AMOPRO®

Amlodipine (as besylate) 5mg

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QUALITATIVE AND QUANTITATIVE COMPOSITION: Each Capsule contains Amlodipine bysylate equivalent to 5mg Amlodipine - Cellulose. microcrystalline. Silicon dioxide, Mg stearate, Sodium starch glycollate, Calcium hydrogen phosphate, Gelatin capsule.

PHARMACOLOGICAL PROPERTIES: Amlodipine besylate is slightly soluble in water and sparingly soluble in ethanol; and has a molecular weight of 567.1 (free base 408.9). Amlodipine besylate is administered in the form of racemic mixture.

Pharmacodynamic Properties: Amlodipine besylate inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on the vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces the total ischemic burden by the following two actions:

1) Amlodipine dilates the 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 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 could oppose the coronary vasoconstriction induced by smoking.

In patients with hypertensions 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 AMOPRESS® 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.

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

Pharmocokinetic properties: *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 one daily dosing. Steady state plasma levels are reached after 7-8 days of consecutive dosing. Amlodipine is extensively metabolized to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

THERAPEUTIC INDICATIONS: AMOPRESS® is indicated for treatment of hypertension and can be used as the sole agent to control blood pressure or in combinations. Patients not adequately controlled on a single antihypertensive agent may benefit from the addition of AMOPRESS® , which has been used in combination with a thiazide diuretic, alpha blockers, beta adrenoceptor blocking agent, or an angiotensin-converting enzyme inhibitor.

AMOPRESS® is indicated for treatment of myocardial ischemia, only if the latter is due to fixed obstruction (stable angina) and/or vasospasm/ vasoconstriction (Prinzmetal's or variant angina) of coronary vasculature. AMOPRESS® 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.

POSOLOGY AND METHOD OF ADMINISTRATION: For both hypertension and angina, the usual initial dose is 5 mg AMOPRESS® once daily, which may be increased to a maximum dose of 10 mg depending on the individual patient's response. AMOPRESS® may be taken before or after a meal, since absorption remains the same in either case. No dose adjustments of AMOPRESS® is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Use in the elderly, in Renal Failure and in patients with impaired hepatic function: Refer to 'Special Precautions' section below.

Use in children: No clinical experience to date has been accumulated on patients under age 6. Use of this drug in children is therefore not recommended at the present stage.

CONTRAINDICATIONS: Amlodipine is contraindicated with a known sensitivity to dihydropyridines, amlodopine, or any of the inert ingredients. Amlodipine is contraindicated in unstable angina, cardiogenic shock, significant aortic stenosis and for 8 days after myocardial infarction.

PRECAUTION: WITHDRAWL: There is some evidence that sudden withdrawal of calcium channel blockers may be assosiated with an exacerbation of angina.

- If you miss a dose, take it as soon as you remember. Do not take (AMOPRESS®) if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time.

SPECIAL PRECAUTIONS: Dihydropyridines may induce acute hypotension which may lead to hypoperfusion and reflex tachycardia (paradoxical angina) although neither effect has been reported, up to now, with amlodipine.

Use in the elderly: Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%. A similar increase in AUC was observed in patients with moderate to severe heart failure. (FDA). 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 study.

Use in Renal Failure: Amlodipine is extensively metabolized to inactive metabolites with 10% excreted as unchanged drug in the urine. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine may be used in such patients at normal doses. Amlodipine is not dialysable.

Use in patients with impaired hepatic function: As with all calcium channel 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.

DRUG 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-infammatory drugs, antibiotics and oral hypoglycemic drugs. Special 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 amlodipine 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 time 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. Whether amlodipine passes into maternal milk has not been established. Therefore, nursing mothers should refrain from using the drug. In the event administration of amlodipine is indispensable, continued nursing is not recommended. Pregnancy risk grade C.

UNDESIRABLE EFFECTS: 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 amlidipine has been observed.

Post-Marketing Data: Voluntary reports of adverse events in patients receiving amlodipine since market introduction have been received. They include the following.

Body as a Whole: allergic reactions, malaise, mood changes (including anxiety).

Cardiovascular: hypotension, syncope, edema. 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 diseases: myocardial infarction, arrhythmia (including ventricular tachycardia and atrial fibrillation and bradycardia), chest pain.

Central and Peripheral nervous System: paresthesia, tremor, insomnia, increased sweating, dry mouth, peripheral neuropathy.

Endocrine: gynecomastia.

Gastrointestinal: altered bowel habits (including diarrhea and constipation), dyspepsia, pancreatitis, gingival hyperplasia, taste perversion.

Hematopoietic: Thombocytopenia.

Liver/Biliary: rare cases of hepatitis. Jaundice and hepatic enzyme elevations have 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.

Musculoskeletal: arthralgia, asthenia, back pain, muscle cramps, myalgia.

Metabolic/Nutritional: hyperglycemia.

Platelet/Bleeding/Clotting: purpura.

Respiratory: dyspnea.

Skin/Appendages: alopecia, pruritis, angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, rash.

Urinary: increased urinary frequency, impotence.

Vascular: vasculitis.

White Blood Cell/RES: leucopenia.

Others: visual disturbances (including diplopia), tinnitus.

OVERDOSE: In humans experience with intentional overdose is limited. In summary, the overdose cases demonstrate the following: (1) In general, overdose with amlodipine with amount <100 mg was not associated with excessive peripheral vasodilatation. (2) Overdosage with amlodipine in amounts >100 mg was associated with 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 AMOPRESS® is highly protein-bound, dialysis is not likely to be benefit. In some cases, gastric lavage can prove helpful.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: The clinical experience accumulated to date does not suggest that amlodipine affects the patient's ability to drive a vehicle or to use machines.

STORAGE: The product should be stored below 30º C.

EXPIRATION DATE: The product should be use before the expiration date specified on the outer package.

PACKAGING: 5mg capsules. Boxes of 28 capsules.

THIS IS A MEDICAMENT

- A drug is a product which acts on your health and its consumption could be dangerous when you do not follow the instructions.
- Follow strictly the doctor's prescriptions, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist know the medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep out of the reach of children.

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