SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Carvedilol 6.25 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 6.25 mg carvedilol

Excipient with known effect:
Each film-coated tablet contains 25 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

6.25 mg film-coated tablets: white, oval, scored on both sides and marked "6.25" on one side.

The 6.25 mg tablets can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Essential hypertension.
- Chronic stable angina pectoris
- Adjunctive treatment in moderate to severe stable heart failure.

4.2 Posology and method of administration

Carvedilol is available in 4 strengths: 3.125 mg, 6.25 mg, 12.5 mg and 25 mg

Essential hypertension
Carvedilol may be used for the treatment of hypertension alone or in combination with other antihypertensives, especially thiazide diuretics. Once daily dosing is recommended, however the recommended maximum single dose is 25 mg and the recommended maximum daily dose is 50 mg.

Adults:
The recommended initial dose is 12.5 mg once a day for the first two days. Thereafter, the treatment is continued at the dose 25 mg/day. If necessary, the dose may be further increased gradually at intervals of at least two weeks.

Elderly:
The recommended initial dose in hypertension is 12.5 mg once a day, which may also be sufficient for continued treatment. However, if the therapeutic response is inadequate at this dose, the dose may be further increased gradually at intervals of at least two weeks.

Chronic stable angina pectoris

Adults:
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. If necessary, the dose may be further increased gradually at intervals of at least two weeks. The recommended maximum daily dose is 100 mg in two doses (50 mg twice daily).

Elderly:
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

Treatment of 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 stabilised for at least 4 weeks prior to treatment. Additionally the patient should have a reduced left ventricular ejection fraction and heart frequency 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 the initial dose is well tolerated, the carvedilol dose can be increased at intervals of at least two weeks, first to 6.25 mg twice daily, then 12.5 mg twice daily followed by 25 mg twice daily. It is recommended that the dose is increased to the highest level tolerated by the patient.

The recommended maximum dose is 25 mg given twice daily for patients weighing less than 85 kg and 50 mg twice daily for patients weighing more than 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 not usually call for discontinuation of treatment, but the dose should not be increased. The patient should be monitored by a physician/cardiologist after starting carvedilol 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 vasodilation (e.g. renal function, body weight, blood pressure, heart rate and heart 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 stabilised. 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.

If carvedilol therapy is discontinued for more than two weeks, it should be reinitiated at 3.125 mg twice daily and increased gradually in accordance with the above recommendation.

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 failure is necessary.

Moderate hepatic dysfunction.
Dose adjustment may be required.

Children and adolescents
There is insufficient data on the efficacy and safety of carvedilol in children and adolescents under 18 years of age.

Elderly
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 coronary patients treatment with carvedilol should be withdrawn gradually (see section 4.4).

Method of administration
The tablets do not need to be taken with a meal. However, it is recommended that heart failure patients take their carvedilol medication with food to allow the absorption to be slower and the risk of orthostatic hypotension to be reduced.

4.3 Contraindications

- Hypersensitivity to carvedilol or to any of the excipients listed in section 6.1
- 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
- Chronic Obstructive Pulmonary Disease (COPD) with bronchospasm or asthma (see section 4.4)

4.4 Special warnings and precautions for use

Chronic congestive heart failure
Carvedilol should be administered principally in addition to diuretics, ACE inhibitors, digitalis and/or vasodilators. Therapy should only be initiated, if the patient is stabilised on conventional basic therapy for at least 4 weeks. Decompensated patients have to be re-compensated. Patients with severe heart failure, salt and volume depletion, elderly patients or patients with low basic blood pressure should be monitored for approximately 2 hours after the first dose or after dose increase as hypotension may occur.

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 (see section 4.5).

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. In heart failure patients with these risk factors, renal function should be monitored during dose titration of carvedilol. If significant worsening of renal function occurs, the carvedilol dose must be reduced or therapy must be discontinued.

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.

First degree AV block
Because of its negative dromotropic action, carvedilol should be administered with caution to patients with first degree heart block.

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. Therefore, close monitoring of diabetic patients receiving carvedilol is required by means of regular blood glucose measurements and adjustment of antidiabetic medication as necessary (see section 4.5).

Peripheral vascular disease
Carvedilol should be used with caution in patients with peripheral vascular disease as beta-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 (e.g. Raynaud's phenomenon) as there may be exacerbation of symptoms.

Thyrotoxicosis
Carvedilol may obscure the symptoms of thyrotoxicosis.

Anaesthesia 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 beta-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions.

Severe skin reactions
Very rare cases of severe skin reactions, such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported during treatment with carvedilol (see section 4.8).

Psoriasis

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

Concomitant use of calcium channel blockers and other antiarrhythmic drugs
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, specifically amiodarone. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrio-ventricular block.

Phaeochromocytoma
In patients with phaeochromocytoma, an alpha- blocking agent should be initiated prior to the use of any beta-blocking agent. Although carvedilol has both alpha- and beta-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 phaeochromocytoma.

Prinzmetal's variant angina
Agents with non-selective beta-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 alpha- 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.

Metabolic acidosis
Carvedilol should be used with caution in patients with metabolic acidosis.

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).

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

Other
Since there is limited clinical experience, carvedilol should not be administered in patients with labile or secondary hypertension, orthostasis, acute inflammatory heart disease, haemodynamically relevant obstruction of heart valves or outflow tract, end-stage peripheral arterial disease, concomitant treatment with $alpha_1$-receptor antagonist or $alpha_2$-receptor agonist.

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

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

Inhibitors as well as inducers of CYP2D6 and CYP2C9 can modify the systemic and/or presystemic metabolism of carvedilol stereoselectively, leading to increased or decreased plasma concentrations of R and S-carvedilol. Patients receiving medicines that induce (*e.g.* rifampicin, carbamazepine and barbiturates) or inhibit (*e.g.* paroxetine, fluoxetine, quinidine, cinacalcet, bupropion, amiodarone and fluconazole) these CYP enzymes have to be monitored closely during concomitant treatment with carvedilol. Some examples observed in patients or in healthy subjects are listed below but the list is not exhaustive.

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 (see section 4.4).

Rifampicin and cimetidine:
In a study in 12 healthy subjects, rifampicin reduced plasma concentrations of carvedilol by about 70%, most likely by induction of P-glycoprotein leading to a decrease of the intestinal absorption of carvedilol. 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 e.g. rifampicin, as serum levels of carvedilol may be reduced, or inhibitors of mixed function oxidases e.g. 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.

Ciclosporin:
Two studies in renal and cardiac transplant patients receiving oral ciclosporin have shown an increase in ciclosporin plasma concentrations following initiation of carvedilol treatment. In about 30% of patients, the dose of ciclosporin had to be reduced in order to maintain ciclosporin concentrations within the therapeutic range, while in the remainder no adjustment was needed. On average, the dose of ciclosporin was reduced by about 20% in these patients. Due to wide interindividual variability in the dose adjustment required, it is recommended that ciclosporin concentrations be

monitored closely after initiation of carvedilol therapy and that the dose of ciclosporin be adjusted as appropriate.

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

Fluoxetine and paroxetine:
In a randomized, cross-over study in 10 patients with heart failure, co- administration of fluoxetine, a strong inhibitor of CYP2D6, resulted in stereoselective inhibition of carvedilol metabolism with a 77% increase in mean R(+) enantiomer AUC. However, no difference in adverse events, blood pressure or heart rate were noted between treatment groups.

The effect of repeated doses of paroxetine, a strong CYP2D6 inhibitor, on the pharmacokinetics of a single oral dose of carvedilol was studies in 12 healthy volunteers. Exposure to R-carvedilol increased by an average of 150% and exposure to S-carvedilol by an average of 90% after concomitant administration with paroxetine.

Pharmacodynamic interactions

Digoxin:
The combined use of beta-blockers and digoxin may result in additive prolongation of atrioventricular (AV) conduction time.

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

Antiarrythmics and calcium channel blockers;
In combination with carvedilol these medicines can increase the risk of AV conduction disturbances (see section 4.4). Isolated cases of conduction disturbance (rarely with haemodynamic compromise) have been observed when carvedilol is co-administered with diltiazem, verapamil and/or amiodarone. As with other agents with beta-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 the risk of AV conduction disorders or risk of cardiac failure are increased (synergistic effect). Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrio-ventricular block.
Close monitoring should be done when co-administering carvedilol, and either a class I antiarrhythmic or amiodarone (oral). Bradycardia, cardiac arrest, and ventricular fibrillation have been reported shortly after initiation of beta-blocker treatment in patients receiving amiodarone.

Antihypertensives:
As with other agents with beta-blocking activity, carvedilol may potentiate the effect of other concomitantly administered drugs that are anti-hypertensive in action (e.g. $alpha_1$-receptor antagonists) or have hypotension as part of their adverse effect profile such as barbiturates, phenothiazines, tricyclic antidepressants, vasodilating agents and alcohol.

Anaesthetic agents:
Careful attention must be paid during anaesthesia due to the synergistic negative inotropic and hypotensive effects of carvedilol and anaesthetic drugs (see section 4.4).

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

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

Beta-agonist bronchodilators:
Non-cardioselective beta blockers oppose the bronchodilator effects of beta-agonist bronchodilators. Careful monitoring of patients is recommended.

The following classes of interactions apply generally to beta-blockers

Epinephrine:
There are ten reports of pronounced hypertension and bradycardia in patients treated with non-selective beta-receptor blockers (including pindolol and propranolol) along with epinephrine (adrenaline). These clinical observations have been confirmed in studies with healthy research subjects. It has also been proposed that epinephrine as a supplement to local anaesthetics may elicit these reactions with intravascular administration. The risk should be substantially reduced with cardioselective beta-receptor blockers.

Phenylpropanolamine:
Phenylpropanolamine (norephedrine) in single doses of 50 mg may increase diastolic blood pressure to pathological values in healthy research subjects. Propranolol generally inhibits the increase in blood pressure elicited by phenylpropanolamine. However, beta-receptor blockers may elicit paradoxical hypertensive reactions in patients who are taking large doses of phenylpropanolamine. In a couple of cases hypertensive crises have been reported during treatment with just phenylpropanolamine.

NSAIDs:
NSAID-type antiphlogistics inhibit the antihypertensive effect of beta-receptor blockers. It is mainly indomethacin that has been studied. This interaction appears not

to occur with sulindac. No such interactions were established in a study involving diclofenac. There is no clinical experience of the combination of carvedilol with NSAIDs.

Barbituric acid preparations: Combinations with barbituric acid preparations should be avoided.

Nitrates:
Increased hypotensive effects.

Ergotamine:
Vasoconstriction increased.

Neuromuscular blocking agents:
Increased neuromuscular block.

4.6 Fertility, pregnancy and lactation

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

Animal studies are insufficient with respect to effects on pregnancy, embryonal/fœtal 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. The treatment should be stopped 2-3 days before expected birth. If this is not possible the newborn has to be monitored for the first 2-3 days of life.

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).

Breast-feeding
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.

Fertility
There are no fertility data for humans.

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: Thrombocytopenia
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 Raynaud'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
Uncommon: Constipation
Very rare: Dry mouth

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
Very rare: Severe cutaneous adverse reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)

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
Very common: Genital oedema
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.

Special populations
Studies in elderly patients with hypertension or angina showed that there was no difference in the undesirable effects profile when compared with younger patients. A further study, which included elderly patients with coronary artery disease, showed no significant difference in reported undesirable effects when compared with those reported for younger patients.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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 norfenefrine 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, beta-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.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: beta- and alpha-$_1$-receptor blocking agents
ATC code: C07AG02

Mechanism of action
Carvedilol is a vasodilatory non-selective beta-blocker, which reduces the peripheral vascular resistance by selective alpha-$_1$receptor blockade and suppresses the renin-angiotensin system through non-selective beta-blockade. Plasma renin activity is reduced and fluid retention is rare.

Carvedilol has no intrinsic sympathomimetic activity (ISA). Like propranolol, it has membrane stabilising properties.

Carvedilol is a racemate of two stereoisomers. Both enantiomers were found to have alpha-adrenergic blocking activity in animal models. Non-selective beta1- and beta2-adrenoceptor blockade is attributed mainly to the S(-) enantiomer.

The antioxidant properties of carvedilol and its metabolites have been demonstrated in in vitro and in vivo animal studies and in vitro in a number of human cell types.

Pharmacodynamic effect

In hypertensive patients, a reduction in blood pressure is not associated with a concomitant increase in peripheral resistance, as observed with pure beta-blocking agents. Heart rate is slightly decreased. Stroke volume remains unchanged. Renal blood flow and renal function remain normal, as does peripheral blood flow, therefore, cold extremities, often observed with beta-blockers, are rarely seen. In hypertensive patients carvedilol increases the plasma norepinephrine concentration.

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.

In patients with coronary heart disease, carvedilol has shown anti-ischaemic and anti-anginal properties which persisted during long-term treatment. Acute haemodynamic studies have shown that carvedilol reduces preload and afterload in the left ventricle.

In patients with left ventricular dysfunction or cardiac insufficiency, carvedilol has been shown to produce beneficial haemodynamic effects and improvements in left ventricular function with respect to ejection fraction and left ventricular dimensions.

Clinical efficacy and safety

Beneficial haemodynamic effects and improved left ventricular function have been observed in clinical studies in patients with ischaemic and non-ischaemic heart failure who have been treated with ACE inhibitors, diuretics, and digitalis, and with carvedilol as a supplementary treatment.

A double-blind, placebo-controlled trial including 1,094 patients with chronic stable mild-to-severe heart failure with impaired left ventricular function (ejection fraction $\leq 35\%$) who were randomised to 4 different treatment protocols based on walking distance showed that carvedilol, given as a supplement to conventional treatment (diuretics, ACE inhibitors and, where indicated, digitalis and nitrates), reduced mortality (3.2% in the carvedilol group, compared with 7.8% in the placebo group, relative reduction 65%; $p < 0.001$) and the need for hospital admission with cardiovascular disease. Carvedilol treatment was associated with increased wellbeing and a delay in disease progression. The study included patients who tolerated carvedilol 6.25 mg and the follow-up period was just seven months (median). Few patients with severe heart failure (NYHA class IV) and patients requiring hospital admission with inotropic support were included.

In the Copernicus study, 2,289 patients with stable severe chronic heart failure (NYHA class IV, ejection fraction < 25%) were randomised to treatment with carvedilol or with placebo as a supplement to conventional treatment. Patients who required intravenous inotropic support or who had symptomatic hypotension or severe renal impairment were not included in the study. The primary endpoint, total mortality, was reduced from 19.7% to 12.8% (relative

reduction 35%, p = 0.00013). Treatment of 1,000 patients with carvedilol over one year prevents an average of 70 deaths, giving an NNT (Number Needed to Treat) of 14.

A 24% relative reduction was observed in the secondary endpoint of total mortality or hospital admission, regardless of cause. There was a significant reduction in sudden death from 7.8% to 4.2%.

During the start of treatment and during titration, the incidence of adverse events was higher in the carvedilol group (22.9% vs 16.0%), mainly as a result of non-severe dizziness or hypotension. The incidence of severe events did not differ between the treatment groups. Throughout the study, the incidence of severe events was lower in the carvedilol group (39.0% vs 45.4%), as was the incidence of severe heart failure (14.5% vs 21.1%).

5.2 Pharmacokinetic properties

Absorption
After oral administration of a 25 mg capsule in healthy volunteers, carvedilol was absorbed rapidly, with a maximum plasma concentration C_{max} of 21 mg/L, which was reached after about 1.5 hours (t_{max}). There is a linear relationship between C_{max} values and dose. Following oral administration carvedilol undergoes an extensive first-pass metabolism which results in an absolute bioavailability of approximately 25 % in healthy human volunteers. Carvedilol is a racemate and the S-(-)-enantiomers appear to be metabolised more rapidly than the R-(+)-enantiomers, giving an absolute oral bioavailability of 15%, compared with 31% for the R-(+)-enantiomers. The maximum plasma concentration of R-carvedilol is about twice as high as that of S-carvedilol.

In vitro studies have shown that carvedilol is a substrate for the efflux transporter P-glycoprotein. P-glycoprotein's role in the disposition of carvedilol was also confirmed *in vivo* in healthy volunteers.

Distribution
Carvedilol is a highly lipophilic compound and shows plasma protein binding of about 95%. Its volume of distribution varies between 1.5 and 2 L/kg.

Biotransformation

Demethylation and hydroxylation at the phenol ring yield three active metabolites with beta-blocking activity. Compared to carvedilol, these three active metabolites have a weak vasodilatory effect. Preclinical studies have shown that the 4'-hydroxyphenolmetabolite has a beta-blocking activity 13 times more potent than that of carvedilol. However, the metabolite concentrations in humans are approximately 10 times lower than those of carvedilol.

The results from an *in vitro study* indicate that different cytochrome P450 isoenzymes may be involved in the oxidation and hydroxylation processes, including CYP2D6, CYP3A4, CYP2E1, CYP2C9 and CYP1A2.

Studies in healthy volunteers and patients have shown that the R-enantiomers are mainly metabolised by CYP2D6. The S enantiomers are mainly metabolised by CYP2D6 and CYP2C9.

Genetic polymorphism
In slow CYP2D6 metabolizers the plasma concentration (AUC) of carvedilol is about twice as high as in rapid CYP2D6 metabolisers. However, available data indicate that CYP2D6 genetic polymorphism may have limited clinical significance in carvedilol treatment.

Elimination
Carvedilol is primarily metabolised in the liver to a number of metabolites that are mainly eliminated via bile and faeces. After a single dose of 50 mg carvedilol, around 16% and 60% of the dose, respectively, is eliminated within 11 days via urine and faeces in the form of metabolites. Less than 1% of the substance is eliminated unmetabolised in the urine. After intravenous infusion of 12.5 mg in healthy volunteers, the plasma clearance of carvedilol was around 600 mL/min. and the elimination half-life was about 2.5 hours. In all individuals the half-life for a 50 mg capsule was about 6.5 hours, which corresponded to the absorption half-life for the capsule. After oral administration, the total clearance for S-carvedilol is about twice that for R-carvedilol.

Properties in the patient
Age has no significant effect on the pharmacokinetics of carvedilol in patients with hypertension.

Studies in children have shown that weight-adjusted clearance is significantly higher in children than in adults.

A pharmacokinetic study in patients with liver cirrhosis has shown that oral clearance for carvidolol was reduced 6.9-fold and that the maximum plasma concentration was increased 4.4-fold in patients with hepatic impairment, when compared with healthy research subjects.
In some of the hypertensive patients with moderate (creatinine clearance 20 to 30 mL/min) or severe (creatinine clearance < 20 mL/min) renal insufficiency, an increase in plasma carvedilol concentrations of approximately 40 to 55 % was seen compared to patients with normal renal function. However, there was a large variation in the results and considerable overlap with normal values.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Cellulose, microcrystalline
Lactose monohydrate
Crospovidone
Povidone
Silica, colloidal anhydrous
Magnesium stearate

Tablet coating:
Hypromellose
Titanium dioxide (E 171)
Triethyl citrate
Macrogol
Polydextrose

6.2 Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package, in order to protect from light.
Do not store above 30°C.

6.5 Nature and contents of container

PVC/Aluminium foil blisters or HDPE bottles with PP lids, available in packs containing: 10, 14, 28, 30, 50, 56, 98, 100 and 250 (plastic bottle only) tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Limited t/a Mylan
Station Close
Potters Bar
Hertfordshire
EN6 1TL
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 04569/0650

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/06/2007

10 DATE OF REVISION OF THE TEXT

16/03/2017