Composition

Probis® AM tablet: Each tablet contains Bisoprolol Fumarate USP 2.5 mg & Amlodipine Besilate BP equivalent to Amlodipine 5 mg.

Pharmacology

Probis® AM is a combination of Bisoprolol Fumarate and Amlodipine Besilate which is a selective antihypertensive agent. Bisoprolol fumarate is a synthetic, β_1-selective (cardioselective) adrenoceptor blocking agent. In acute administration in patients with coronary heart disease without chronic heart failure Bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases. Amlodipine is a dihydropyridine calcium antagonist that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. Amlodipine reduces total ischaemic burden by dilating peripheral arterioles and thus reduces the total peripheral resistance (afterload) against which the heart works and dilating 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). This combination allows to increase the antihypertensive and anti-anginal efficacy by complementary mechanism of actions of the two active compounds: vasoselective effect of the calcium channel blocker amlodipine (decrease of peripheral resistance) and cardioselective beta-blocker bisoprolol (decrease of cardiac output).

Indication

Probis® AM is indicated for the treatment of hypertension as substitution therapy in patients adequately controlled with the individual products given concurrently at the same doses level as in the combination, but as separate tablets.

Dose and administration

Route of administration: **Probis® AM** should be taken in oral route with or without food.

Adult

One tablet once daily in the morning in patients whose blood pressure is adequately controlled with separately administered monocomponent preparations of the same doses as the recommended fixed dose combination. Treatment must not be abruptly discontinued, as it may lead to temporary deterioration of clinical condition. Treatment must not be abruptly discontinued especially in case of patients suffering from ischemic heart disease. Gradual decrease of the dose is recommended.

Hepatic impairment

In case of severe hepatic impairment, the daily dose of bisoprolol must not exceed 10 mg. In case of hepatic impairment elimination of amlodipine may be elongated. Exact dosage recommendations concerning amlodipine have not been established, but the drug should therefore be administered with special caution in these patients.

Renal impairment

No dosage adjustment is required for patients with mild to moderate renal impairment. In case of severe renal impairment (creatinine clearance < 20 ml/min) the daily dose of bisoprolol must not exceed 10 mg. Amlodipine should be administered with particular caution to patients undergoing dialysis.

Contraindication

This combination is contraindicated in patients with hypersensitivity to bisoprolol fumarate and amlodipine besilate or any other components this product. It is also contraindicated in patients with acute heart failure, cardiogenic shock, second or third degree AV block (without a pacemaker), sick sinus syndrome, sinoatrial block, symptomatic bradycardia, symptomatic hypotension, severe bronchial asthma, severe forms of peripheral arterial occlusive disease, severe forms of Raynaud's syndrome, untreated phaeochromocytoma, metabolic acidosis, shock (including cardiogenic shock), obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis), haemodynamically unstable heart failure after acute myocardial infarction.

Warning and precaution

Since the abrupt withdrawal of bisoprolol may lead to a transitory worsening of the clinical condition, especially in patients with ischemic heart disease, the treatment must not be stopped abruptly. Bisoprolol should be administered with special caution in patients with hypertension or angina associated with heart failure. Bisoprolol must be used with caution in diabetes mellitus with large fluctuations in blood glucose values, symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating), strict fasting/diet, concomitant desensitisation therapy, first degree AV block, Prinzmetal's angina, peripheral arterial occlusive disease, patients with psoriasis or with a history of psoriasis, phaeochromocytoma, in patients undergoing general anaesthesia. Beta-blockers should be avoided in patients with obstructive airways diseases unless there are compelling clinical reasons for their use. Due to the bisoprolol component treatment must be used with caution in bronchospasm (bronchial asthma, chronic obstructive airways disease). The safety and efficacy of amlodipine in hypertensive crisis has not been established. Patients with heart failure should be treated with caution. Caution should be advised in patients with impaired hepatic function. Amlodipine should be administered with particular caution to patients undergoing dialysis.

Side effects

The most common side effects associated with this combination are dizziness, headache, somnolence, flushing, feeling of coldness or numbness in the extremities, gastrointestinal complaints (nausea, vomiting, diarrhea, constipation), abdominal pain, edema (e.g. ankle edema), dyspnoea, fatigue, asthenia, visual disturbances (including diplopia).

Use in pregnancy & lactation

Pregnancy: There are no adequate and well-controlled studies in pregnant women. This combination should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation: It is not known whether bisoprolol fumarate or amlodipine is excreted in human milk. This combination is not recommended during breastfeeding.

Use in children and adolescent

The safety and efficacy of this combination in children and adolescents below 18 years of age have not been established.

Drug Interaction

Drug interaction with medication: Concomitant use of centrally acting antihypertensive drugs (e.g. clonidine, methyldopa, moxonidine, rilmenidine) with bisoprolol may lead to reduction of heart rate and cardiac output. In combination anesthetic agents with bisoprolol, reflex tachycardia may be attenuated and the risk of hypotension may be increased. Concomitant use of cardiac glycosides (digitalis) with bisoprolol may lead to a reduction of heart rate or an increase of atrio-ventricular conduction time. Concomitant use of amlodipine with strong or moderate inhibitors of CYP3A4 (e.g. protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) can be expected to increase the plasma concentrations of amlodipine to a clinically relevant extent.

Drug interaction with food & others: Not applicable.

Overdose

The most common signs expected with overdose of bisoprolol and amlodipine are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycemia, peripheral vasodilatation and possibly reflex tachycardia. If overdose occurs, discontinuation of treatment and supportive and symptomatic treatment is recommended.

Storage

Store in a cool (below 30°C) and dry place protected from light. Keep away from the reach of children.

Packing

Probis® AM tablet: Carton of 30 tablets in blister pack.

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