinical trials involving patients with hypertension or angina, the most commonly observed side effects were headache, edema, fatigue, somnolence, nausea, abdominal pain, flushing, palpitations, and dizziness. In these clinical trials no pattern of clinically significant laboratory test abnormalities related to amlodipine has been observed.

Less commonly observed side effects in marketing experience include alopecia, altered bowel habits, arthralgia, asthenia, back pain, dyspepsia, dyspnea, gingival hyperplasia, gynecomastia, hyperglycemia, impotence, increased urinary frequency, leucopenia, malaise, mood changes, dry mouth, muscle cramps, myalgia, peripheral neuropathy, pancreatitis, increased sweating, syncope, thrombocytopenia, vasculitis, and visual disturbances. In many instances, causal association is uncertain.

Rarely, allergic reaction including pruritus, rash, angioedema, and erythema multiforme.

Hepatitis, jaundice and hepatic enzyme elevations have also been reported very infrequently (mostly consistent with cholestasis). Some cases severe enough to require hospitalization have been reported in association with use of amlodipine. In many instances, causal association is uncertain.

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

OVERDOSE
In humans, experience with intentional overdose is limited. Gastric lavage may be worthwhile in some cases. Available data suggest that gross overdosage could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension. 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.

FOR SPECIALIST'S USE ONLY.

PACKING / PACK SIZE
5mg: Blister packs of 3 x 10's and 10 x 10's.
10mg: Blister packs of 3 x 10's and 10 x 10's.
Not all pack sizes available locally

STORAGE CONDITIONS
Keep container tightly closed.
Store in a dry place below 30°C.
Protect from light and moisture.
Keep out of reach of children.
Jauhkan daripada kanak-kanak.
Shelf life: Please refer to outer carton.

Product Registration Holder:
Duopharma Manufacturing (Bangi) Sdn. Bhd.
Lot No. 2, 4, 6, 8 & 10, Jalan P/7, Section 13,
Bangi Industrial Estate, 43650 Bandar Baru Bangi,
Selangor, Malaysia.

Manufacturer:
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Selangor, Malaysia.

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