SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Carvedilol 3.125 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 3.125mg of Carvedilol

Excipient(s) with known effect: Each tablet contains 15.735mg of lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Carvedilol Tablets are cream coloured, circular, biconvex tablets, 5.30 mm-5.70 mm in diameter, marked ‘C3’ on one face and plain on the reverse face.

SUMMARY OF PRODUCT CHARACTERISTICS

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

Oral use.

Posology

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 two weeks or more rarely.

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 two weeks or more rarely.

Chronic stable angina pectoris:

A twice-daily regimen is recommended.

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:

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.

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 dysfunction
Dose adjustment may be required.

Paediatric population (< 18 years)
Carvedilol is not recommended for the use in children below 18 years of age due to insufficient data on the efficacy and safety of carvedilol.

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 patients with coronary disease, the withdrawal of carvedilol should be done gradually (see section 4.4).

Method of administration:

The tablets should be taken with an adequate supply of fluid. 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.

SUMMARY OF PRODUCT CHARACTERISTICS

4 CLINICAL PARTICULARS

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
• Heart failure belonging to NYHA Class IV of the heart failure classification with marked fluid retention or overload requiring intravenous inotropic treatment.
• Chronic obstructive pulmonary disease with bronchial obstruction (see section 4.4).
• Clinically significant hepatic dysfunction.
• Bronchial asthma.
• AV block, degree II or III (unless a permanent pacemaker is in place).
• Severe bradycardia (<50 bpm).
• Sick sinus syndrome (incl. sino-atrial block).
• Cardiogenic shock.
• Severe hypotension (systolic blood pressure below 85 mmHg).
• Prinzmetal's angina.
• Untreated phaeochromocytoma.
• Metabolic acidosis.
• Severe peripheral arterial circulatory disturbances.
Concomitant intravenous treatment with verapamil or diltiazem (see section 4.5).

4.4 Special warnings and precautions for use

Warnings to be considered particularly in heart failure patients
In chronic heart failure patients carvedilol should be administered principally in addition to diuretics, ACE inhibitors, digitalis and/or vasodilators. Initiation of therapy should be under the supervision of a hospital physician. Therapy should only be initiated, if the patient is stabilized on conventional basic therapy for at least 4 weeks. Patients with severe heart failure, salt and volume depletion, elderly 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. Hypotension due to excessive vasodilatation is initially treated by reducing the dose of the diuretic.

If symptoms still persist, the dose of any ACE inhibitor may be reduced. At the start of therapy or during up-titration of Carvedilol worsening of heart failure or fluid retention may occur. In these cases, the dose of diuretic should be increased. However, sometimes it will be necessary to reduce or withdraw carvedilol medication. The carvedilol dose should not be increased before symptoms due to the worsening of heart failure or hypotension due to vasodilatation are under control.

Since, to date, there are few data in patients with congestive heart failure class IV of the NYHA, if it is necessary to treat this group of patients with carvedilol, it should be done with special precaution. It is recommended to follow the instructions indicated in this section.

Reversible deterioration of renal function has been observed during carvedilol therapy in heart failure patients with low blood pressure (systolic BP < 100 mm Hg), ischaemic heart disease and generalized atherosclerosis, 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 past 48 hours, and the dose of the ACE inhibitor should have been stable for at least the past 24 hours.

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).

Other warnings as regards carvedilol and beta-blockers in general
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. However, caution should be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.

Patients with a chronic obstructive pulmonary disease with a tendency towards bronchospasms who are not treated with oral or inhalation medicine should only be given carvedilol if the expected improvement outweighs the possible risk. Patients should be monitored closely in the initial phase, and titration of carvedilol and carvedilol dose should be reduced in case of bronchospasms.

Carvedilol may mask symptoms and signs of acute hypoglycaemia. 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 closely monitored after a longer period of fasting.

Carvedilol may mask features (symptoms and signs) of thyrotoxicosis.

Carvedilol may cause bradycardia. If there is a decrease in pulse rate to less than 55 beats per minute, and symptoms associated with bradycardia occur, the carvedilol dose should be reduced.

When carvedilol is used concomitantly with calcium channel blocking agents such as verapamil and diltiazem or with other antiarrhythmics, specifically amiodarone, the patient's blood pressure and ECG have to be monitored.

Intravenous co-administration should be avoided (see section 4.5).

Cimetidine should be administered only with caution concomitantly as effects of carvedilol may be increased (see section 4.5).
Persons wearing contact lenses should be advised of a possible reduction of the secretion of lacrimal fluid.

Care should be taken in administrating 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. Cautions should be exercised when prescribing beta-blockers to patients with psoriasis since skin reactions may be aggravated.

Severe cutaneous adverse reactions (SCARs): Very rare cases of severe cutaneous adverse reactions such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported during treatment with Carvedilol (see section 4.8). Carvedilol should be permanently discontinued in patients who experience severe cutaneous adverse reactions possibly attributable to Eucardic.

Carvedilol should be used with caution in patients with peripheral vascular diseases, as beta-blockers may aggravate symptoms of the disease. The same also applies to those with Raynaud's syndrome, as there may be exacerbation or aggravation of symptoms.

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.

In patients with phaeochromocytoma, an initial treatment with alpha-blockers should be started before using any betablocker.

Although carvedilol exercises alpha and beta blockade there is not sufficient experience in this disease, therefore caution should be advised in these patients.
Because of its negative dromotropic action, carvedilol should be given with caution to patients with first degree heart block.
Beta-blockers reduce the risk of arrhythmias at anasthesia, however the risk of hypotension may be increased as well. Caution should therefore be observed with the use of certain anaesthetic medicines. Newer studies suggest however, a benefit of beta-blockers in preventing perioperative cardiac morbidity and reduction of the incidence of cardiovascular complications.

As with other beta-blockers, carvedilol should not be discontinued abruptly. This applies in particular to patients with ischaemic heart disease. Carvedilol therapy must be discontinued gradually within two weeks, e.g. by reducing the daily dose to half every three days. If necessary, at the same time replacement therapy should be initiated to prevent exacerbation of angina pectoris.

Carvedilol contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, fructose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Information on sodium content

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Antiarrhythmics.
Isolated cases of conduction disturbance (rarely compromised haemodynamics) have been reported, if oral carvedilol and oral diltiazem verapamil and/or amiodarone are given concomitantly. As with other beta-blockers, ECG and blood pressure should be monitored closely when concomitantly administering calcium-channel-blockers of the verapamil and diltiazem type due to the risk of AV conduction disorder or risk of cardiac failure (synergetic effect). 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.
Concomitant treatment with reserpine, guanethidine, methyldopa, guanfacine and monoamine oxidase inhibitors (exception MAO-B inhibitors) can lead to

additional decrease in heart rate. And hypotension Monitoring of vital signs is recommended.

Dihydropyridines.
The administration of dihydropyridines and carvedilol should be done under close supervision as heart failure and severe hypotension have been reported.

Nitrates.
Increased hypotensive effects.

Cardiac glycosides.
An increase of steady state digoxin levels by approximately 16% and of digitoxin by approximately 13% has been seen in hypertensive patients in connection with the concomitant use of carvedilol and digoxin. Monitoring of plasma digoxin concentrations is recommended when initiating, discontinuing or adjusting treatment with carvedilol.

Other antihypertensive medicines.
Carvedilol may potentiate the effects of other concomitantly administered antihypertensives (e.g. α1-receptor antagonists) and medicines with antihypertensive adverse reactions such as barbiturates, phenothiazines, tricyclic antidepressants, vasodilating agents and alcohol.

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

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. (see section 5.2). Some examples observed in patients or in healthy subjects are listed below but the list is not exhaustive.

Amiodarone
An in vitro study with human liver microsomes has shown that amiodarone and desethylamiodarone inhibited the oxidation of R and S-carvedilol. The trough concentration of R and S-carvedilol was significantly increased by 2.2-fold in heart failure patients receiving carvedilol and amiodarone concomitantly as compared to patients receiving carvedilol monotherapy. The effect on S-carvedilol was attributed to desethylamiodarone, a metabolite of amiodarone, which is a strong inhibitor of CYP2C9. A monitoring of the β-

blockade activity in patients treated with the combination carvedilol and amiodarone is advised.

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(+) enantiomerAUC, and a non-statistically 35% increase of the S(-) enantiomer's AUC as compared to the placebo group. However, no difference in adverse events, blood pressure or heart rate were noted between treatment groups. The effect of single dose paroxetine, a strong CYP2D6 inhibitor, on carvedilol pharmacokinetics was investigated in 12 healthy subjects following single oral administration. Despite significant increase in R and S-carvedilol exposure, no clinical effects were observed in these healthy subjects.

Antidiabetics including insulin.
The blood sugar-lowering effect of insulin and oral diabetic medicines may be intensified. Symptoms of hypoglycaemia may be masked. In diabetic patients regular monitoring of blood glucose levels is necessary.

Clonidine.
In case of withdrawal of both carvedilol and clonidine, carvedilol should be withdrawn several days before the stepwise withdrawal of clonidine.

Inhalational anaesthetics.
Caution is advised in case of anaesthesia due to synergistic, negative inotrope and hypotensive effect of carvedilol and certain anaesthetics.

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

Medicines inducing or inhibiting cytochrome P450 enzymes.
Patients receiving medicines that induce (e.g. rifampicin and barbiturates) or inhibit (e.g. cimetidine, ketoconazole, fluoxetine, haloperidol, verapamil, erythromycine) cytochrome P450 enzymes have to be monitored closely during concomitant treatment with carvedilol as serum carvedilol concentrations may be reduced by the first agents and increased by the enzyme inhibitors.
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 e.g. rifampicin, as serum levels of carvedilol may be reduced, or inhibitors of mixed function oxidases e.g. cimetidine, as serum levels 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.

Sympathomimetics with alpha-mimetic and beta-mimetic effects.
Risk of hypertension and excessive bradycardia.

Ergotamine.
Vasoconstriction increased.

Neuromuscular blocking agents.
Increased neuromuscular block.

Beta-agonist bronchodilators:
Non-cardioselective beta blockers oppose the bronchodilator effects of beta-agonist bronchodilators.

SUMMARY OF PRODUCT CHARACTERISTICS

4 CLINICAL PARTICULARS

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of carvedilol in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
Beta-blockers reduce placental perfusion which may result in intrauterine foetal death and immature and premature deliveries. In addition, adverse reactions (especially hypoglycaemia, hypotension, bradycardia, respiratory depression and hypothermia) may occur in the foetus and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Carvedilol should not be used during pregnancy unless clearly necessary (that is if the potential benefit for the mother outweighs the potential risk for the foetus/neonate). The treatment should be stopped 2-3 days before expected birth. If this is not possible the new-born has to be monitored for the first 2-3 days of life.

Breast-feeding
Carvedilol is lipophilic and according to results from studies with lactating animals, carvedilol and its metabolites are excreted in breast milk and, therefore, mothers receiving carvedilol should not breast-feed.

SUMMARY OF PRODUCT CHARACTERISTICS

4 CLINICAL PARTICULARS

4.7 Effects on ability to drive and use machines

This medicinal product has minor influence on the ability to drive and use machines. Some individuals may have reduced alertness especially on initiation and adjustment of medication

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 to < 1/10)

Uncommon (≥1/1000 to <1/100)

Rare (≥1/10000 to <1/1000)

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: Leucopenia.

Immune system disorders

Very rare: Hypersensitivity (allergic reaction)

Metabolism and nutrition disorders

Common: Weight increases, hypercholesterolaemia, impaired blood glucose control (hyperglycaemia, hypoglycaemia) in patients with pre-existing diabetes

Psychiatric disorders

Common: Depression, depressed mood

Uncommon: Sleep disorders, confusion

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
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 and increased sweating), 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
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.

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 Yellow Card Scheme; www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Paly or Apple App Store.

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

Gastric lavage or induced emesis may be useful in the first few hours after ingestion.
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: Alpha and beta blocking agents.

ATC code: C07AG02

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.

Some of the limitations of traditional β-blockers do not appear to be shared by some of the vasodilating β-blockers, such as carvedilol.

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.

Clinical studies have shown that the balance of vasodilation and beta-blockade provided by carvedilol results in the following effects: In hypertensive patients, a reduction in blood pressure is not associated with a concomitant increase in total 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 peripheral blood flow, therefore, cold extremities, often observed with beta-blockers, are rarely seen. In hypertensive patients carvedilol increases the plasma norepinephrine concentration.

In prolonged treatment of patients with angina, carvedilol has seen to have an anti-ischaemic effect and to alleviate pain. Haemodynamic studies demonstrated that carvedilol reduces ventricular pre- and after-load.

In patients with left ventricular dysfunction or congestive heart failure, carvedilol has a favourable effect on haemodynamics and left ventricular ejection fraction and dimensions.

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 and in hypertensive patients with dyslipidaemia favourable effects on the serum lipids have been reported after six months of oral therapy. Clinical efficacy Renal impairment Several open studies have shown that carvedilol is an effective agent in patients with renal hypertension. The same is true in patients with chronic renal failure or those on haemodialysis or after renal transplantation. Carvedilol causes a gradual reduction in blood pressure both on dialysis and non-dialysis days, and the blood pressure-lowering effects are comparable with those seen in patients with normal renal function. On the basis of results obtained in comparative trials on haemodialysed patients, it was concluded that carvedilol was more effective than calcium channel blockers and was better tolerated. In two studies, Carvedilol 25mg b.i.d. was compared with other anti-anginal drugs of recognised value in patients with chronic stable exertional angina. The dose regimens that were chosen were those widely used in clinical practice. Both trials had a double-blind, parallel group design. The primary objective was total exercise time (TET)

Report no:	Control (dose)	Patient numbers carvedilol/comparator drug	Duration of treatment
060	Verapamil (120mg t.i.d.)	126/122	12 weeks

061	ISDN s.r. (40mg b.i.d.)	93/94	12 weeks

The results of both trials clearly demonstrated that for TET at trough blood drug levels after 12 weeks of therapy there was no statistically significant difference between treatment groups. However the risk ratios obtained from the Cox proportional hazards model showed a trend in favour of carvedilol indicating that on average carvedilol was 114% as effective as verapamil (90% CI: 85-152%) and 134% as effective as ISDN (90%CI: 96-185%). This was also true for time to angina (TTA) and ST-segment depression (TST) at trough. The increase in TET was about 50 seconds in all groups; the improvements for TTA and TST were about 30 seconds, which is clinically relevant. In study 060, 48h Holter monitoring data measurements demonstrated a reduction of number and duration of ST-segment depressions (silent myocardial ischaemia) in both treatment groups. Carvedilol also decreased premature atrial and ventricular contractions (PAC, PVC), couplets and runs.

5.2 Pharmacokinetic properties

Absorption
Carvedilol is rapidly absorbed after oral administration. In healthy subjects, maximum serum concentration is achieved approximately 1 hour after administration. The absolute bioavailability of carvedilol in humans is approximately 25%.
There is a linear relationship between dose and serum concentrations of carvedilol. Food intake did not affect the bioavailability or the maximum serum concentration, although the time needed to reach maximum serum concentration is prolonged.

Following oral administration of a 25 mg capsule to healthy subjects, carvedilol is rapidly absorbed with a peak plasma concentration Cmax of 21 mg/L reached after approximately 1.5 hour (tmax). The Cmax values are linearly related to the dose. Following oral administration, carvedilol undergoes extensive first pass metabolism that results in an absolute bioavailability of about 25% in healthy male subjects. Carvedilol is a racemate and the S-(-)-enantiomer appears to be metabolized more rapidly than the R-(+)-enantiomer, showing an absolute oral bioavailability of 15% compared to 31% for the R-(+)-enantiomer . The maximal plasma concentration of R-carvedilol is approximately 2 fold higher than that of S-carvedilol. In vitro studies have shown that carvedilol is a substrate of the efflux transporter Pglycoprotein. The role of P-glycoprotein in the disposition of carvedilol was also confirmed in vivo in healthy subjects. Food does not affect bioavailability, residence time or the maximum serum concentration, although the time to reach maximum serum concentration is delayed.

Distribution
Carvedilol is highly lipophilic. The plasma protein binding is about 98% to 99%. The volume of distribution is approximately 2 l/kg and increases in patients with liver cirrhosis.
Biotransformation

In humans and in animal species studied, carvedilol is extensively metabolized to several metabolites which are excreted primarily in bile. The first pass effect after oral administration is 60 - 75%. The enterohepatic circulation of the parent substance was demonstrated in animals.
Carvedilol is extensively metabolized in the liver, glucuronidation being one of the main reactions. The demethylation and hydroxylation at the phenol ring produce 3 active metabolites with blocking activity of beta-adrenergic receptors.
According to preclinical studies, the beta-blocking activity of the metabolite 4 - hydroxyphenol is approximately 13 times higher than that of carvedilol. The three active metabolites have a weak vasodilating activity, compared with carvedilol. In humans, their concentrations are about 10 times lower than the parent substance.
Two of the carbazolehydroxy metabolites are extremely potent antioxidants, showing a potency 30-80 times that of carvedilol.
Elimination
The average half-life of elimination of carvedilol is approximately 6 hours. The plasma clearance is approximately 500-700 ml/min. Elimination is mainly via the bile, and excretion mainly via faeces. A minor part is eliminated renally in the form of various metabolites.
Following a single oral administration of 50 mg carvedilol, around 60% are secreted into the bile and eliminated with the faeces in the form of metabolites within 11 days. Following a single oral dose, only about 16% are excreted into the urine in form of carvedilol or its metabolites. The urinary excretion of unaltered drug represents less than 2%. After intravenous infusion of 12.5 mg to healthy volunteers, the plasma clearance of carvedilol reaches around 600 mL/min and the elimination half-life around 2.5 hours. The elimination half-life of a 50 mg capsule observed in the same individuals was 6.5 hours corresponding indeed to the absorption half-life from the capsule. Following oral administration, the total body clearance of the S-carvedilol is approximately two times larger than that of the R-carvedilol.

Pharmacokinetics in Special Populations
Patients with renal impairment
In some of the hypertensive patients with moderate to severe renal impairment (creatinine clearance < 30 ml/min), an increase in plasma carvedilol concentrations of approximately 40-50 % was seen compared to patients with normal renal function. Peak plasma concentrations in patients with renal insufficiency increased also by an average of 10-20 %. However, there was a large variation in the results. Since carvedilol is primarily excreted via the faeces, significant accumulation in patients with renal impairment is unlikely.
In patients with moderate to severe renal impairment there is no need to modify carvedilol dosage (see section 4.2)
Patients with liver failure
In patients with liver cirrhosis, the systemic availability of carvedilol is increased 80% due to reduced first pass effect. Therefore, carvedilol is contraindicated in patients with clinically manifest hepatic impairment (see section 4.3 Contraindications).
Use in elderly

Age had a statistically significant effect on pharmacokinetic parameters of carvedilol in hypertensive patients. A study in elderly hypertensive patients showed no difference between the adverse event profile of this group and younger patients. Another study involving elderly patients with coronary artery disease showed no difference in reported adverse reactions vs. those that were reported by younger patients.

Use in paediatrics

The available information on pharmacokinetics in subjects younger than 18 years is limited.

Diabetic patients

In hypertensive patients with type 2 diabetes was not observed effect of carvedilol on blood glucose (fasting or postprandial) and glycosylated haemoglobin A1, it was not necessary to change the dose of antidiabetic drugs. In patients with type 2 diabetes, carvedilol had no statistically significant influence on the glucose tolerance test. In nondiabetic hypertensive patients with altered insulin sensitivity (Syndrome X), carvedilol increased insulin sensitivity. The same results were observed in hypertensive patients with type 2 diabetes.

Heart failure

In a study in 24 patients with heart failure, the clearance of R-and S-carvedilol was significantly lower than previously estimated in healthy volunteers. These results suggested that the pharmacokinetics of R-and S-carvedilol is significantly altered by heart failure.

SUMMARY OF PRODUCT CHARACTERISTICS

5 PHARMACOLOGICAL PROPERTIES

5.3 Preclinical safety data

Carvedilol demonstrated no mutagenic or carcinogenic potential.

High doses of carvedilol impaired fertility and affected pregnancy in rats (increased resorptions). Decreased foetal weight and delayed skeletal development were also seen in rats. Embryotoxicity (increased post-implantation loss) occurred in rats and rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Microcrystalline cellulose (Avicel pH 102)

Low-substituted hydroxypropyl cellulose (E463)
Maize starch
Yellow iron oxide (E172)
Colloidal anhydrous silica
Purified talc
Magnesium stearate (E572)

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 moisture

SUMMARY OF PRODUCT CHARACTERISTICS

6 PHARMACEUTICAL PARTICULARS

6.5 Nature and contents of container

PVC/PVDC Aluminium foil
Pack sizes: of 28 or 56 tablets.

Not all pack sizes may be marketed.

SUMMARY OF PRODUCT CHARACTERISTICS

6 PHARMACEUTICAL PARTICULARS

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Torrent Pharma (UK) Ltd,

3rd Floor, Nexus Building
4 Gatwick Road
Crawley
West Sussex
RH10 9BG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 36687/0269

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/01/2025

10 DATE OF REVISION OF THE TEXT

07/01/2025