Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Carvedilol Krka 6.25 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 6.25 mg carvedilol.

Excipients: Each tablet contains 72.25 mg lactose monohydrate and 5 mg sucrose.

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Tablets.

Appearance:

Oval, slightly biconvex, white tablet marked S2 on one side and scored on the reverse.
The tablet can be divided into equal halves.

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

Posology

Symptomatic congestive heart failure
The dosage must be titrated to individual requirements and patients' clinical status should be monitored for 2 - 3 hours after initiation and any dose increase 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 Carvedilol Krka 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 25 mg 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 85 kg (187 lbs) and 50 mg twice daily in patients weighing more than 85 kg. During up-titration of the dose in patients with systolic blood pressure < 100 mmHg, deterioration of renal and/or cardiac functions may occur. Therefore, before each dose increase, these patients should be evaluated by the physician for renal function and symptoms of worsening heart failure or vasodilation. Transient worsening of heart failure, vasodilation or fluid retention may be treated by adjusting doses of diuretics or ACE inhibitors or by modifying or temporarily discontinuing Carvedilol Krka treatment. Under these circumstances, the dose of Carvedilol Krka should not be increased until symptoms of worsening heart failure or vasodilation have been stabilised.
If Carvedilol Krka is discontinued for more than two weeks, therapy should be recommenced at 3.125 mg twice daily and uptitrated 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 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 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 of age have not been established.

Patients with co-existing hepatic disease
Carvedilol Krka is contra-indicated in patients with hepatic dysfunction (see sections *4.3* and 5.2).

Patients with co-existing renal dysfunction
No dose adjustment is anticipated as long as systolic blood pressure is above 100 mmHg (see also sections 4.4 and 5.2).

Method of administration

The tablets should be taken with fluid. For CHF patients Carvedilol Krka should be given with food to slow the rate of absorption and reduce the incidence of orthostatic effects

4.3 Contraindications

Carvedilol Krka is contra-indicated in patients with:

- hypersensitivity to carvedilol 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 A-V 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 < 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, diuretic 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 Krka should be used with caution in combination with digitalis glycosides, as both drugs slow AV conduction.

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.

Diabetes
Care should be taken in the administration of Carvedilol Krka 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 Carvedilol Krka is initiated or up-titrated and hypoglycaemic therapy adjusted accordingly (see section 4.5).

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

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

Withdrawal syndrome
Carvedilol treatment should not be discontinued abruptly, particularly in patients suffering from ischaemic heart disease. The withdrawal of Carvedilol Krka should be gradual (over a period of two weeks).

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, glucosegalactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Peripheral vascular disease and Raynaud's phenomenon
Carvedilol Krka should be used with caution in patients with peripheral vascular disease (e.g. Raynaud's phenomenon). Pure beta-blockers can precipitate or aggravate symptoms of arterial insufficiency. However, as Carvedilol Krka also has alpha-blocking properties, this effect is largely counterbalanced.

Thyrotoxicosis
Carvedilol Krka, as with other agents with beta-blocking activity, may mask/obscure the symptoms of thyrotoxicosis.

Bradycardia
If Carvedilol Krka induces bradycardia, with a decrease in pulse rate to less than 55 beats per minute, the dosage of Carvedilol Krka should be reduced.

Hypersensitivity
Care should be taken in administering Carvedilol Krka 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 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 Krka 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 phaeochromocytoma, an alpha-blocking agent should be initiated prior to the use of any beta-blocking agent. Although Carvedilol Krka has both α and β-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 Krka to patients suspected of having phaeochromocytoma.

Prinzmetal's variant angina
Agents with non-selective beta-blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There is no clinical experience with Carvedilol Krka in these patients, although the alpha-blocking activity of Carvedilol Krka may prevent such symptoms. However, caution should be taken in the administration of Carvedilol Krka 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 bronchospastic reactions, 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.

4.5 Interaction with other medicinal products and other forms of interactions

Pharmacokinetic interactions

Effects of carvedilol 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. 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.

Cyclosporin: Two studies in renal and cardiac transplant patients receiving oral cyclosporin have shown an increase in cyclosporin plasma concentrations following initiation of carvedilol treatment. 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 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. 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 beta-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, co-administration 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 β-blocking properties may enhance the blood-sugar-reducing effect of insulin and oral hypoglycaemics. The signs of hypoglycaemia may be masked or attenuated (especially tachycardia). In patients taking insulin or oral hypoglycaemics, regular monitoring of blood glucose is therefore recommended.

Catecholamine-depleting agents: Patients taking both agents with 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.

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-dihydropyridinescalcium 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 withβ-blocking properties may potentiate bloodpressure- and heart-rate-lowering effects. When treatment with agents with β-blocking properties and clonidine together is to be terminated, the β-blocking agent should be withdrawn first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage.

Anaesthetic agents: careful monitoring of vital signs is recommended during anaesthesia to the synergistic negative inotropic and hypotensive effects of carvedilol and anaesthetic drugs (see section 4.4).

Antihypertensives: As with other agents with -blocking activity, carvedilol may potentiate the effect of other concomitantly administered drugs that are antihypertensive in action (e.g. alpha$_1$-receptor antagonists) or have hypotension as part of their adverse effect profile.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no adequate experience with Carvedilol Krka 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 Krka 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 hypoglycaemiaand 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).

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 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 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

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 to <1/10;
uncommon ≥ 1/1000 to < 1/100;
rare ≥1/10,000 to < 1/1000;
very rare < 1/10,000;

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

Blood and lymphatic system disorders
Common: Anaemia
Rare: 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 mellitus (see section 4.4).

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

Nervous system disorders
Very common: dizziness, headaches
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 and 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, flu-like symptoms

Gastro-intestinal disorders
Common: nausea, diarrhoea, dyspepsia, vomiting and abdominal pain.
Uncommon: constipation
Rare: dry mouth

Hepatobiliary disorders
Very rare: Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyltransferase (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
When Carvedilol is taken for Hypertension, Psoriatic skin lesions may occur or existing lesions exacerbated.

Musculoskeletal and connective tissue disorders
Common: Pain in extremities

Renal and urinary disorders
Common: acute renal failure and renal function abnormalities in patients with diffuse vascular disease and/or underlying renal insufficiency (see section 4.4).
Rare: micturition disorder
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: Oedema, pain

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).

Cardiac failure was a very 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 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 the online reporting option (preferred method) accessible from the IMB homepage (www.imb.ie). A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost' (see details below). Alternatively, the traditional post-paid 'yellow card' option may also be used.

FREEPOST
Pharmacovigilance Section
Irish Medicines Board
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.imb.ie
e-mail: imbpharmacovigilance@imb.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 b-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 are to be expected.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: beta- and alpha$_1$-receptor blockers, ATC code: C07 AG02

Carvedilol is a vasodilating non-selective beta blocking agent with antioxidant properties. Vasodilation is predominantly mediated through alpha$_1$ receptor antagonism.

Carvedilol reduces the peripheral vascular resistance through vasodilation and suppresses the renin-angiotensinaldosterone system through beta blockade. The activity of plasma renin is reduced and fluid retention is rare. Some of the limitations of traditional b-blockers do not appear to be shared by some of the vasodilating b-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.Serum lipid profile and electrolytes are not affected.

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 metabolised in the liver via oxidation and conjugation into a variety of various metabolites, which are mainly eliminated in bile.

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.

5.3 Preclinical safety data

Animal studies revealed no special findings relevant to clinical use (although see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Lactose monohydrate
Povidone K25
Colloidal anhydrous silica
Crospovidone
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

HDPE container and PP closures: Store in the original container.
Blister (OPA/A1/PVC foil-aluminium foil): Store in the original blister.

6.5 Nature and contents of container

Blister (laminated OPA/A1/PVC foil – aluminium foil) and HDPE containers (PP closure and desiccant insert of PE filled with silica gel) containing 14, 28, 30, 50, 56, 60, and 100 tablets.

Not all pack sizes may be marketed.

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

Krka d.d
Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/037/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 August 2003

Date of last renewal: 22 August 2008

10 DATE OF REVISION OF THE TEXT

October 2019