SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Carvedilol EG 6.25 mg tablets
Carvedilol EG 25 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 6.25 mg of carvedilol.

Excipients with known effect:
One tablet contains 72.25 mg lactose monohydrate and 5.00 mg sucrose.

One tablet contains 25 mg of carvedilol.

Excipients with known effect:
One tablet contains 85.00 mg lactose monohydrate and 60.00 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Length: 8.8-9.2mm, width: 3.8-4.2mm, thickness: 2.6-3.3mm oval tablets, slightly biconvex and white, with a break line on one side and S2 on the other side. The tablets can be divided into equal doses.

Diameter: 7.8-8.2mm, thickness: 3.1-3.8mm round, slightly biconvex, white tablets with a beveled edge and a break line on one side. The tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Essential hypertension
- Chronic stable angina pectoris

Adjunctive treatment of moderate to severe stable chronic heart failure

4.2 Posology and method of administration

Posology
Carvedilol EG is available in 2 strengths: 6.25 mg and 25 mg tablets.

Essential hypertension
Carvedilol EG can be used in the treatment of hypertension alone or in combination with other antihypertensive agents, including thiazide diuretics. It is recommended to take a single daily dose; however, the maximum recommended single dose is 25 mg and the maximum recommended daily dose is 50 mg.

Adults

The recommended starting dose is 12.5 mg once daily for the first two days. The treatment is then continued based on a dosage of 25 mg / day. If necessary, the dosage may be gradually increased at intervals of two weeks or more rarely.

Elderly patients
The recommended starting dose for hypertension is 12.5 mg once daily which may be sufficient for continued treatment. However, if this dosage does not produce the desired therapeutic result, it may be gradually increased at intervals of two weeks or more rarely.

Chronic stable angina pectoris
It is recommended to take a dose twice a day.

Adults
The recommended initial dosage is 12.5 mg twice a day for the first two days. Thereafter, the treatment is continued at the dose 25 mg twice a day. If necessary, the dose may be further increased gradually at intervals of two weeks or more rarely to the recommended maximum dose of 100 mg a day divided into two doses (twice daily).

Elderly patients
The recommended initial dose is 12.5 mg twice daily for two days. Thereafter, the treatment is continued at the dose 25 mg twice daily, which is the recommended maximum daily dose.

Heart failure
Carvedilol is given in moderate to severe heart failure in addition to conventional basic therapy with diuretics, ACE inhibitors, digitalis, and/or vasodilators. The patient should be clinically stable (no change in NYHA-class, no hospitalisation due to heart failure) and the basic therapy must be stabilized for at least 4 weeks prior to treatment. Additionally, the patient should have a reduced left ventricular ejection fraction and heart rate should be > 50 bpm and systolic blood pressure > 85 mm Hg (see section 4.3).

The initial dose is 3.125 mg twice a day for two weeks. If this dose is tolerated, the dose may be increased slowly with intervals of not less than two weeks up to 6.25 mg twice a day, then up to 12.5 mg twice a day and finally up to 25 mg twice a day. The dosage should be increased to the highest tolerable level.

The recommended maximum dosage is 25 mg twice a day for patients with a body weight of less than 85 kg, and 50 mg twice a day for patients with a body weight above 85 kg, provided that the heart failure is not severe. A dose increase to 50 mg twice daily should be performed carefully under close medical supervision of the patient.

Transient worsening of symptoms of heart failure may occur at the beginning of treatment or due to a dose increase, especially in patients with severe heart failure and/or under high dose diuretic treatment. This does usually not call for discontinuation of treatment, but dose should not be increased. The patient should be monitored by a physician/cardiologist for two hours after starting treatment or increasing the dose. Before each dose increase, an examination should be performed for potential symptoms of worsening heart failure or for symptoms of excessive vasodilatation (e.g. renal function, body weight, blood pressure, heart rate and rhythm). Worsening of heart failure or fluid retention is treated by increasing the dose of diuretic, and the dose of carvedilol should not be increased until the patient is stabilized. If bradycardia appears or in case of lengthening of AV conduction, the level of digoxin should first be monitored. Occasionally it may be necessary to reduce the carvedilol dose or temporarily discontinue treatment altogether. Even in these cases, carvedilol dose titration can often be successfully continued.

Renal function, thrombocytes and glucose (in case of NIDDM and/or IDDM) should be monitored regularly during dose titration. However, after dose titration the frequency of monitoring can be reduced.

If carvedilol has been withdrawn for more than two weeks, the therapy should be reinitiated with 3.125 mg twice a day and increased gradually according to the above recommendations.

Special populations

Renal insufficiency
Dosage must be determined for each patient individually, but according to pharmacokinetic parameters there is no evidence that dose adjustment of carvedilol in patients with renal impairment is necessary.

Moderate hepatic insufficiency
Dosage adjustment may be necessary.

Children and adolescents (<18 years old)
Efficacy and safety data for carvedilol are insufficient.

Elderly patients
Elderly patients may be more susceptible to the effects of carvedilol and should be monitored more carefully.

As with other beta-blockers and especially in patients with coronary disease, the withdrawal of carvedilol should be done gradually (see section 4.4).

Method of administration

The tablets should be swallowed with an adequate amount of liquid. They should not be taken with food. Taking carvedilol with food is however recommended in patients with heart failure to allow for slower absorption and to reduce the risk of orthostatic hypotension.

The tablets can be divided into equal doses.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Unstable / decompensated heart failure, cardiac insufficiency belonging to the class NYHA IV of the classification of cardiac insufficiencies that require intravenous inotropic treatment
- History of bronchospasm or asthma
- Chronic obstructive pulmonary disease with bronchial obstruction or asthma (see section 4.4)
- Clinically significant hepatic dysfunction
- AV block of the second or third degree (unless a permanent pacemaker is in place)
- Severe bradycardia (<50 beats / min.)
- Sinus bradycardia (including sinoatrial block)
- Cardiogenic shock
- Severe hypotension (systolic blood pressure <85 mmHg)
- Metabolic acidosis
- Concomitant intravenous treatment with verapamil or diltiazem (see section 4.5)

4.4 Special warnings and precautions for use

Chronic congestive heart failure
In patients with chronic heart failure, carvedilol should be administered first in combination with diuretics, ACE inhibitors, digitalis and / or vasodilators. Treatment should be started under the supervision of a hospital doctor. Treatment can begin only if the patient's condition is stabilized on conventional basic therapy for at least 4 weeks. Patients with severe heart failure, hyponatremia and hypovolemia, elderly patients or those with low baseline blood pressure should be monitored for

approximately two hours after the first dose or after an increase in dosage, given the risks of hypotension. Hypotension following excessive vasodilation is treated first by reducing the dosage of the diuretic. If symptoms persist, the dosage of the ACE inhibitor / AIIRA may be reduced. At the beginning of treatment or during up-titration of carvedilol, there may be worsening of heart failure or fluid retention. In these cases, it is necessary to increase the dosage of the diuretic. However, the reduction or discontinuation of carvedilol may sometimes be necessary. The dosage of carvedilol may not be increased until symptoms due to worsening of heart failure or hypotension following vasodilation are under control.

In patients with chronic heart failure treated with digitalis, carvedilol should be given with caution, as digitalis and carvedilol both lengthen the AV conduction time (see section 4.5).

Renal function in congestive heart failure
Reversible deterioration of renal function has been observed during treatment with carvedilol in patients with heart failure and low blood pressure (systolic <100 mm Hg), ischemic heart disease and atherosclerosis, diffuse vascular disease, and or underlying renal failure. In patients with heart failure and with these risk factors, renal function should be monitored during dose titration of carvedilol. If significant worsening of renal function occurs, the dosage of carvedilol should be decreased or treatment stopped.

Dysfunction of the left ventricle after acute myocardial infarction
Before initiation of carvedilol treatment, the patient must be clinically stable and have received an ACE inhibitor for at least 48 hours, and the dose of the ACE inhibitor must have been stable for at least 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 benefits outweigh the potential risk. In patients with a tendency towards bronchospasms, respiratory distress may occur due to a possible increase in airway resistance. Patients should be carefully monitored during initiation of treatment and up-titration of carvedilol and the dosage of carvedilol should be reduced if evidence of bronchospasm is observed during treatment.

Diabetes
Carvedilol may mask symptoms and signs of acute hypoglycemia. Impaired blood glucose control may occasionally occur in patients with diabetes mellitus and heart failure in connection with the use of carvedilol. Therefore, close monitoring of diabetic patients receiving carvedilol is required by means of regular blood glucose measurements, especially during dose titration, and adjustment of antidiabetic medication as necessary (see section 4.5). Blood glucose levels should also be carefully monitored after a long period of fasting.

Peripheral vascular disease
Carvedilol should be used with caution in patients with peripheral vascular disease as β-blockers may accelerate or worsen symptoms of arterial insufficiency.

Raynaud's syndrome
Carvedilol should be used with caution in patients with peripheral circulatory disorders (eg, Raynaud's syndrome) as symptoms may worsen.

Thyrotoxicosis
Carvedilol may mask 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 anesthetic agents.

Although beta-blockers reduce the risk of arrhythmias during anesthesia, the risk of hypotension may increase. Therefore, caution should be used when certain anesthetics are used. More recent studies, however, suggest that beta-blockers have a positive effect in preventing perioperative cardiac morbidity and in reducing the incidence of cardiovascular complications.

Bradycardia
Carvedilol can cause bradycardia. If the heart rate falls below 55 beats per minute, the dose of carvedilol should be decreased.

Hypersensitivity
Special attention is required when carvedilol is administered to patients with a history of severe hypersensitivity reactions and to patients on desensitization therapy, as beta-blockers may increase sensitivity to allergens and the severity of anaphylactic reactions.

Psoriasis
Patients with a history of psoriasis associated with beta-blocker therapy should take carvedilol only after a benefit / risk assessment.

Concomitant use of calcium channel blockers
Close monitoring of ECG and blood pressure is necessary in patients treated with calcium channel blockers such as verapamil or diltiazem or with other antiarrhythmics.

Pheochromocytoma
In patients with pheochromocytoma, alpha-blocker therapy should be initiated prior to the use of any beta-blocker. Although carvedilol has alpha and beta blocking activity, there is not enough experience with this disease. Caution is therefore recommended in these patients.

Prinzmetal's variant angina
Agents with nonselective beta-blocking activity may cause chest pain in patients with Prinzmetal's angina. Although the alpha blocking activity of carvedilol may prevent such symptoms, there is no clinical experience with carvedilol in these patients. However, caution is advised when carvedilol is administered to patients suspected of having Prinzmetal's angina.

Contact lenses
Wearers of contact lenses should be warned of a risk of reduced tear secretion.

Withdrawal syndrome
As with other beta-blockers, carvedilol should not be stopped abruptly. This is particularly applicable for patients with ischemic heart disease. Treatment with carvedilol should be stopped gradually over two weeks, for example by reducing the daily dose by half every three days. If necessary, alternative treatment should be initiated at the same time to prevent further angina pectoris.

Other warnings
Patients who are known as poor metabolizers of debrisoquine, should be closely monitored during initiation of therapy (see section 5.2).

Since there is limited clinical experience, carvedilol should not be administered in patients with labile or secondary hypertension, orthostasis, acute inflammatory heart disease, haemodynamic relevant obstruction of heart valves or outflow tract, end-stage peripheral arterial disease, concomitant treatment with α1-receptor antagonist or α2-receptor agonist.

Due to its negative dromotropic effect, carvedilol should be administered with caution to patients with first-degree heart block.

Excipients
This medicine contains lactose. This medicine is contraindicated in patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption syndrome (rare hereditary diseases).

This medicine contains sucrose. This drug is contraindicated in patients with fructose intolerance, glucose-galactose malabsorption or sucrase/isomaltase deficiency (rare hereditary diseases).

4.5 Interactions with other drugs and other forms of interactions

Pharmacokinetic interactions
Carvedilol is a substrate and inhibitor of P-glycoprotein. Therefore, the bioavailability of drugs transported by P-glycoprotein can be increased with concomitant carvedilol administration. In addition, the bioavailability of carvedilol can be modified by inducers or inhibitors of P-glycoprotein.

Inhibitors and inducers of CYP2D6 and CYP2C9 may alter stereoselective systemic and/or pre-systemic metabolism of carvedilol, resulting in increased or decreased plasma concentrations of R- and S-enantiomers of carvedilol. Some examples observed in patients or healthy subjects are indicated below, but the list is not exhaustive.

Digoxin/digitoxin
An increase of steady state digoxin levels by approximately 16% and of digitoxin by approximately 13% has been seen in connection with the concomitant use of carvedilol and digoxin. Digoxin and carvedilol slow AVII conduction. More frequent monitoring of plasma digoxin concentrations is recommended when initiating, discontinuing or adjusting treatment with carvedilol (see section 4.4).

Inducers and inhibitors of hepatic metabolism
In a study in 12 healthy subjects, rifampicin administration decreased carvedilol plasma concentrations by approximately 70%, most likely by induction of P-glycoprotein resulting in decreased intestinal absorption of carvedilol. Cimetidine increased AUC by approximately 30% but did not result in a change in Cmax. However, based on the relatively limited effect of cimetidine on carvedilol levels, the likelihood of any clinically important interaction occurring is minimal. Patients receiving drugs that induce (eg, rifampicin and barbiturates) or inhibit (eg, cimetidine, ketoconazole, fluoxetine, haloperidol, verapamil, erythromycin, clarithromycin, telithromycin) cytochrome P450 enzymes should be used with care in case of concomitant treatment with carvedilol, because enzyme inducers may reduce carvedilol serum concentrations while enzyme inhibitors may increase serum carvedilol concentrations.

Ciclosporin
Two studies in patients who had undergone renal or cardiac transplantation and received ciclosporin orally, showed increased plasma concentrations of ciclosporin after initiation of carvedilol treatment. Approximately 30% of the patients had to reduce the ciclosporin dose to maintain ciclosporin concentrations within the therapeutic range, while no adjustment was required for other patients. On average, the dose of ciclosporin was reduced by approximately 20% in these patients. Due to the large interindividual variability of the required dosage adjustment, it is recommended to monitor ciclosporin concentrations closely after initiating carvedilol treatment and to adjust the ciclosporin dosage if necessary.

Antiarrhythmics
Close monitoring should be done in case of co-administration of carvedilol and amiodarone therapy (oral) or class I antiarrhythmics. Bradycardia, cardiac arrest, and ventricular fibrillation have been reported shortly after initiation of beta-blocker treatment in patients receiving amiodarone. There is a risk of cardiac failure in case of class Ia or Ic antiarrhythmics concomitant intravenous therapy.

Amiodarone
In patients with heart failure, amiodarone decreased the clearance of S-carvedilol, probably by inhibition of CYP2C9. The mean plasma concentration of R-carvedilol was not influenced. Consequently, there is a potential risk of increased β-blockade caused by an increase in the plasma concentration of S-carvedilol.

Fluoxetine
In a randomized crossover study in 10 patients with heart failure, concomitant use of potent CYP2D6 inhibitor fluoxetine resulted in stereoselective inhibition of carvedilol metabolism with a 77% increase in Average AUC of the R (+) enantiomer. However, between the treated groups no difference was found with respect to adverse effects, blood pressure or heart rate.

Pharmacodynamic interactions

Insulin or oral hypoglycemic agents
The reducing effect of blood sugar levels of insulin and oral diabetic medications can be augmented. Symptoms of hypoglycemia may be masked or reduced (especially tachycardia). In diabetic patients taking insulin or oral hypoglycemic agents, regular monitoring of blood glucose levels is required.

Antihypertensives or centrally acting MAOIs
Concomitant treatment with reserpine, guanethidine, methyldopa, guanfacine, and monoamine oxidase inhibitors (such as moclobemide or phenelzine, with the exception of MAOB inhibitors) may result in new hypotension and / or severe bradycardia. It is recommended to monitor vital functions.

Digoxin
The combination of beta-blockers and digoxin can lead to additional prolongation of atrioventricular (AV) conduction time.

Verapamil, diltiazem, amiodarone or other antiarrhythmic agents
In combination with carvedilol, these may increase the risk of AV conduction disorders (see section 4.4).

Clonidine
Concomitant administration of clonidine and agents with beta-blocking properties may intensify the reducing effects of blood pressure and heart rate. In case of withdrawal of both the beta-blocker and clonidine, the beta-blocker should be discontinued first. Clonidine treatment can be stopped a few days later by gradually reducing the dose.

Calcium antagonists
Isolated cases of conduction disturbances (rarely with haemodynamic risk) have been observed when carvedilol and diltiazem are co-administered. As with other agents with beta-blocking properties, ECG and blood pressure should be monitored if carvedilol is to be administered orally with calcium antagonists such as verapamil or diltiazem (see section 4.4).

Dihydropyridines
Administration of dihydropyridines (such as amlodipine, felodipine, nifedipine) and carvedilol should be closely monitored as heart failure and severe hypotension have been reported.

Other blood pressure lowering agents

Carvedilol may potentiate the effects of other concomitantly administered antihypertensive agents (e.g. alpha-1-receptor antagonists) and medicines with antihypertensive side effects such as barbiturates, phenothiazines, tricyclic antidepressants, vasodilators, and alcohol or have hypotension as part of their side effect profile.

Anesthetics
During anesthesia, particular attention should be given to the synergistic, negative inotrope and hypotensive effect of carvedilol and anesthetic agents (see section 4.4).

NSAIDs, estrogens and corticosteroids
The antihypertensive effect of carvedilol is decreased due to water and sodium retention.

Sympathomimetics with alphamimetic and betamimetic action
Risk of hypertension and excessive bradycardia.

Beta-agonist bronchodilators
Non-cardioselective beta-blockers counteract the bronchodilating effects of beta-agonist bronchodilators. Close monitoring of patients is recommended.

Ergotamine
Increased vasoconstriction

Neuromuscular blocking agents
Increased neuromuscular block.

Nitrates
Hypotensive effects increased.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no adequate clinical experience with carvedilol in pregnant women.

Studies in animals are insufficient for effects on pregnancy, embryonal/fetal development, parturition and postnatal development (see section 5.3). The potiential risk to humans is unknown.

Carvedilol should only be used in pregnant women if the potential benefit to the mother outweighs the potential risk.

Beta-blockers decrease placental perfusion, which can result in intrauterine fetal death, miscarriage, and premature birth. In addition, adverse effects may occur in the fetus and neonate (especially hypoglycemia, bradycardia, respiratory depression and hypothermia). There is an increased risk of cardiac and pulmonary complications for the newborn during the postnatal period. Animal studies have shown no substantial evidence of teratogenicity with carvedilol. Treatment should be stopped 2 to 3 days before the expected day of birth. If this is not possible, the newborn must be monitored for 2 to 3 days after birth.

Breastfeeding
Studies in animals have shown that carvedilol or its metabolites are excreted in breast milk. It is not known whether carvedilol is excreted in milk in women. Therefore, breastfeeding is not recommended during treatment with carvedilol.

4.7 Effects on ability to drive and use machines

The effects of carvedilol on the ability to drive or use machines have not been studied.

Due to the individual variability of the reactions (e.g. dizziness, fatigue), the ability to drive, use machines or work without stable support may be impaired, especially at the start of treatment, after an increase in the dosage, when the medication is changed and if it is taken with alcohol.

4.8 Side effects

Summary of the safety profile

The frequency of adverse events is not dose-related, with the exception of dizziness, visual disturbances and bradycardia.

Table of adverse effects

The risk associated with most adverse effects associated with carvedilol is the same for all indications.

Exceptions are destailed in the description of selected adverse reactions subsection.

In this section, the frequencies of side effects are defined as follows: Very common (≥ 1/10); common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000); frequency not known (cannot be estimated from the data available).

	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations		Bronchitis, pneumonia, upper respiratory tract infection, urinary tract infection			
Blood and lymphatic system disorders		Anaemia		Thrombocytopaenia	Leukopenia
Immune system disorders					Hypersensitivity (allergic reaction)
Metabolism and nutrition disorders		Weight increase, hypercholesterolaemia, impaired blood glucose control (hyperglycaemia, hypoglycaemia) in patients with pre-existing diabetes			
Psychiatric disorders		Depression, depressed mood	Sleep disorders, confusion		
Nervous system disorders	Dizziness, headache		Presyncope, syncope, paraesthesia		
Eye disorders		Visual impairment, lacrimation decreased (dry eye), eye irritation			
Cardiac disorders	Cardiac failure	Bradycardia, oedema, hypervolaemia, fluid overload	Atrioventricular block, angina pectoris		

Vascular disorders	Hypotension	Orthostatic hypotension, disturbances of peripheral circulation (cold extremities, peripheral vascular disease, exacerbation of intermittent claudication and Reynaud's phenomenon)			
Respiratory, thoracic and mediastinal disorders		Dyspnoea, pulmonary oedema, asthma in predisposed patients		Nasal congestion	
Gastrointestinal disorders		Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain			
Hepatobiliary disorders					Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gammaglutamyltransferase (GGT) increased
Skin and subcutaneous tissue disorders			Skin reactions (e.g. allergic exanthema, dermatitis, urticaria, pruritus, psoriatic and lichen planus like skin lesions and increased sweating), alopecia		Severe cutaneous adverse reactions (e.g. Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)

Musculoskeletal and connective tissue disorders		Pain in extremities			
Renal and urinary disorders		Renal failure and renal function abnormalities in patients with diffuse vascular disease and/or underlying renal insufficiency, micturition disorders			Urinary incontinence in women
Reproductive system and breast disorders			Erectile dysfunction		
General disorders and administration site conditions	Asthenia (fatigue)	Pain			

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Belgium
AFMPS – Division Vigilance – Boîte Postale 97 – B-1000 Bruxelles Madou
Internet Site: www.afmps.be

Luxembourg
Centre Régional de Pharmacovigilance de Nancy
Bâtiment de Biologie Moléculaire et de Biopathologie (BBB)
CHRU de Nancy – Hôpitaux de Brabois
Rue du Morvan
54 511 VANDOEUVRE LES NANCY CEDEX
Tel.: (+33) 3 83 65 60 85 / 87
Fax: (+33) 3 83 65 61 33
E-mail: crpv@chru-nancy.fr

Or

Direction de la Santé
Division de la Pharmacie et des Médicaments
Allée Marconi – Villa Louvigny
L-2120 Luxembourg
Tel.: (+352) 2478 5592
Fax: (+352) 2479 5615
E-mail: pharmacovigilance@ms.etat.lu

Form link: http://www.sante.public.lu/fr/politique-sante/ministere-sante/directionsante/div-pharmacie-medicaments/index.html

4.9 Overdose

Symptoms
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 generalized 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 in cases of excessive bradycardia. To maintain cardiovascular function, administration of intravenous glucagon or sympathomimetics (dobutamine, isoprenaline) is recommended. If a positive inotropic effect is required, administration of phosphodiesterase (PDE) inhibitors should be considered. If peripheral vasodilatation is the predominant symptom of the intoxication pattern, norfenephrine or noradrenaline should be administered with continuous monitoring of the circulation. In case of drug-resistant bradycardia, it is recommended to place a pacemaker.

For bronchospasm, β-sympathomimetics (aerosol or intravenous) or intravenous aminophylline should be administered to the patient by slow injection or infusion. In the event of seizures, it is recommended to administer diazepam or clonazepam by slow intravenous injection.

In cases of severe overdose with symptoms of shock, supportive treatment should continue for a sufficiently long period of time, i.e. until the patient's condition has stabilised, as a prolongation of the elimination half-life and redistribution of carvedilol from deeper compartments is to be expected.

Carvedilol is highly protein-bound. Therefore, it cannot be eliminated by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha and beta blocking agents, ATC code: C07AG02

Carvedilol is a vasodilatory non-selective beta-blocker with antioxidant properties. It has been shown that vasodilation occurs mainly by blocking the selective alpha 1-receptor. Vasodilatation caused by carvedilol reduces peripheral vascular resistance and beta-blocking controls the renin-angiotensin system. Plasma renin activity is reduced and fluid retention is rare.

Carvedilol does not have intrinsic sympathomimetic activity (ISA). Like propranolol, it has membrane stabilising properties.

Carvedilol is a racemic compound that consists of two stereoisomers. In animal-based models, the two enantiomers showed a blocking effect on alpha-adrenergic receptors. Non-selective blockade of beta1 and beta2 adrenergic receptors is mainly caused by the S (-) enantiomer.

Carvedilol is a powerful antioxidant and absorbs free radicals from oxygen. The antioxidant properties of carvedilol and its metabolites have been demonstrated in in vitro and in vivo animal experiments and in vitro in a number of human cell types.

Clinical studies have shown that vasodilatation and beta-blockade caused by carvedilol have the following effects on patients: patients with hypertension experience a decrease in blood pressure while peripheral resistance does not increase, contrary to drugs with only beta-blocking properties. The heart rate decreases slightly. Circulation and renal function remain normal, as well as peripheral circulation, so that cases of cold extremities, a frequent phenomenon with beta-blockers, are rare.

In long-term treatment in patients with angina, it has been shown that carvedilol reduces myocardial ischemia and alleviates pain. Hemodynamic studies have shown that carvedilol decreases ventricular pre-load and after-load. Carvedilol has a beneficial effect on hemodynamics and left ventricular ejection fraction and its size in patients with left ventricular dysfunction or congestive heart failure. Carvedilol reduces mortality and the need for hospital-based treatment for cardiovascular disease in patients with heart failure.

Carvedilol has no negative effect on the serum lipid profile or electrolytes. The ratio of HDL (high-density lipoproteins) and LDL (low-density lipoproteins) remains normal.

5.2 Pharmacokinetic properties

General description

The absolute bioavailability of carvedilol is approximately 25%. Peak plasma concentrations are reached after about one hour. The ratio of dose to serum concentration is linear. In case of slow hydroxylation of debrisoquine, plasma concentrations of carvedilol are 2 to 3 times higher than those found in cases of rapid hydroxylation of debrisoquine. Diet has no effect on bioavailability, although maximum plasma levels are reached later. Carvedilol is an extremely lipophilic compound. Carvedilol is bound to plasma proteins at about 98-99%. Its volume of distribution is approximately 2 l/kg and is higher in patients with cirrhosis of the liver. The effect of first pass metabolism after oral administration is approximately 60 to 75%; Animal studies have demonstrated enterohepatic circulation of the unmetabolized drug.

The elimination half-life of carvedilol ranges from 6 to 10 hours. Plasma clearance is 590 ml/min. Elimination is mainly by bile. Carvedilol is mostly eliminated in the stool. A small part of the drug is excreted by the kidneys as metabolites.

Studies in animals and humans have shown that carvedilol is largely metabolized to a variety of metabolites that are primarily removed by bile. Carvedilol is metabolized in the liver, mainly by oxidation of the aromatic ring and glucuronidation. The demethylation and hydroxylation of the phenol ring causes the appearance of three active metabolites, which exert a blocking action on beta-receptors. Preclinical studies indicate that the 4'-hydroxyphenol metabolite has a beta-blocking effect approximately 13-fold greater than carvedilol. Compared to carvedilol, these three active metabolites have weak vasodilatory action. In humans, metabolite concentrations are approximately 10-fold lower than those of carvedilol. Two of the carvedilol hydroxycarbazole metabolites are very potent antioxidants, 30 to 80 times more potent than carvedilol.

Special populations
The pharmacokinetics of carvedilol are influenced by age. Plasma concentrations of carvedilol are approximately 50% higher in older patients compared to young people.

In a study in patients with cirrhosis of the liver, the bioavailability of carvedilol was four times higher, the maximum plasma concentrations five times higher and the volume of distribution three times higher than in healthy subjects.

Some patients with hypertension and moderate (creatinine clearance 20-30 mL / min) or severe renal impairment (creatinine clearance <20 mL / min) had carvedilol plasma concentrations of approximately 40-55% higher than patients with intact renal function.

The results were, however, very variable.

5.3 Preclinical safety data

Studies in rats and mice have shown no carcinogenic effect of carvedilol at doses of 75 mg/kg and 200 mg/kg (38 to 100 times the maximum daily dosage in humans) .

Mutagenic action of carvedilol has not been demonstrated in in vitro or in vivo studies in mammals or other animals.

After high doses of carvedilol were administered to pregnant rats (≥ 200 mg/kg, corresponding to ≥ 100 times the maximum daily dosage in humans), adverse effects on pregnancy and fertility were observed. Growth and physical development of the fetus were delayed with doses of ≥ 60 mg/kg (≥ 30 times the maximum daily dosage in humans). Embryonic toxicity (increased mortality after embryo implantation) was observed. However, no malformation was observed in rats or rabbits at doses of 200 mg/kg and 75 mg/kg respectively (38 to 100 times the maximum daily dosage in humans).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Lactose monohydrate
Povidone K25
Crospovidone
Silica colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicine does not require any special storage precautions.

6.5 Nature and contents of the pack

Alu/Alu blister strips.

Package sizes:

5, 10, 14, 20, 28, 30, 40, 50, 56, 60, 90, 98, 100, 120, 150, 200, 250, 300, 400, 500 and 1000 tablets or 5x1, 10x1, 14x1, 20x1, 28x1, 30x1, 40x1, 50x1, 60x1, 90x1, 98x1, 100x1, 120x1, 150x1, 200x1, 250x1, 300x1, 400x1, 500x1, 1000x1 tablets (unit dose)

5, 7, 10, 14, 20, 28, 30, 32, 40, 50, 56, 60, 90, 98, 100, 150, 200, 250, 300, 400, 500 and 1000 tablets or 5x1, 7x1, 10x1, 14x1, 20x1, 28x1, 30x1, 32x1, 40x1, 50x1, 56x1, 60x1, 90x1, 98x1, 100x1, 150x1, 200x1, 250x1, 300x1, 400x1, 500x1, 1000x1 tablets (unit dose)

Not all package sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

EG (Eurogenerics) SA
Esplanade Heysel b22
1020 Brussels

8. MARKETING AUTHORISATION NUMBERS

Carvedilol EG 6.25 mg tablets: BE260531
Carvedilol EG 25 mg tablets: BE260583

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

Date of first authorisation: 23 September 2002
Date of last renewal: 23 September 2007

10. DATE OF REVISION OF THE TEXT

04/2020