BIZORAN®

Amlodipine & Olmesartan Medoxomil 5 mg/20 mg and 5 mg/40 mg Tablet

Description

Bizoran® is a combination product containing Amlodipine, a calcium channel blocker and Olmesartan, an angiotensin II receptor blocker. It is used for the treatment of hypertension (high blood pressure) alone or with other antihypertensive agents.

Mode of Action

Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle & cardiac muscle. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance & a reduction in blood pressure.

Olmesartan is an angiotensin II receptor blocker that acts on AT1 subtype. By blocking the action of angiotensin II, Olmesartan dilates blood vessels and reduces blood pressure without affecting pulse rate.

Indications

Bizoran® is indicated for the treatment of hypertension, alone or with other antihypertensive agents.

Bizoran® may also be used as initial therapy in patients who are likely to need multiple antihypertensive agents to achieve their blood pressure goals.

Patients with moderate or severe hypertension are at relatively high risk for cardiovascular events (such as strokes, heart attacks, and heart failure), kidney failure, and vision problems, so prompt treatment is clinically relevant. The decision to use a combination as initial therapy should be individualized and should be shaped by considerations such as baseline blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination compared to monotherapy. Individual blood pressure goals may vary based upon the patient's risk.

Dosage and Administration

The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). The tablet should not be chewed and should be taken at the same time each day. Bizoran® may be taken with or without food.

Initial Therapy:

The usual recommended dosage of Bizoran® is one tablet once daily.

Bizoran® (5 mg/20 mg) Tablet may be administered in patients whose blood pressure is not adequately controlled by 20 mg olmesartan medoxomil or 5 mg amlodipine alone.

Bizoran® 5/40 may be administered in patients whose blood pressure is not adequately controlled by Bizoran® (5 mg/20 mg) Tablet.

A step-wise titration of the dosage of the individual components is recommended before changing to the fixed combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered. Maximum antihypertensive effects are attained within 2 weeks after a change in dose.

For convenience, patients receiving olmesartan medoxomil and amlodipine from separate tablets may be switched to Bizoran® tablets containing the same component doses.

Initial therapy with Bizoran® is not recommended in patients ≥ 75 years old or with hepatic impairment.

Replacement Therapy:

Bizoran® may be substituted for its individually titrated components. When substituting for individual components, the dose of one or both of the components can be increased if blood pressure control has not been satisfactory.

Add-on Therapy:

Bizoran® may be used to provide additional blood pressure lowering for patients not adequately controlled with amlodipine (or another dihydropyridine calcium channel blocker) alone or with olmesartan medoxomil (or another angiotensin II receptor blocker) alone.

Pediatric Use

The safety and effectiveness of Amlodipine & Olmesartan combination in pediatric patients have not been established.

Elderly

Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal impairment

Maximum 20 mg of Olmesartan daily if eGFR is 20–60 mL/minute/1.73 m^2. Avoid if eGFR is less than 20 mL/minute/1.73 m^2.

Monitoring of potassium levels and creatinine is advised in patients with moderate renal impairment.

Hepatic impairment

Use with caution in moderate impairment— initially 10 mg daily, maximum 20 mg daily. Avoid in severe impairment—no information available.

Contraindications

Hypersensitivity to the active substances, to dihydropyridine derivatives or to any of the excipients.

Second and third trimesters of pregnancy.

Severe hepatic insufficiency and biliary obstruction.

The concomitant use of Bizoran® with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m^2)

Due to the component amlodipine, Bizoran® is also contraindicated in patients with:

- severe hypotension.
- 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

Special Warnings and Precautions

1. Fetal/Neonatal Morbidity and Mortality:

When pregnancy is detected, this combination should be discontinued as soon as possible.

2. Hypotension in Volume- or Salt-Depleted Patients:

Symptomatic hypotension may occur after initiation of treatment.

3. Vasodilatation:

Caution should be exercised when administering the drug, particularly in patients with severe aortic stenosis.

4. Patients with Severe Obstructive Coronary Artery Disease:

Patients may develop increased frequency, duration, or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase.

5. Patients with Congestive Heart Failure:

Calcium channel blockers should be used with caution in patients with heart failure.

6. Patients with Impaired Renal Function:

Caution should be exercised when administering the drug to patients with renal impairment.

7. Patients with Hepatic Impairment:

Caution should be exercised when administering the drug to patients with severe hepatic impairment.

Drug Interaction

In clinical trials, Amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs. No significant drug interactions were reported in studies in which Olmesartan medoxomil was co-administered with digoxin or warfarin, antacids. Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes.

Fertility, Pregnancy and Lactation

Pregnancy

US FDA pregnancy category D.

When pregnancy is detected, discontinue Bizoran® as soon as possible. When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.

Lactation

Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother. Excreted into human milk: Yes (amlodipine); Unknown (olmesartan). Excreted into animal milk: Yes (olmesartan).

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility.

Side Effects

The most common side effects include peripheral edema, flushing, palpitations, dizziness. Other adverse reactions that occurred in placebo-controlled clinical trials are orthostatic hypotension, diarrhea, rash, abdominal pain, fatigue, back pain, pruritus, rhabdomyolysis.

Overdose

Symptoms:

There is no experience of overdose with Amlodipine & Olmesartan combination.

The most likely effects of olmesartan medoxomil overdosage are hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurred.

Amlodipine overdosage can be expected to lead to excessive peripheral vasodilatation with marked hypotension and possibly a reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome has been reported.

Treatment:

If intake is recent, gastric lavage may be considered. In healthy subjects, the administration of activated charcoal immediately or up to 2 hours after ingestion of amlodipine has been shown to reduce substantially the absorption of amlodipine.

Clinically significant hypotension due to an overdose of Amlodipine & Olmesartan combination requires active support of the cardiovascular system, including close monitoring of heart and lung function, elevation of the 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. The dialyzability of olmesartan is unknown.

Pharmaceutical Precautions

Keep out of the reach of children. Store below 30°C. Keep in the original package in a cool & dry place in order to protect from light and moisture.

Commercial Pack

Bizoran® Tablet: Box containing 30 tablets in 3 x 10's alu-alu form packs. Each tablet contains Amlodipine Besilate BP equivalent to Amlodipine 5 mg and Olmesartan Medoxomil BP 20 mg.

Bizoran® 5/40 Tablet: Box containing 30 tablets in 3 x 10's alu-alu form packs. Each tablet contains Amlodipine Besilate BP equivalent to Amlodipine 5 mg and Olmesartan Medoxomil BP 40 mg.

BEXIMCO PHARMA

Manufactured by

BEXIMCO PHARMACEUTICALS LTD.

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