Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Eucardic 3.125mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Carvedilol 3.125 mg.

Excipients: each tablet contains 55.98mg lactose monohydrate and 20.625mg sucrose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Round, pink tablets, scored on both sides, marked BM on one side and K1 on the other.
The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Treatment of hypertension.

4.2 Posology and method of administration

The tablets should be taken with fluid. For Congestive Heart Failure (CHF) patients Eucardic should be given with food to slow the rate of absorption and reduce the incidence of orthostatic effects.

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 drugs should be stabilised prior to initiation of Eucardic treatment.

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, to 6.25 mg twice daily, followed by 12.5 mg twice daily and thereafter 25mg twice daily. Dosing should be increased to the highest level tolerated by the patient.

The recommended maximum daily dose is 25 mg given twice daily in patients weighing less than 85kg (187 lbs) and 50 mg twice daily in patients weighing more than 85 kg.

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 Eucardic treatment. Under these circumstances, the dose of Eucardic should not be increased until symptoms of worsening heart failure or vasodilation have been stabilised.

If Eucardic 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.

Children
Safety and efficacy in children (under 18 years) has not been established.

Hypertension
Once daily dosing is recommended.

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 50mg 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 daily 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.

Children
Safety and efficacy in children (under 18 years) has not been established.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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 Eucardic. If such symptoms occur, diuretics should be increased and the Eucardic dose should not be further increased until clinical stability resumes. Occasionally it may be necessary to lower the Eucardic dose or, in rare cases, temporarily discontinue it. Such episodes do not preclude subsequent successful up-titration of Eucardic.

Eucardic should be used with caution in combination with digitalis glycosides, since both drugs slow A-V conduction (see section 4.5).

Renal function in congestive heart failure: Reversible deterioration of renal function has been observed with Eucardic 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 Eucardic and the drug discontinued or dosage reduced if worsening of renal failure occurs.

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 Eucardic should be reduced if any evidence of bronchospasm is observed during treatment.

Diabetes: Care should be taken in the administration of Eucardic to patients with diabetes mellitus, as it may be associated with worsening control of blood glucose, or 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 Eucardic is initiated or up-titrated and hypoglycaemic therapy adjusted accordingly (see section 4.5).

Peripheral vascular disease and Raynaurd's phenomenon: Eucardic 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: Eucardic may obscure the symptoms of thyrotoxicosis.

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

Hypersensitivity: Care should be taken in administering Eucardic 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.

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 Eucardic (see section 4.8). Eucardic should be permanently discontinued in patients who experience severe cutaneous adverse reactions possibly attributable to Eucardic.

Psoriasis: Patients with a history of psoriasis associated with beta-blocker therapy should be given Eucardic 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 drugs (e.g., digoxin, ciclosporin, rifampicin, anaesthetic drugs, anti-arrhythmic drug. See section 4.5).

Pheochromocytoma: In patients with pheochromocytoma, an alpha-blocking agent should be initiated prior to the use of any beta-blocking agent. Although Eucardic 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 Eucardic to patients suspected of having pheochromocytoma.

Prinzmetal's variant angina: Agents with non-selective beta-blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There is no clinical experience with carvedilol in these patients, although the alpha-blocking activity of Eucardic may prevent such symptoms. Caution should be taken in the administration of Eucardic to patients suspected of having Prinzmetal's variant angina.

Contact lenses: Wearers of contact lenses should be advised of the possibility of reduced lacrimation.

Withdrawal syndrome: Although angina has not been reported on stopping treatment, discontinuation should be gradual (over a period of 2 weeks), particularly in patients with ischaemic heart disease, as Eucardic has beta-blocking activity.

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

Sucrose: This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Usage of carvedilol in patients with symptomatic congestive heart failure has not been shown to reduce mortality.

4.5 Interaction with other medicinal products and other forms of interactions

Pharmacokinetic interactions:

Effects of Eucardic on the pharmacokinetics of other drugs

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

Inhibitors as well as inducers of CYP2D6 and CYP2C9 can modify the systemic and/or presystemic metabolism of carvedilol stereoselectively, leading to increased or decreased plasma concentrations of R and S-carvedilol. (see section 5.2). Some examples observed in patients or in healthy subjects are listed below but the list is not exhaustive.

Digoxin: An increased exposure of digoxin of up to 20% has been shown in some studies in healthy subjects and patients with heart failure. A significantly larger effect has been seen in male patients compared to female patients. Therefore monitoring of digoxin levels is recommended when initiating, adjusting or discontinuing carvedilol (see section 4.4). Carvedilol had no effect on digoxin administered intravenously.

Ciclosporin: Two studies in renal and cardiac transplant patients receiving oral ciclosporin have shown an increase in ciclosporin plasma concentration following the initiation of carvedilol. It appears that carvedilol increases exposure to oral ciclosporin by around 10 to 20%. In an attempt to maintain therapeutic ciclosporin levels, an average 10-20% reduction of the ciclosporin dose was necessary. The mechanism for the interaction is not known but inhibition of intestinal P glycoprotein by carvedilol may be involved. Due to wide interindividual variability of ciclosporin levels, it is recommended that ciclosporin concentrations are monitored closely after initiation of carvedilol therapy and that the dose of ciclosporin be adjusted as appropriate. In case of IV administration of ciclosporin, no interaction with carvedilol is expected.

Effects of other drugs on the pharmacokinetics of Carvedilol

Rifampicin: In a study in 12 healthy subjects, exposure to carvedilol decreased by around 60% during concomitant administration with rifampicin and a decrease effect of carvedilol on the systolic blood pressure was observed. The mechanism for the interaction is not known but it may be due to the induction of the intestinal P glycoprotein by rifampicin. A close monitoring of the β-blockade activity in patients receiving concomitant administration of carvedilol and rifampicin is appropriate.

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, coadministration of fluoxetine, a strong inhibitor of CYP2D6, resulted in stereoselective inhibition of carvedilol metabolism with a 77% increase in mean R(+) enantiomer's AUC, and a non-statistically 35% increase of the S(-) enantiomer's AUC as compared to the placebo group. However, no differences 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.

Pharmacodynamic interactions:
Insulin or oral hypoglycaemics: Agents with beta-blocking properties may enhance the blood-sugar-reducing effect of insulin and oral hypolycaemics. The signs of hypoglycaemia may be masked or attenuated (especially tachycardia). In patients taking insulin or oral hypoglycaemics, regular monitoring of blood glucose is therefore recommended (see section 4.4).

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

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

Non-dihydropyridines calcium channel blockers or other antiarrhythmics: In combination with carvedilol can increase the risk of AV conduction disturbances (see section 4.4). Isolated cases of conduction disturbance (rarely with haemodynamic compromise) have been observed when carvedilol is co-administered with diltiazem. As with other agents with β-blocking properties, if carvedilol is to be administered orally with non-dihydropyridines calcium channel blockers of the verapamil or diltiazem type, amiodarone or other antiarrhythmics it is recommended that ECG and blood pressure be monitored.

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.

Antihypertensives: As with other agents with beta-blocking activity, Eucardic may potentiate the effect of other concomitantly administered drugs that are anti-hypertensive in action (e.g. alpha1-receptor antagonists) or have hypotension as part of their adverse effect profile.

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

NSAIDs: The concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) and beta-adrenergic blockers may result in an increase in blood pressure and impairment of blood pressure control.

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

4.6 Fertility, pregnancy and lactation

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

Animal studies are insufficient with respect to effects on pregnancy, embryonal/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.

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).

Lactation
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 β-blockers, in particular lipophilic compounds, will pass into human breast milk although to a variable extent. Breast feeding 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 drugs 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 or changing treatment and in conjunction with alcohol.

4.8 Undesirable effects

The following undesirable effects have been reported to occur when carvedilol is administered:

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

Table 1 Adverse Drug Reactions

System Organ Class	Adverse Reaction	Frequency
Blood and Lymphatic System Disorders	Anaemia	Common
	Thrombocytopenia	Rare
	Leukopenia	Very rare
Cardiac Disorders	Cardiac failure	Very common
	Bradycardia	Common
	Hypervolaemia	Common
	Fluid overload	Common
	Oedema	Common
	Atrioventricular block	Uncommon
	Angina pectoris	Uncommon
Eye Disorders	Visual impairment	Common
	Lacrimation decreased (dry eye)	Common
	Eye irritation	Common
Gastrointestinal Disorders	Nausea	Common
	Diarrhoea	Common
	Vomiting	Common
	Dyspepsia	Common
	Abdominal pain	Common
	Constipation	Uncommon
	Dry mouth	Rare
General Disorders and Administration Site Conditions	Asthenia (fatigue)	Very common
	Oedema	Common
	Pain	Common
Hepatobiliary disorders	Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT) increased	Very rare
Immune System Disorders	Hypersensitivity (allergic reactions)	Very rare
Infections and Infestations	Pneumonia	Common
	Bronchitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
Metabolism and Nutrition Disorders	Weight increase	Common
	Hypercholesterolaemia	Common

System Organ Class	Adverse Reaction	Frequency
	Impaired blood glucose control (hyperglycaemia, hypoglycaemia) in patients with pre-existing diabetes	Common
Musculoskeletal and Connective Tissue Disorders	Pain in extremities	Common
Nervous System Disorders	Dizziness	Very common
	Headache	Very Common
	Syncope, presyncope	Common
	Paraesthesia	Uncommon
Psychiatric Disorders	Depression, depressed mood	Common
	Sleep disorders	Uncommon
Renal and urinary disorders	Renal failure and renal function abnormalities in patients with diffuse vascular disease and/or underlying renal insufficiency	Common
	Micturition disorders	Rare
	Urinary incontinence in women	Very rare
Reproductive system and breast disorders	Erectile dysfunction	Uncommon
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	Common
	Pulmonary oedema	Common
	Asthma in predisposed patients	Common
	Nasal congestion, flu-like symptoms	Rare
Skin and Subcutaneous Disorders	Skin reactions (e.g. allergic exanthema, dermatitis, urticaria, pruritus, psoriatic and lichen planus like skin lesions), alopecia	Uncommon
Vascular Disorders	Hypotension	Very common
	Orthostatic hypotension,	Common
	Disturbances of peripheral circulation (cold extremities, peripheral vascular disease, exacerbation of intermittent claudication and Reynaud's phenomenon)	Common
	Hypertension	Common

Description of selected adverse reactions
The frequency of adverse reactions is not dose-dependent, with the exception of dizziness, abnormal vision and bradycardia. 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 Warnings and Precautions).

Cardiac failure was a very commonly reported adverse event in both placebo (14.5%) and carvedilol-treated (15.4%) patients, 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 Warnings and Precautions).

The following adverse events have been identified during post-marketing use of carvedilol. Because these events are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency and/or establish a causal relationship to drug exposure:

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.

Severe cutaneous adverse reactions (Toxic epidermal necrolysis, Stevens-Johnson syndrome (see section 4.4).

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2. Tel: +353 1 6764971; Fax: +353 1 6762517, Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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:
The patients should be monitored for the above mentioned signs and symptoms and managed according to the best judgment of the treating physicians and according to standard practice for patients with β-blocker overdose (e.g. atropine, transvenous pacing, glucagon, phosphodiesterase inhibitor such as amrinone or milrinone, β-sympathomimetics).

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 as described should be continued for a sufficiently long period of time, i.e. until the patient stabilises, since prolonged elimination half life and redistribution of carvedilol from deeper compartments can be expected.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Carvedilol is a vasodilating non-selective beta blocking agent. Vasodilation is predominantly mediated through alpha1 receptor antagonism.

Carvedilol reduces the peripheral vascular resistance through vasodilation and suppresses the renin-angiotensin-aldosterone system through beta blockade. The activity of plasma renin 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 and like propranolol, it has membrane stabilising properties.

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. Renal blood flow and renal function are maintained. Peripheral blood flow is maintained, therefore cold extremities (often observed with drugs possessing beta-blocking activity) are rarely seen.

- In patients with left ventricular dysfunction or congestive heart failure, carvedilol has demonstrated favourable effects on haemodynamics and improvements in left ventricular ejection fraction and dimensions.

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.

Carvedilol reduces morbidity and mortality in dialysis patients with dilated cardiomyopathy. A meta-analysis of placebo-controlled clinical trials including a large number of patients (>4000) with mild to moderate chronic kidney disease supports carvedilol treatment of patients with left ventricular dysfunction with or without symptomatic heart failure to reduce rates of all cause of mortality as well as heart failure related events.

5.2 Pharmacokinetic properties

Absorption
Following oral administration of a 25 mg capsule to healthy subjects, carvedilol is rapidly absorbed with a peak plasma concentration C_{max} of 21 mg/L reached after approximately 1.5 hour (t_{max}). The C_{max} 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 or the maximum serum concentration although the time to reach maximum serum concentration is delayed.

Distribution
Carvedilol is highly lipophilic, showing a plasma protein of around 95%. The distribution volume ranges between 1.5 and 2L/kg and increased in patients with liver cirrhosis.

Metabolism
In humans, carvedilol is extensively metabolized in the liver via oxidation and conjugation into a variety of metabolites that are eliminated mainly in the bile. Enterohepatic circulation of the parent substance has been shown in animals.

Pharmacokinetic studies in human have shown that the oxidative metabolism of carvedilol is stereoselective. The results of an in vitro study suggested that different cytochrome P450 isoenzymes may be involved in the oxidation and hydroxylation processes including CYP2D6, CYP3A4, CYP2E1, CYP2C9, as well as CYP1A2.

Studies in healthy volunteers and in patients have shown that the R-enantiomer is predominantly metabolized by CYP2D6. The S-enantiomer is mainly metabolized by CYP2D6 and CYP2C9.

Genetic polymorphism
The results of clinical pharmacokinetic studies in human subjects have shown that CYP2D6 plays a major role in the metabolism of R and of S-carvedilol. As a consequence plasma concentrations of R and S-carvedilol are increased in CYP2D6 slow metabolisers. The importance of CYP2D6 genotype in the pharmacokinetics of R and S-carvedilol was confirmed in population pharmacokinetics studies, whereas other studies did not confirm this observation. It was concluded that CYP2D6 genetic polymorphism may be of limited clinical significance.

Elimination
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.

Special populations
Elderly: Age has no statistically significant effect on the pharmacokinetics of carvedilol in hypertensive patients.

Children: Investigation in paediatrics has shown that the weight-adjusted clearance is significantly larger in paediatrics as compared to adults.

Hepatic impairment: In a study in patients with cirrhotic liver disease, the bioavailability of carvedilol was four times greater and the peak plasma level five times higher than in healthy subjects.

Renal impairment: Since carvedilol is primarily excreted via the faeces, significant accumulation in patients with renal impairment is unlikely.

Heart failure: In a study in 24 Japanese 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 in Japanese patients.

5.3 Preclinical safety data

There is no evidence from animal studies that carvedilol has any teratogenic effects. Embryotoxicity was observed only after large doses in rabbits. The relevance of these findings for humans is uncertain. In addition, animal studies have shown that carvedilol crosses the placental barrier and therefore the possible consequences of alpha and beta blockade in the human foetus and neonate should also be borne in mind (although see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Sucrose
Povidone
Crospovidone
Colloidal Anhydrous Silica
Magnesium stearate (E572)
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

Oriented Polyamide/Aluminium/PVC blister

Blisters are packed in cartons containing 28 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Cheplapharm Arzneimittel GmbH
Ziegelhof 24
17489
Greifswald
Germany

8 MARKETING AUTHORISATION NUMBER

PA2239/001/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th June 2000

Date of last renewal: 3rd April 2008

10 DATE OF REVISION OF THE TEXT

January 2018