Carvedilol

Core Safety Profile

Alpha (a) and beta (b) adrenergic receptor blocking agents
Pharmaceutical form and dosages
Tablets: 3.125 mg, 6.25 mg, 12.5 mg and 25 mg
Active ingredient: carvedilol

4.3 Contraindications

Hypersensitivity to carvedilol or any component of the product
Unstable/decompensated heart failure
Clinically manifest liver dysfunction
2nd and 3rd degree AV block (unless a permanent pacemaker is in place)
Severe bradycardia (<50 bpm)
Sick sinus syndrome (including sino-atrial block)
Severe hypotension (systolic blood pressure <85 mmHg)
Cardiogenic shock
History of bronchospasm or asthma

4.4 Special warnings and precautions for use

Chronic Congestive Heart Failure

In congestive heart failure patients, worsening cardiac failure or fluid retention may occur during up-titration of carvedilol. If such symptoms occur, diuretics 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, in rare cases, temporarily discontinue it.
Such episodes do not preclude subsequent successful titration of carvedilol. Carvedilol should be used with caution in combination with digitalis glycosides, as both drugs slow AV conduction.

Renal function in Congestive Heart Failure

Reversible deterioration of renal function has been observed with carvedilol therapy in chronic heart failure patients with low blood pressure (systolic BP <100 mmHg), ischaemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency.

Left ventricular dysfunction following acute myocardial infarction

Before treatment with carvedilol is initiated the patient must be clinically stable and should have received an ACE inhibitor for at least the preceding 48 hours, and the dose of the ACE inhibitor should have been stable for at least the preceding 24 hours.

Chronic obstructive pulmonary disease

Carvedilol should be used with caution, in patients with chronic obstructive pulmonary disease (COPD) with a bronchospastic component who are not receiving oral or inhaled medication, and only if the potential benefit outweighs the potential risk.
In patients with a tendency to bronchospasm, respiratory distress can occur as a result of a possible increase in airway resistance. Patients should be closely

monitored during initiation and up-titration of carvedilol and the dose of carvedilol should be reduced if any evidence of bronchospasm is observed during treatment.

Diabetes
Care should be taken in the administration of carvedilol to patients with diabetes mellitus, as the early signs and symptoms of acute hypoglycaemia may be masked or attenuated. In chronic heart failure patients with diabetes, the use of carvedilol may be associated with worsening control of blood glucose.

Peripheral vascular disease
Carvedilol should be used with caution in patients with peripheral vascular disease as b-blockers can precipitate or aggravate symptoms of arterial insufficiency.

Raynaud's phenomenon
Carvedilol should be used with caution in patients suffering from peripheral circulatory disorders (eg Raynaud's phenomenon) as there may be exacerbation of symptoms.

Thyrotoxicosis
Carvedilol may obscure the symptoms of thyrotoxicosis.

Anesthesia and major surgery
Caution should be exercised in patients undergoing general surgery, because of the synergistic negative inotropic effects of carvedilol and anaesthetic drugs.

Bradycardia
Carvedilol may induce bradycardia. If the patient’s pulse rate decreases to less than 55 beats per minute, the dosage of carvedilol should be reduced.

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

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

Concomitant use of calcium channel blockers
Careful monitoring of ECG and blood pressure is necessary in patients receiving concomitant therapy with calcium channel blockers of the verapamil or diltiazem type or other antiarrhythmic drugs.

Pheochromocytoma
In patients with pheochromocytoma, an a-blocking agent should be initiated prior to the use of any b-blocking agent. Although carvedilol has both a- and b-blocking pharmacological activities, there is no experience with its use in this condition. Caution should therefore be taken in the administration of carvedilol to patients suspected of having pheochromocytoma.

Prinzmetal's variant angina
Agents with non-selective b-blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There is no clinical experience with carvedilol in these patients although the a-blocking activity of carvedilol may prevent such symptoms. Caution should, however, be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.

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

Withdrawal syndrome
Carvedilol treatment should not be discontinued abruptly, particularly in patients suffering from ischaemic heart disease. The withdrawal of carvedilol should be gradual (over a period of two weeks).
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions
Digoxin: Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Both digoxin and carvedilol slow AV conduction. Increased monitoring of digoxin levels is recommended when initiating, adjusting or discontinuing carvedilol.

Insulin or oral hypoglycemics: Agents with β-blocking properties may enhance the bloodsugar- reducing effect of insulin and oral hypoglycemics. The signs of hypoglycaemia may be masked or attenuated (especially tachycardia). In patients taking insulin or oral hypoglycemics, regular monitoring of blood glucose is therefore recommended.

Inducers and inhibitors of hepatic metabolism: Rifampicin reduced plasma concentrations of carvedilol by about 70% Cimetidine increased AUC by about 30% but caused no change in Cmax. Care may be required in those patients receiving inducers of mixed function oxidases eg rifampicin, as serum levels of carvedilol may be reduced, or inhibitors of mixed function oxidases eg cimetidine, as serum levels of carvedilol may be increased.

However, based on the relatively small effect of cimetidine on carvedilol drug levels, the likelihood of any clinically important interaction is minimal.

Catecholamine-depleting agents: Patients taking both agents with β-blocking properties and a drug that can deplete catecholamines (eg reserpine and monoamine oxidase inhibitors) should be observed closely for signs of hypotension and/or severe bradycardia.

Cyclosporin: Modest increases in mean trough cyclosporin concentrations were observed following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30% of patients, the dose of cyclosporin had to be reduced in order to maintain cyclosporin concentrations within the therapeutic range, while in the remainder no adjustment was needed. On average, the dose of cyclosporin was reduced about 20% in these patients. Due to wide interindividual variability in the dose adjustment required, it is recommended that cyclosporin concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporin be adjusted as appropriate.

Verapamil, diltiazem, or other antiarrhythmics: In combination with carvedilol can increase the risk of AV conduction disturbances (see section 4.4 Special warnings and precautions for use).

Pharmacodynamic interactions
Clonidine: Concomitant administration of clonidine with agents with β-blocking properties may potentiate blood-pressure- and heart-rate-lowering effects. When concomitant treatment with agents with β-blocking properties and clonidine is to be terminated, the β-blocking agent should be discontinued first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage.

Calcium channel blockers (see section 4.4 Special warnings and precautions for use). Isolated cases of conduction disturbance (rarely with haemodynamic compromise) have been observed when carvedilol is co-administered with diltiazem. As with other agents with β-blocking properties, if carvedilol is to be administered orally with calcium channel blockers of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored.

As with other agents with b-blocking activity, carvedilol may potentiate the effect of other concomitantly administered drugs that are anti-hypertensive in action (eg a1-receptor antagonists) or have hypotension as part of their adverse effect profile.

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

4.6 Pregnancy and lactation

There is no adequate clinical experience with carvedilol in pregnant women.
Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development (see section 5.3). The potential risk for humans is unknown.
Carvedilol should not be used during pregnancy unless the potential benefit outweighs the potential risk.
Beta blockers reduce placental perfusion, which may result in intrauterine foetal death, and immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia) may occur in the foetus and neonate. There may be an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Animal studies have not shown substantive evidence of teratogenicity with carvedilol (see also section 5.3).

Animal studies demonstrated that carvedilol or its metabolites are excreted in breast milk. It is not known whether carvedilol is excreted in human milk. Breast feeding is therefore not recommended during administration of carvedilol.

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects of carvedilol on patients' fitness to drive or to operate machinery.
Because of individually variable reactions (e.g. dizziness, tiredness), the ability to drive, operate machinery, or work without firm support may be impaired. This applies particularly at the start of treatment, after dose increases, on changing products, and in combination with alcohol.

4.8 Undesirable Effects

(a) Summary of the safety profile
The frequency of adverse reactions is not dose-dependent, with the exception of dizziness, abnormal vision and bradycardia.

(b) Tabulated list of adverse reactions
The risk of most adverse reactions associated with carvedilol is similar across all indications. Exceptions are described in subsection (c).

Frequency categories are as follows:
Very common ≥ 1/10
Common ≥ 1/100 and < 1/10
Uncommon ≥ 1/1,000 and < 1/100
Rare ≥ 1/10,000 and < 1/1,000
Very rare < 1/10,000

Infections and infestations
Common: Bronchitis, pneumonia, upper respiratory tract infection, urinary tract infection

Blood and lymphatic system disorders
Common: Anaemia
Rare: Thrombocytopaenia
Very rare: Leukopenia

Immune system disorders
Very rare: Hypersensitivity (allergic reaction)

Metabolism and nutrition disorders
Common: Weight increase, hypercholesterolaemia, impaired blood glucose control (hyperglycaemia, hypoglycaemia) in patients with pre-existing diabetes

Psychiatric disorders
Common: Depression, depressed mood
Uncommon: Sleep disorders

Nervous system disorders
Very common: Dizziness, headache

Uncommon: Presyncope, syncope, paraesthesia

Eye disorders
Common: Visual impairment, lacrimation decreased (dry eye), eye irritation

Cardiac disorders
Very common: Cardiac failure
Common: Bradycardia, oedema, hypervolaemia, fluid overload
Uncommon: Atrioventricular block, angina pectoris

Vascular disorders
Very common: Hypotension
Common: Orthostatic hypotension, disturbances of peripheral circulation (cold extremities, peripheral vascular disease, exacerbation of intermittent claudication and Reynaud's phenomenon)

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea, pulmonary oedema, asthma in predisposed patients
Rare: Nasal congestion

Gastrointestinal disorders
Common: Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain
Hepatobiliary disorders
Very rare: Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gammaglutamyltransferase (GGT) increased

Skin and subcutaneous tissue disorders
Uncommon: Skin reactions (e.g. allergic exanthema, dermatitis, urticaria, pruritus, psoriatic and lichen planus like skin lesions), alopecia

Musculoskeletal and connective tissue disorders
Common: Pain in extremities

Renal and urinary disorders
Common: Renal failure and renal function abnormalities in patients with diffuse vascular disease and/or underlying renal insufficiency, micturition disorders
Very rare: Urinary incontinence in women

Reproductive system and breast disorders
Uncommon: Erectile dysfunction

General disorders and administration site conditions
Very common: Asthenia (fatigue)
Common: Pain

(c) Description of selected adverse reactions

Dizziness, syncope, headache and asthenia are usually mild and are more likely to occur at the beginning of treatment.
In patients with congestive heart failure, worsening cardiac failure and fluid retention may occur during up-titration of carvedilol dose (see section 4.4).

Cardiac failure is a commonly reported adverse event in both placebo and carvedilol-treated patients (14.5% and 15.4% respectively, in patients with left ventricular dysfunction following acute myocardial infarction).
Reversible deterioration of renal function has been observed with carvedilol therapy in chronic heart failure patients with low blood pressure, ischaemic heart disease and diffuse vascular disease and/or underlying renal insufficiency (see section 4.4).
As a class, beta-adrenergic receptor blockers may cause latent diabetes to become manifest, manifest diabetes to be aggravated, and blood glucose counter-regulation to be inhibited.
Carvedilol may cause urinary incontinence in women which resolves upon discontinuation of the medication.

4.9 Overdose

Symptoms and signs
In the event of overdose, there may be severe hypotension, bradycardia, heart failure, cardiogenic shock and cardiac arrest. There may also be respiratory problems, bronchospasm, vomiting, disturbed consciousness and generalised seizures.

Treatment
In addition to general supportive treatment, the vital parameters must be monitored and corrected, if necessary, under intensive care conditions.
Atropine can be used for excessive bradycardia, while to support ventricular function intravenous glucagon, or sympathomimetics (dobutamine, isoprenaline) are recommended. If positive inotropic effect is required, phosphodiesterase inhibitors (PDE) should be considered. If peripheral vasodilation dominates the intoxication profile then norfenephrine or noradrenaline should be administered with continuous monitoring of the circulation. In the case of drug-resistant bradycardia, pacemaker therapy should be initiated.
For bronchospasm, β-sympathomimetics (as aerosol or intravenous) should be given, or aminophylline may be administered intravenously by slow injection or infusion. In the event of seizures, slow intravenous injection of diazepam or clonazepam is recommended.
In cases of severe overdose with symptoms of shock, supportive treatment must be continued for a sufficiently long period, i.e. until the patient's condition has stabilised, as a prolongation of elimination half-life and redistribution of carvedilol from deeper compartments are to be expected.