Amdopril®

Amlodipine and Benazepril Hydrochloride

Capsule

Description

The combination of Amlodipine and Benazepril is used to treat high blood pressure. Benazepril and benazeprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and in animals. While the mechanism through which Benazepril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, Benazepril has an antihypertensive effect even in patients with low-renin hypertension. Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. The rate and extent of absorption of Benazepril and Amlodipine from Amdopril® are not significantly different, respectively, from the rate and extent of absorption of Benazepril and Amlodipine from individual tablet formulations. Following oral administration of Amdopril®, peak plasma concentrations of Benazepril are reached in 0.5-2 hours. Peak plasma concentrations of Amlodipine are reached 6-12 hours after administration of Amdopril®; the extent of absorption is 64%-90%. Over 700 patients received Benazepril/Amlodipine once daily in five double-blind, placebo-controlled studies. Benazepril/Amlodipine lowered blood pressure within 1 hour, with peak reductions achieved 2-8 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. Once-daily doses of Benazepril/Amlodipine using Benazepril doses of 10-20 mg and Amlodipine doses of 2.5-10 mg decreased seated pressure (systolic/diastolic) 24 hours after dosing by about 10-25/6-13 mmHg.

Dosage & Administration

Amlodipine is an effective treatment of hypertension in once-daily doses of 2.5-10 mg while Benazepril is effective in doses of 10-80 mg.

It is usually appropriate to begin therapy with Amdopril® only after a patient has either (a) failed to achieve the desired antihypertensive effect with one or the other monotherapy, or (b) demonstrated inability to achieve adequate antihypertensive effect with Amlodipine therapy without developing edema.

Dose Titration Guided by Clinical Effect: A patient whose blood pressure is not adequately controlled with Amlodipine (or another dihydropyridine) alone or with Benazepril (or another ACE inhibitor) alone may be switched to combination therapy with Amdopril®. All patient groups benefit from the reduction in Amlodipine-induced edema. Dosage must be guided by clinical response; steady-state levels of Benazepril and Amlodipine will be reached after approximately 2 and 7 days of dosing respectively. In patients whose blood pressures are adequately controlled with Amlodipine but who experience unacceptable edema, combination therapy may achieve similar (or better) blood-pressure control without edema. Especially in nonblacks, it may be prudent to minimize the risk of excessive response by reducing the dose of Amlodipine as Benazepril is added to the regimen.

Replacement Therapy : For convenience, patients receiving Amlodipine and Benazepril from separate tablets may instead wish to receive Amdopril® capsules containing the same component doses. In small, elderly, or hepatically impaired patients, the recommended initial dose of Amlodipine, as monotherapy or as a component of combination therapy, is 2.5 mg.

Indications

Amdopril® is indicated for the treatment of hypertension. This fixed combination drug is not indicated for the initial therapy of hypertension.

Contraindications

Amdopril® is contraindicated in patients who are hypersensitive to Benazepril, to any other ACE inhibitor, or to Amlodipine.

Precaution

Impaired Renal Function : Amdopril® should be used with caution in patients with severe renal disease.

Hyperkalemia: This may occur in only a few patients but generally are reversible.

Patients With Hepatic Failure : Since Amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering Amdopril® to patients with severe hepatic impairment.

Cough : ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia : In patients undergoing surgery or during anesthesia with agents that produce hypotension, Benazepril will block the angiotensin II formation that could otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Carcinogenesis, Mutagenesis, Impairment of Fertility : No evidence of carcinogenicity, mutagenicity or impairment of fertility was found when the Benazepril/Amlodipine combination were given orally.

Geriatric Use : Clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pediatric Use : Safety and effectiveness in pediatric patients have not been established.

Overdosage

Human overdoses with any combination of Amlodipine and Benazepril have not been reported. In scattered reports of human overdoses with Benazepril and other ACE inhibitors, there are no reports of death.

Use in Pregnancy and Lactation

Pregnancy Categories C (first trimester) and D (second and third trimesters):

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, Amdopril® should be discontinued as soon as possible.

Minimal amounts of unchanged Benazepril and of benazeprilat are excreted into the breast milk of lactating women treated with Benazepril, so that a newborn child ingesting nothing but breast milk would receive less than 0.1% of the maternal doses of Benazepril and benazeprilat. It is not known whether Amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while Amdopril® is administered.

Side Effect

Benazepril/Amlodipine has been evaluated for safety in patients with hypertension for at least 6 months and more than 1 year. The reported side effects were generally mild and transient, and there was no relationship between side effects and age, sex, race or duration of therapy. Discontinuation of therapy due to side effects was required in approximately 4% of patients treated with Benazepril/Amlodipine and in 3% of patients treated with placebo. The most common reasons for discontinuation of therapy with Benazepril/Amlodipine in U.S. studies were cough and edema. The side effects considered possibly or probably related to study drug that occurred in U.S. placebo-controlled trials in more than 1% of patients treated with Benazepril/Amlodipine are cough, headache, dizziness and edema.

The incidence of edema was statistically greater in patients treated with Amlodipine monotherapy than in patients treated with the combination. Edema and certain other side effects are associated with Amlodipine monotherapy in a dose-dependent manner, and appear to affect women more than men. The addition of Benazepril resulted in lower incidences as shown in study; the protective effect of Benazepril was independent of race and (within the range of doses tested) of dose.

Other rare side effects are angioedema, asthenia, fatigue, insomnia, nervousness, anxiety, tremor, decreased libido, flushing, hot flashes, rash, skin nodule, dermatitis, dry mouth, nausea, abdominal pain, constipation, diarrhea, dyspepsia, esophagitis, hypokalemia, pharyngitis etc.

Drug Interaction

Diuretics: Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Benazepril/Amlodipine.

Potassium Supplements and Potassium-Sparing Diuretics : Benazepril can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (Spironolactone, Amiloride, Triamterene and others) or potassium supplements can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

Others : Benazepril has been used concomitantly with oral anticoagulants, beta-adrenergic-blocking agents, calcium-blocking agents, Cimetidine, diuretics, Digoxin, Hydralazine, and Naproxen without evidence of clinically important adverse interactions.

In clinical trials, Amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, Digoxin, Warfarin, nonsteroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Storage

Store at 25^{0}C, protect from moisture. Keep out of reach of children.

Commercial Pack

Amdopril® 2.5/10 capsule : Box containing 6 blister strips of 10 capsules. Each capsule contains Amlodipine Besilate BP equivalent to Amlodipine 2.5 mg and Benazepril Hydrochloride INN 10 mg.

Amdopril® 5/10 capsule : Box containing 6 blister strips of 10 capsules. Each capsule contains Amlodipine Besilate BP equivalent to Amlodipine 5 mg and Benazepril Hydrochloride INN 10 mg.

Amdopril® 5/20 capsule : Box containing 3 blister strips of 10 capsules. Each capsule contains Amlodipine Besilate BP equivalent to Amlodipine 5 mg and Benazepril Hydrochloride INN 20 mg.

Amdopril® 10/20 capsule : Box containing 3 blister strips of 10 capsules. Each capsule contains Amlodipine Besilate BP equivalent to Amlodipine 10 mg and Benazepril Hydrochloride INN 20 mg.

BEXIMCO PHARMA

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BEXIMCO PHARMACEUTICALS LTD.

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148x210 mm