Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Carvedilol 25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains carvedilol 25 mg.

Excipient: lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

25 mg film-coated tablets: white, oval, scored on both sides and marked "25" on one side

The 25 mg tablets can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension:
Carvedilol may be used as monotherapy, or in combination with other antihypertensive preparations, especially thiazide diuretics or calcium antagonists of the nifedipine type.

Supplementary treatment of heart failure:
Carvedilol is given to supplement diuretics and ACE inhibitors in the treatment of symptomatic cardiac insufficiency (CHF) irrespective of the aetiology.

4.2 Posology and method of administration

The tablets must be swallowed with water.

Hypertension:
The recommended dose is taken once a day.

Adults
12.5 mg is initially given once a day for the first two days. Thereafter 25 mg once a day is recommended. If required the dose may be increased in successive stages, with an interval of at least four weeks, up to the recommended maximum daily dose of 50 mg given as a single dose or divided into two separate doses.

Elderly (> 65 years)
12.5 mg once a day is recommended initially. If the response is inadequate, the dose may be increased by titration at intervals of at least four weeks up to the recommended maximum daily dose of 50 mg.

Supplementary treatment of heart failure
The treatment should be supervised by a specialist, and the dosage of diuretics and ACE inhibitors, with or without digitalis, must be stable.
3.125 mg twice a day for two weeks is recommended initially. If this dose is tolerated, the dose may be increased in successive stages at intervals of at least two weeks, up to 6.25 mg twice a day, followed by 12.5 mg twice a day and thereafter 25 mg twice a day. The dose should be increased to the maximum tolerance level. The maximum recommended dose in mild to moderate heart failure is 25 mg twice a day to patients who weigh less than 85 kg, and 50 mg twice a day to patients who weigh more than 85 kg.
The maximum recommended dose in severe heart failure is 25 mg twice a day.
Before each dose increase, the patient should be examined by a doctor for symptoms of worsening heart failure and/or vascular dilatation. Occasional worsening of the heart failure or increased water retention should be treated with increased doses of diuretics. It may sometimes be necessary to reduce the carvedilol dose or temporarily discontinue treatment with carvedilol.

4.3 Contraindications

Hypersensitivity to carvedilol or any component of the product
Unstable/decompensated heart failure
Clinically manifest liver dysfunction
2nd and 3rd degree AV block (unless a permanent pacemaker is in place)
Severe bradycardia (<50 bpm)
Sick sinus syndrome (including sino-atrial block)
Severe hypotension (systolic blood pressure <85 mmHg)
Cardiogenic shock
History of bronchospasm or asthma
Chronic obstructive pulmonary disease with bronchial obstruction (*see 4.4 "Special warnings and precautions for use"*)

4.4 Special warnings and precautions for use

Chronic Congestive Heart Failure
In congestive heart failure patients, worsening cardiac failure or fluid retention may occur during up-titration of carvedilol. If such symptoms occur, diuretics should be increased and the carvedilol dose should not be advanced until clinical stability resumes. Occasionally, it
may be necessary to lower the carvedilol dose or, in rare cases, temporarily discontinue it. Such episodes do not preclude subsequent successful titration of carvedilol. Carvedilol should be used with caution in combination with digitalis glycosides, as both drugs slow AV
conduction.

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

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

Chronic obstructive pulmonary disease
Carvedilol should be used with caution, in patients with chronic obstructive pulmonary disease (COPD) with a bronchospastic component who are not receiving oral or inhaled medication, and only if the potential benefit outweighs the potential risk.
In patients with a tendency to bronchospasm, respiratory distress can occur as a result of a
possible increase in airway resistance. Patients should be closely monitored during initiation and up-titration of carvedilol and the dose of carvedilol should be reduced if any evidence of bronchospasm is observed during treatment.

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

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

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

Thyrotoxicosis
Carvedilol may obscure the symptoms of thyrotoxicosis.

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

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

Labile or secondary hypertension
Carvedilol must be given with caution to patients with labile or secondary hypertension until further clinical experience is available.

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Inducers and inhibitors of hepatic metabolism: Rifampicin reduced plasma concentrations of carvedilol by about 70% Cimetidine increased AUC by about 30% but caused no change in Cmax. Care may be required in those patients receiving inducers of mixed function oxidases
eg rifampicin, as serum levels of carvedilol may be reduced, or inhibitors of mixed function oxidases eg cimetidine, as serum levels of carvedilol may be increased. However, based on the relatively small effect of cimetidine on carvedilol drug levels, the likelihood of any clinically important interaction is minimal.

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

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

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

Pharmacodynamic interactions
Clonidine: Concomitant administration of clonidine with agents with β-blocking properties may potentiate blood-pressure- and heart-rate-lowering effects. When concomitant treatment with agents with β-blocking properties and clonidine is to be terminated, the β-blocking agent should be discontinued first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage. Calcium channel blockers (see section 4.4 Special warnings and precautions for use). Isolated cases of conduction disturbance (rarely with haemodynamic compromise) have been observed when carvedilol is co-administered with diltiazem.

As with other agents with β-blocking properties, if carvedilol is to be administered orally with calcium channel blockers of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored.

As with other agents with β-blocking activity, carvedilol may potentiate the effect of other concomitantly administered drugs that are anti-hypertensive in action (eg α1-receptor antagonists) or have hypotension as part of their adverse effect profile.

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

Additionally, the following class interactions generally apply to beta-blockers:
Epinephrine: Some ten reports are available of pronounced hypertension and bradycardia in patients treated with non-selective beta-receptor blockers (e.g. pindolol and propranolol) to whom epinephrine (adrenaline) was administered. These clinical findings have been confirmed in studies in healthy volunteers. It has also been proposed that epinephrine as a supplement to local anaesthetics can trigger these reactions during intravascular
administration. The risk is probably considerably lower with cardioselective beta-receptor blockers.

NSAIDs: Anti-inflammatories of the NSAID type counteracts the antihypertensive activity of beta-receptor blocking substances. The substance studied is primarily indomethacin. This interaction is not thought to occur with sulindac. In one diclofenac study, no such interaction has been demonstrated. No experience of the combination of carvedilol and NSAID is available.

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

Phenylpropranolamine: Phenylpropranolamine (norephedrine) in single doses of 50 mg can raise the diastolic blood pressure to pathological levels in healthy volunteers. Propranolol generally counteracts the increase in blood pressure triggered by phenyl propranololamine. However, beta-receptor blockers can trigger paradoxical hypertensive reactions in patients taking large doses of phenyl propranolamine. Hypertensive crises during treatment with phenyl propranolamine alone have been described in a few cases.

4.6 Fertility, pregnancy and lactation

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

Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development (*see section 5.3*). The potential risk for humans is unknown.

Carvedilol should not be used during pregnancy unless the potential benefit outweighs the potential risk. 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.

Beta blockers reduce placental perfusion, which may result in intrauterine foetal death, and immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia) may occur in the foetus and neonate. There may be an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Animal studies have not shown substantive evidence of teratogenicity with carvedilol (*see also section 5.3*).

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Frequency categories are as follows:

Very common ≥ 1/10
Common ≥ 1/100 and < 1/10
Uncommon ≥ 1/1,000 and < 1/100
Rare ≥ 1/10,000 and < 1/1,000
Very rare < 1/10,000

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

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

Immune system disorders
Very rare: Hypersensitivity (allergic reaction)

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

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

Nervous system disorders
Very common: Dizziness, headache
Uncommon: Presyncope, syncope, paraesthesia

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

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

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

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

Gastrointestinal disorders
Common: Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain
Rare: Constipation

Hepatobiliary disorders
Very rare: Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gammaglutamyltransferase (GGT) increased

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

Musculoskeletal and connective tissue disorders
Common: Pain in extremities

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

Very rare: Urinary incontinence in women

Reproductive system and breast disorders
Uncommon: Erectile dysfunction

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

(c) Description of selected adverse reactions
Dizziness, syncope, headache and asthenia are usually mild and are more likely to occur at the beginning of treatment.

In patients with congestive heart failure, worsening cardiac failure and fluid retention may occur during up-titration of carvedilol dose (see section 4.4).

Cardiac failure is a commonly reported adverse event in both placebo and carvedilol-treated patients (14.5% and 15.4% respectively, in patients with left ventricular dysfunction following acute myocardial infarction).

Reversible deterioration of renal function has been observed with carvedilol therapy in chronic heart failure patients with low blood pressure, ischaemic heart disease and diffuse vascular disease and/or underlying renal insufficiency (see section 4.4).

As a class, beta-adrenergic receptor blockers may cause latent diabetes to become manifest, manifest diabetes to be aggravated, and blood glucose counter-regulation to be inhibited.

Carvedilol may cause urinary incontinence in women which resolves upon discontinuation of the medication.

4.9 Overdose

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

Treatment
In addition to general supportive treatment, the vital parameters must be monitored and corrected, if necessary, under intensive care conditions.

Atropine can be used for excessive bradycardia, while to support ventricular function intravenous glucagon or sympathomimetics (dobutamine, isoprenaline) are recommended. If positive inotropic effect is required, phosphodiesterase inhibitors (PDE) should be considered.

If peripheral vasodilation dominates the intoxication profile then norfenephrine or noradrenaline should be administered with continuous monitoring of the circulation. In the case of drug-resistant bradycardia, pacemaker therapy should be initiated.

For bronchospasm, β-sympathomimetics (as aerosol or intravenous) should be given, or aminophylline may be administered intravenously by slow injection or infusion. In the event of seizures, slow intravenous injection of diazepam or clonazepam is recommended.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Carvedilol is a non-selective beta-receptor blocker which also selectively blocks alpha$_1$-receptors. The peripheral vascular resistance diminishes during alpha$_1$-receptor blockade, while the activity in the renin-angiotensin-aldosterone system decreases due to blockade of beta-receptors. Antioxidant properties of carvedilol and its metabolites have been demonstrated in animal studies in vitro and in vivo, and in a number of human cell types in vitro.

In hypertensive patients a lowering of the blood pressure is not associated with a simultaneous increase in the total peripheral vascular resistance which is seen in the case of pure beta-blocking substances. The heart rate is reduced less with carvedilol than with beta-blockers alone. The renal blood flow and kidney function remains unchanged. Peripheral blood flow remains unchanged and cold extremities therefore rarely occur. Cardiac output is unchanged.

A normal HDL/LDL ratio is maintained and no increase in serum cholesterol is observed.

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 left-ventricular preload and after-load.

In patients with left-ventricular dysfunction or cardiac insufficiency, carvedilol has shown beneficial haemodynamic effects and improvements of the left-ventricular function in respect of the ejection fraction and dimensions of the left ventricle.

Beneficial haemodynamic effects and improved left-ventricular function are observed in clinical studies in patients with heart failure of ischaemic and non-ischaemic origin who are being treated with ACE inhibitors, diuretics, digitalis and with supplementary carvedilol.

A double-blind, placebo-controlled study including 1094 patients with chronic, stable mild-to-severe heart failure with reduced left-ventricular function (ejection fraction ≤ 35%) randomised to four different treatment protocols on the basis of walking distance shows that carvedilol as a supplement to conventional treatment (diuretics, ACE inhibitors and when indicated digitalis and nitrates) reduces mortality (3.2% in the carvedilol group versus 7.8% in the placebo group, relative reduction 65%; $p<0.001$) and the requirement for hospitalisation on account of cardiovascular disease. Carvedilol treatment was associated with increased well-being and produced a delay in the progression of the disease. The study included patients who tolerated carvedilol 6.25 mg, and the follow-up period was barely seven months (median). A few patients with severe heart failure (NYHA class IV) and patients requiring hospitalisation with inotropic support were included.

In the Copernicus study, 2289 patients with stable, chronic severe heart failure (NYHA class IV, ejection fraction < 25%) were randomised to treatment with carvedilol or placebo as a supplement to conventional treatment. Patients who required i.v. inotropic support or those with symptomatic hypotension or severely impaired kidney function were not included in the study. The primary effect variable, total mortality, was reduced from 19.7% to 12.8% (relative reduction 35%, $p=0.00013$). Treatment of 1000 patients with carvedilol for one year prevents on average 70 deaths, which gives an NNT (Number Needed To Treat) of 14.

A 24% relative reduction in the secondary effect variable, total mortality or hospitalisation irrespective of cause, was observed. There was a significant reduction in sudden death from 7.8% to 4.2%.

At the start and during the titration phase, the occurrence of adverse events was higher in the carvedilol group (22.9% versus 16.0%) principally due to non-serious dizziness or hypotension. The occurrence of serious events did not differ between the treatment groups. Throughout the study the occurrence of serious events was lower in the carvedilol group (39.0% versus 45.4%), as was the occurrence of severe heart failure (14.5% versus 21.1%).

In-vitro and animal experimentation has shown that two hydroxycarbazole metabolites of carvedilol are extremely potent antioxidants which are 30-80 times more potent than carvedilol.

5.2 Pharmacokinetic properties

The absolute bioavailability of carvedilol in humans is on average 25-35%, with great individual variation. The peak plasma concentration is reached 1 hour after oral administration. There is a linear relationship between dose and serum concentrations. Concomitant food intake does not influence the bioavailability or the peak plasma concentration, although the time to the peak plasma concentration increases somewhat. Carvedilol is highly lipophilic, and about 98%-99% is bound to plasma proteins. The distribution volume is about 2 l/kg.

The average half-life time of carvedilol is 6 to 10 hours. The plasma clearance is about 590 ml/min. In humans carvedilol is largely metabolised to a number of metabolites which are mainly excreted via the bile and in the faeces. A smaller proportion is excreted via the kidneys in the form of various metabolites.

Demethylation and hydroxylation at the phenol ring produces three active metabolites with beta-receptor blocking activity. On the basis of pre-clinical studies, the 4'-hydroxyphenol metabolite is about 13 times more potent for beta blockade than carvedilol. Compared with carvedilol the three active metabolites demonstrate a weak vasodilative effect. In humans their concentrations are about ten times lower than the parent compound.

Special populations
The pharmacokinetic properties of carvedilol are influenced by age; the plasma levels are about 50% higher in elderly as compared with younger persons. In a study of patients with cirrhosis of the liver, the bioavailability of carvedilol was four times higher and the peak plasma level five times higher than in healthy subjects. In patients with cirrhosis of the liver the volume of distribution is three times higher.

In hypertensive patients with moderate renal insufficiency (creatinine clearance 20-30 ml/min) to severe renal insufficiency (creatinine clearance < 20 ml/min), an approximate 40-55% increase in the plasma concentration of carvedilol (based on the AUC) was seen as compared with hypertensive patients with normal kidney function. There was a large variation and a considerable overlap with normal values.

5.3 Preclinical safety data

Toxicity studies reveal no hazards for humans in respect of genotoxicity and carcinogenicity.

Administration of carvedilol to pregnant rats in doses toxic to females resulted in fertility disturbance (low mating rate, fewer corpora lutea and implementations), together with retarded growth/development in the offspring. Embryotoxicity (increased post-implantation death but no malformations were seen in rats and rabbits at doses toxic to females.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Lactose monohydrate
Crospovidone
Povidone
Anhydrous colloidal silicon dioxide
Magnesium stearate

Tablet coat:
Hydroxypropylmethyl cellulose
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.
Plastic bottle: Do not store above 25°C.
Blister pack: Do not store above 30°C.

6.5 Nature and contents of container

Plastic bottle (HDPE) or blister pack (PVC/Alu)
Pack sizes: 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

McDermott Laboratories Ltd
Trading as Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13

8 MARKETING AUTHORISATION NUMBER

PA 577/53/4

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