SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Carvedilol 6.25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 6.25 mg of carvedilol.

Excipients: Each tablet contains 57.25 mg of lactose monohydrate and 1.250 mg of sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Film-coated tablets white to off-white, oval, engraved with "F57" on one side and scored on the other side. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypertension

Adjunctive therapy for the treatment of symptomatic congestive heart failure to reduce morbidity and increase patient well-being.

4.2 Posology and method of administration

Posology

Symptomatic congestive heart failure

The dosage must be titrated to individual requirements and monitored during up-titration.

For those patients receiving diuretics and/or digoxin and/or ACE inhibitors, dosing of these other medicinal products should be stabilised prior to initiation of carvedilol treatment.

Hypertension

Adults:

The recommended dose for initiation of therapy is 12.5 mg once a day for the first two days. Thereafter the recommended dosage is 25 mg once a day. Although this is an adequate dose in most patients, if necessary the dose may be titrated up to a recommended daily maximum dose of 50 mg given once a day or in divided doses.

Dose titration should occur at intervals of at least two weeks.

Elderly:

An initial dose of 12.5 mg is recommended. This has provided satisfactory control in some cases. If the response is inadequate the dose may be titrated up to the recommended daily maximum dose of 50 mg given once a day or in divided doses.

Adults

The recommended dose for the initiation of therapy is 3.125 mg twice a day for two weeks. If this dose is tolerated, the dosage should be increased subsequently, at intervals of not less than two weeks, up to 6.25 mg twice a day, followed by 12.5 mg twice daily and thereafter 25 mg twice daily. Dosing should be increased to the highest level tolerated by the patient.

The maximum recommended dose is 25 mg twice daily for patients with severe CHF and for patients with mild to moderate CHF weighing less than 85 kg (187 lbs). In patients with mild or moderate CHF weighing more than 85 kg, the maximum recommended dose is 50 mg twice daily.

Before each dose increase the patient should be evaluated by the physician for symptoms of worsening heart failure or vasodilation. Transient worsening of heart failure, vasodilation or fluid retention may be treated with increased doses of diuretics or ACE inhibitors or by modifying or temporarily discontinuing carvedilol treatment. Under these circumstances, the dose of carvedilol should not be increased until symptoms of worsening heart failure or vasodilation have been stabilised.

If carvedilol treatment is discontinued for more than one week, therapy should be recommenced at a lower dose level (twice daily) and up-titrated in line with the above dosing recommendation.

If carvedilol is discontinued for more than two weeks, therapy should be recommenced at 3.125 mg twice daily and up-titrated in line with the above dosing recommendation.

Elderly

As for adults.

Special dosage instructions

As with all beta-blockers, treatment should not be stopped abruptly; it should be gradually reduced at weekly intervals, particularly in patients with concomitant coronary heart disease**.**

Renal impairment

Pharmacokinetic data and clinical studies in patients with renal impairment (including renal failure) suggest no dose adjustment is needed in moderate to severe renal impairment (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Carvedilol in children and adolescents aged under 18 years has not been established (see section 5.1).

Method of administration

Carvedilol film-coated tablets are for oral use only.

The tablets should be taken with fluid.

For Congestive Heart Failure (CHF) patients, carvedilol should be given with food to slow the rate of absorption and reduce the incidence of orthostatic effects.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Unstable/decompensated heart failure requiring intravenous inotropic support
- Clinically manifest liver dysfunction

As with other beta-blocking agents:

- History of bronchospasm or asthma
- 2nd and 3rd degree atrioventricular (AV) heart block, (unless a permanent pacemaker is in place)
- Severe bradycardia (< 50 bpm)
- Cardiogenic shock
- Sick sinus syndrome (including sino-atrial block)
- Severe hypotension (systolic blood pressure < 85 mmHg).

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 further increased 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 up-titration of Carvedilol.

Carvedilol should be used with caution in combination with digitalis glycosides, since both medicinal products slow AV conduction (see section 4.5).

Renal function in congestive heart failure: Reversible deterioration of renal function has been observed during 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 CHF patients with these risk factors, renal function should be monitored during up-titration of carvedilol and the medicinal product discontinued or dosage reduced if worsening of renal failure occurs.

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 thepast 48 hours, and the dose of the ACE inhibitor should have been stable for at least the past 24 hours.

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.

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 it may be associated with worsening control of blood glucose. Furthermore, the early signs and symptoms of acute hypoglycaemia may be masked or attenuated. Alternatives to beta-blocking agents are generally preferred in insulin-dependent patients. Therefore, regular monitoring of blood glucose is required in diabetics when Carvedilol is initiated or up-titrated and hypoglycaemic therapy adjusted accordingly (see section 4.5).

Peripheral vascular disease and Raynaud's phenomenon: Carvedilol should be used with caution in patients with peripheral vascular disease (e.g. Raynaud's phenomenon) as beta-blockers can precipitate or aggravate symptoms of arterial insufficiency.

Thyrotoxicosis: Carvedilol may obscure the symptoms of thyrotoxicosis.

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 patients undergoing desensitisation therapy as beta-blockers may increase both the sensitivity towards allergens and

the severity of hypersensitivity reactions.

Risk of Anaphylactic Reaction: While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be

unresponsive to the usual doses of epinephrine used to treat allergic reaction.

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 Carvedilol.

Psoriasis: Patients with a history of psoriasis associated with beta-blocker therapy should be given Carvedilol only after consideration of the risk-benefit ratio.

Interactions with other medicinal products: There are a number of important pharmacokinetic and pharmacodynamic interactions with other medicinal products (e.g. digoxin, ciclosporin, rifampicin, anaesthetics, antiarrhythmics. See section 4.5).

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 of the use of carvedilol in this condition. Therefore, caution should be taken in the administration of Carvedilol to patients suspected of having phaeochromocytoma.

Carvedilol contains lactose monohydrate and sucrose. Patients with rare hereditary problems of galactose intolerance, fructose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, sucrase-isomaltase insufficiency should not take this medicine.

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.
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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.

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.

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.

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.

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

Beta-blockers reduce placental perfusion which may result in intrauterine foetal death and immature and premature deliveries. In addition, adverse reactions (especially hypoglycaemia, hypotension, bradycardia, respiratory depression and hypothermia) may occur in the fetus and neonate. There is 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).

Breastfeeding

Animal studies demonstrated that carvedilol and/or its metabolites are excreted in rat breast milk. The excretion of carvedilol in human milk has not been established. However, most beta-blockers, in particular lipophilic compounds, will pass into human breast milk although to a variable extent. Breastfeeding is therefore not recommended following administration of carvedilol.

4.7 Effects on ability to drive and use machines

No studies of the effects on ability to drive and use machines have been performed.

As for other medicinal products which produce changes in blood pressure, patients taking carvedilol should be warned not to drive or operate machinery if they experience dizziness or related symptoms. This applies particularly when starting, dose increasing or changing treatment and in conjunction 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, 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),Hypertension

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
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, Oedema

(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, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play 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 generalized seizures.

Treatment

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

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 $beta_1$- and $beta_2$-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 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.

In prolonged treatment of patients with angina, carvedilol has been seen to have an anti-ischaemic effect and to alleviate pain. Haemodynamic studies demonstrated that carvedilol reduces ventricular pre- and after-load with consequent improvement in left ventricular systolic and diastolic function without substantial changes in the cardiac output. 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 P-glycoprotein. 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 about 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 carbazole-hydroxy 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 the 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 pediatrics

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.

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 fetal 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

Tablet core

Lactose monohydrate

Silica colloidal anhydrous

Crospovidone (Type A)

Crospovidone (Type B)

Povidone 30

Sucrose

Magnesium stearate

Tablet coating

Macrogol 400

Polysorbate 80

Titanium dioxide (E 171)

Hypromellose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30 º C

6.5 Nature and contents of container

PVC / PE / PVDC - Aluminum:

Package sizes: 5, 7, 10, 14, 15, 20, 28, 30, 40, 50, 56, 60, 90, 98, 100, 120, 150, 200, 250, 300, 400, 500 and 1000 film-coated tablets.

Bottle of high density polyethylene (HDPE) with a white cap, opaque polypropylene

Package sizes: 30, 50, 60, 100, 250, 500 and 1000 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Milpharm Limited
1 Roundwood Avenue,
Stockley Park,
Uxbridge,
UB11 1AF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 16363/0352

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/10/2012

10 DATE OF REVISION OF THE TEXT

10/04/2026