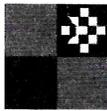


CARVEDILOL

VASOLEXIN

6.25 mg, 25 mg Tablet

Beta-Blocker



FORMULATION:

Each tablet contains:

Carvedilol 6.25 mg

Carvedilol 25 mg

DESCRIPTION

6.25 mg: White, round tablets, engraved with "CD" on the scored side and "UT" on the other side.
25 mg: White, round tablets, engraved with "C/D" on the scored side and "UT" on the other side.

PHARMACOKINETICS

Carvedilol is well absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism in the liver; the absolute bioavailability is about 25%. Peak plasma concentrations occur 1 to 2 hours after an oral dose. It has high lipid solubility. Carvedilol is more than 98% bound to plasma proteins. It is extensively metabolized in the liver, primarily by the cytochrome P450 isoenzymes CYP2D6 and CYP2C9, and the metabolites are excreted mainly in the bile. The elimination half-life is about 6 to 10 hours. Carvedilol has been shown to accumulate in breast milk in animals.

INDICATIONS

For the treatment of hypertension; angina; and as adjunct to diuretic, digoxin, or ACE inhibitor in symptomatic chronic heart failure.

DOSE AND ADMINISTRATION

In hypertension, an initial dose of 12.5 mg once daily by mouth, increased after 2 days to 25 mg once daily. Alternatively, an initial dose of 6.25 mg is given twice daily, increased after one to two weeks to 12.5 mg twice daily. The dose may be increased further if necessary, at intervals of at least 2 weeks to 50 mg once daily or in divided doses. A dose of 12.5 mg once daily may be adequate for elderly patients.

In angina pectoris, an initial dose of 12.5 mg is given twice daily by mouth, increased after two days to 25 mg twice daily.

In heart failure, the initial dose is 3.125 mg twice daily by mouth. It should be taken with food to reduce the risk of hypotension. If tolerated, the dose should be doubled after 2 weeks to 6.25 mg twice daily and then increased gradually, at intervals of not less than 2 weeks, to the maximum dose tolerated by the patient; this should not exceed 25 mg twice daily in patients weighing less than 85 Kg or 50 mg twice daily in patients weighing more than 85 Kg. Patients should be monitored for 2-3 hours after initiation and after each dose increase.

This drug should be administered to patients with left ventricular ejection fraction less than 45% and cardiac rate more than 65 times/min during a break and stable patients having fundamental treatment of angina at least before 4 weeks (in case of no change to NYHA class or basic treatment and no occurrence of hospitalization by aggravation of symptoms).

In case of every up-titration, physician should certainly check whether aggravation of cardiac failure and side effects by vasodilatation (e.g. descending blood pressure and dizziness) to patients, regular medical examination (e.g. renal function, weight, blood pressure and cardiac rate etc.) should be instituted. In congestive heart failure patients, worsening cardiac failure or fluid retention may occur during up-titration of carvedilol. If such symptoms occur, diuretic should be increased and the carvedilol dose should not be advanced until clinical stability resumes. Occasionally, it may be necessary to lower the carvedilol dose or temporarily discontinue it. When given again after discontinuing administration over 2 weeks, it should start from initial dose (3.125 mg, twice a day).

Or as prescribed by the physician.

The safety and efficacy of carvedilol in patients under 18 years have not been established.

CONTRAINDICATIONS

Patients with cardiogenic shock or those with NYHA (New York Heart Association) Class IV decompensated heart failure requiring IV inotropic support.

Patients with respiratory disease such as asthma and Chronic Obstructive Pulmonary Disease (COPD) with a bronchospastic component.

Patients with secondary hypertension.

Patients with acute pulmonary arterial embolism.

Patients who especially stimulate or block cardiac conduction such as 2nd and 3rd-degree AV block, sick-sinus syndrome and sinoatrial block.

Patients with severe bradycardia.

Patients with metabolic acidosis.

Patients taking MAO inhibitor (excluding MAO-B inhibitor).

Patients with severe hypotension (systolic blood pressure < 90 mmHg).

Patients with hypersensitivity to this drug.

Patients with hepatic impairment.

Patients with acute myocardial infarction within 4 weeks after onset of disease.

Patients with sick sinus syndrome.

WARNINGS & PRECAUTIONS

Patients with pheochromocytoma.

Care should be taken in the administration of carvedilol to patients with diabetes mellitus, as the early signs and symptoms of acute hypoglycemia may be masked or attenuated. In congestive heart failure patients with diabetes, the use of carvedilol may be associated with worsening control of blood glucose. Therefore, regular monitoring of blood glucose is required in diabetics when carvedilol is initiated or up-titrated and hypoglycemic therapy adjusted accordingly.

Care should be taken in administration of carvedilol to patients with a history of serious hypersensitivity reactions and in those undergoing desensitization therapy as β -blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions.

Patients with a history of psoriasis associated with β -blocker therapy should take carvedilol only after consideration of the risk-benefit ratio.

When administered to patients who have ischemic heart disease, diffuse angiosis or renal adequacy with hypotension (systolic blood pressure < 100 mmHg), reversible renal dysfunction may occur. Therefore, in case of initial administration and dosage increase, renal function should be monitored. So, dosage of this drug should be reduced or discontinued in case of aggravation of renal dysfunction.

Clinical experiences of unstable angina have been few. It should be taken with caution in administering this drug to patients who have these signs or symptoms.

Since β -blocker may aggravate or stimulate symptoms of blood flow, patients with peripheral vascular disease should be careful, particularly in case of Raynaud's disease, symptoms may be aggravated.

When it is administered initially or dosage is increased to patients with cardiac failure over NYHA class II, insufficiency of salts and/or body fluids (administering high dosage of diuretic), hypotension (administration of initial systolic BP less than 100 mmHg) and the elderly over 70 years, effects of descending blood pressure may be amplified. Therefore, it should be taken with caution and observed until 2 hours after administration.

When treatment with carvedilol and clonidine together is to be terminated, carvedilol should be withdrawn first, several days before gradually decreasing the dosage of clonidine (Except in case of some adequate reason).

Carvedilol treatment should not be discontinued abruptly (particularly, frequency and pain of angina seizure may be severe in patients suffering from chronic stable angina and ischemic heart disease, rarely, myocardial infarction or transient blood pressure rise may occur). The withdrawal of carvedilol in these patients should be gradual (1-2 weeks).

Agents with non-selective β -blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There has been no clinical experience with carvedilol in these patients although the α -blocking activity may prevent such symptoms. However, caution should be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.

When cardiac rate drops to less than 55 times/min, dosage is gradually reduced and it should be carefully administered in case of 1st degree AV block.

Carvedilol, like other agents with β -blocking properties, may obscure the symptoms of cardiotoxicity.

Wearers of contact lenses should bear in mind the possibility of reduced lacrimation.

Individual varying reactions can impair alertness such as patients' capacity for driving or operating machinery. This applies particularly when starting or changing treatment and in conjunction with alcohol.

ADVERSE EFFECTS

Central nervous system: Occasionally, dizziness, headache and fatigue may occur. These symptoms are commonly mild and especially occur in the initial therapy. Rarely, hallucination, opposition, depression, sleep disorder, incubus and psychosis may occur.

Cardiovascular system: Serious side effects such as high-degree bradycardia and complete AV block and cardiac failure. Cardiac function test should be regularly performed. If those symptoms appear, appropriate treatment should be instituted to reduce dose or discontinue administration.

When taking this drug initially, increasing dose or suddenly standing up, blood pressure may be rarely remarkably low. Loss of consciousness may occur with symptoms such as dizziness and blurred eye vision.

Frequently, pulse frequency may be reduced and rarely, extremity frigidity may occur. These symptoms may be worse in patients with intermittent claudication, Raynaud's disease, angina, edema and Prinzmetal's angina.

Dizziness may frequently occur in patients with cardiac failure, edema of variant nidus and size (especially in case of dosage increase) aggravation of AV block and cardiac failure may rarely occur.

Kidney: Systemic vascular disorder may occur or renal function may be worse or rarely, renal failure may occur in patients with impaired renal function. Acute renal failure and renal abnormalities have been reported in patients with heart failure who also suffered from diffuse vascular disease and/or renal impairment.

Respiratory system: Resistance of respiratory tract may be increased. Dyspnoea and asthmatic attack, stuffy nose may rarely occur in patients with bronchospasms.

Gastrointestinal system: Nausea, diarrhea, abdominal pain and vomiting and constipation may rarely occur.

Skin: Urticaria, pruritus and lichen planus-like reaction have been reported. Allergic exanthema may rarely occur. Drugs having β -blocking activity may cause psoriasis vulgaris, aggravate symptom of this disease or cause psoriasis eruption.

Haematology: Change in liver function indicator (e.g. serum transaminases), thrombocytopenia and leucopenia have been rarely reported.

Metabolic: Due to the β -blocking properties, it is also possible for latent diabetes mellitus to be manifested, manifested diabetes to be aggravated and blood glucose counter-regulation to be inhibited. Hypercholesterolaemia, weight increase and hyperglycaemia in patients with pre-existing diabetes mellitus may occur in patients with heart function failure.

Hepatic: Liver function abnormalities, reversible on stopping treatment with carvedilol, have been reported rarely.

Others: Frequently, pain in the extremities, rarely, disorder of sensation (paraesthesia), disturbed vision, eye irritation, dryness of the mouth, disturbances of micturition and sexual impotence may occur.

DRUG INTERACTIONS

Following concomitant administration of carvedilol and digoxin, steady-state trough concentrations of digoxin were increased by approximately 13%, 16% in hypertensive patients. Increased monitoring of digoxin levels is recommended when initiating, adjusting or discontinuing carvedilol. When given concomitantly with cardiac glycoside, cardiac rate may be remarkably low and AV conduction may be delayed.

Reaction of drugs having other activity of descending blood pressure or descending blood pressure as side effects like sedatives such as barbiturate and phenothiazine, antidepressant, vasodilator, alcohol, etc. may be increased and when given concomitantly with reserpine, guanethidine, methyl dopa, clonidine and guanfacine, cardiac rate may be more reduced.

Isolated cases of conduction disturbances (rarely with haemodynamic compromise) have been observed when carvedilol and diltiazem were co-administered orally. Therefore, as with other drugs with β -blocking activity, careful monitoring of ECG and blood pressure should be undertaken when concomitantly administering calcium-channel blockers of the verapamil or diltiazem type, or class I antiarrhythmic drugs. These drugs should not be co-administered IV. Cyclo-oxygenase inhibitor (e.g. acetyl salicylic acid and corticosteroid etc.) may reduce effect of descending blood pressure.

The effects of insulin or oral hypoglycemics may be enhanced. The signs and symptoms of hypoglycemia may be masked or attenuated (especially tachycardia).

Care may be required in those patients receiving inducers of mixed function oxidases such as rifampicin, as serum levels of carvedilol may be reduced or inhibitors of mixed function oxidases such as cimetidine, as serum levels may be increased.

Careful attention must be paid during anaesthesia to the synergistic negative inotropic and hypotensive effects of carvedilol and anesthetic drugs.

It is recommended that cyclosporine concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporine be adjusted as appropriate.

USE IN PREGNANCY AND LACTATION

There is no adequate clinical experience with carvedilol in pregnant women. Carvedilol should not be used during pregnancy unless the anticipated benefits outweigh the potential risks.

Carvedilol and/or its metabolites are excreted in breast milk. Therefore, breastfeeding is not recommended during administration of carvedilol.

OVERDOSAGE

Overdosage may cause severe hypotension, bradycardia, cardiac insufficiency, cardiogenic shock and cardiac arrest. Respiratory problems, bronchospasms, vomiting, lapses of consciousness and generalized seizures may also occur. If these symptoms occur, patients should consult a physician. Apply supportive treatment as necessary.

CAUTION

FOODS, DRUGS, DEVICES AND COSMETICS Act prohibits dispensing without prescription.

STORAGE

Store at temperatures not exceeding 30°C. Protect from light.

AVAILABILITY

In Alu-PVC Blister Pack of 10's; Box of 100's.

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