SmPC: Summary of Product characteristics

Amlodipine Tablets
5mg & 10mg

SUMMARY OF PRODUCT CHARACTERISTICS

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

BW-Amlodipine Tablets 5mg & 10mg

2. Qualitative and quantitative composition

Each uncoated tablet contains amlodipine besylate USP equivalent to amlodipine 5 mg or 10mg.

3. Pharmaceutical form: Tablets

4. Clinical particulars

4.1 Therapeutic indications

Amlodipine is indicated for the first line treatment of hypertension and can be used as asole agent to control blood pressure in the majority of patients.Patients not adequatelycontrolled on a single antihypertensive agent may benefit from the addition ofamlodipine, which has been used in combination with a thiazide diuretic, alphablockers, beta adrenoceptor blocking agent, or an angiotensin-converting enzymeinhibitor.

Amlodipine is indicated for the first line treatment of myocardial ischemia, whether dueto fixed obstruction (stable angina) 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.

4.2 Posology and method of 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 de pending on the individual patient response.

No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretic, beta blockers, 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

Use in children

Safety and effectiveness of amlodipine in children have not been established,

Use in Patients with Impaired Hepatic function.

As with all calcium antagonist, 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.

Use in Renal Failure

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

4.3 Contraindications

Amlodipine is contraindicated in patients with known sensitivity to dihydropyridines, amlodipine, or any of the inert ingredients.

4.4 Special warnings and precautions for use

WARNINGS

Use in Patients with Impaired Hepatic function

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4.5 Interaction with other medicinal products and other forms of interaction

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,

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.

4.6 Fertility, 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.

4.7 Effects on ability to drive and use machines

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 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, palpitation 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 and rarely, erythema multi-forme. In many cases, causal association is uncertain.

Rarely, allergic reactions 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.

4.9 Overdose

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

Clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support including frequent monitoring of cardiac andrespiratory function,elevation of extremities, and attention to circulating fluid volume andurine output, A vasoconstrictor may be helpful in restoring vascular tone and bloodpressure, provided that there is no contraindication to its use . Intravenous calciumgluconate may be beneficial in reversing the effects of calcium channel blockade. Sinceamlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects.

ATC code: C08CA01

Amlodipine is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist)and inhibits the trans-membrane influx of calcium ions into cardiac and smooth muscle.The mechanism of action of f amlodipine, is due to a direct relaxant effect on vascularsmooth muscle. The precise mechanism by which amlodipine relieves angins has notbeen fully determined but amlodipine reduces total ischemic burden by the following twoactions

Amlodipine dilates peripheral arterioles and thus, reduces the total peripheralresistance (afterload)against which the heart works. Since the heart rate remains stable,thusunloading of the heart reduces myocardial energy consumption and oxygenrequiremengts.

The mechanism of action of amlodipine also probably involves dilation of the maincoronary arteries and arterioles,both in normal and ischemic regions.

This dilation increases myocardial oxygen delivery in patients with coronary artery spasm(Prinzmetals'or variant angina)and blunts smoking induced coronary vasoconstriction.Inpatients with hypertension once daily dosing provides clinically significant reductions ofblood pressure in both the supine and standing positions throughout the 24hour interval.Due to slow onset-of action, acute hypotension is not a feature of amlodipineadministration.

5.2 Pharmacokinetic properties

In patients with angina, once daily administration of amlodipine increases total exerciseTime,time to angina onset and time to 1 mm ST segment depression and decreases bothangina attack frequency and nitroglycerin tablets consumption. Amlodipine has not beenassociated with any adverse metabolic effects or changes in plasma lipids and is suitablefor use in patients with asthma, diabetes and gout. Invitro studies have shown thatapproximately 97.5% of circulating amlodipine is bound in plasma proteins.

After oral administration of therapeutic doses, amlodipine is well absorbed with peakblood levels between 6-12 hours post dose.Absolute bioavailability has been estimated tobe between 64 and 80% The volume of distribution is approximately 21L/kg. Steady stateplasma levels are reached after 7-8 days of consecutive dosing.

Absorption of amlodipine is unaffected by consumption of food, the terminal plasmaelimination half life is about 35-50 hours and is consistent with once daily dosing.Amlodipine is extensively metabolized by the liver to inactive metabolites with 10%of theparent compound and 60% of metabolites excreted in the urine.

Hemodynamic studies and exercise based controlled clinical trials in NHYA class II-IVheart failure patients have shown that amiodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinicalsymptomatology.

“Aplacebo controlled study(PRAISE) designed to evaluate patients in NHYA classIII-IV heart failure receiving digoxin,diuretics and ACE inhibitors has shown thatamlodipine did not lead to an increase in risk of mortality or combined mortality andmorbidity in patients with heart failure”.

5.3 Preclinical safety data

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity.

The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

* Based on patient weight of 50kg.

6. Pharmaceutical particulars

6.1 List of excipients

Corn starch, lactose, microcrystalline cellulose, povidone k.30, methyl and propyl parabens, sodium lauryl sulphate, sodium starch glycollate. Magnesium stearate and talcum powder.

6.2 Incompatibilities

None stated.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a cool, dry and dark place at a temperature not exceeding 30℃.Keep medicines out of the reach of children.

6.5 Nature and contents of container

Aluminum/Polyvinyl chloride blisters of 1 x 10 tablets.

6.6 Special precautions for disposal and other handling

None stated.

6.7 Marketing Authorization Holder

Blueworld Pharmaceuticals,, Foods & Cosmetics Ltd.

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