SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Carvedilol 3.125mg Tablets

Carvedilol 6.25mg Tablets

Carvedilol 12.5mg Tablets

Carvedilol 25mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Carvedilol 3.125mg Tablets

Each tablet contains Carvedilol 3.125mg

Excipient with known effect: Also contains Lactose monohydrate 7mg

Carvedilol 6.25mg Tablets

Each tablet contains Carvedilol 6.25mg

Excipient with known effect: Also contains Lactose monohydrate 7mg

Carvedilol 12.5mg Tablets

Each tablet contains Carvedilol 12.5mg

Excipient with known effect: Also contains Lactose monohydrate 7mg

Carvedilol 25mg Tablets

Each tablet contains Carvedilol 25mg

Excipient with known effect: Also contains Lactose monohydrate 7mg

For the full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Tablets.

Carvedilol 3.125mg Tablets

Pink coloured, circular, biconvex uncoated tablets with ‘C’ breakline ‘1’ debossed on one side and plain on the other.
The scoreline is not intended for breaking the tablet.

Carvedilol 6.25mg Tablets

Cream coloured, circular, biconvex uncoated tablets with 'C' breakline '2' debossed on one side and plain on the other.
The scoreline is not intended for breaking the tablet.

Carvedilol 12.5mg Tablets

Light pink coloured, circular, biconvex uncoated tablets with 'C' breakline '3' debossed on one side and plain on the other.
The scoreline is not intended for breaking the tablet.

Carvedilol 25mg Tablets

White to off white, circular, biconvex uncoated tablets with 'C' breakline '4' debossed on one side and plain on the other.
The scoreline is not intended for breaking the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- ***Symptomatic chronic heart failure (CHF)***

  Carvedilol is indicated for the treatment of stable mild, moderate and severe chronic heart failure as adjunct to standard therapies e.g. diuretics, digoxin, and ACE inhibitors in patients with euvolemia.

- ***Hypertension***

  Carvedilol is indicated for the treatment of hypertension.

- ***Angina***

  Carvedilol is indicated for the prophylactic treatment of stable angina.

4.2 Posology and method of administration

Posology

Symptomatic chronic heart failure

Initiation of therapy with Carvedilol should only be under the supervision of a hospital physician, following a thorough assessment of the patient's condition.

Prior to any subsequent titration of the dose, the patient must be clinically evaluated on the day of up-titration by a health-care professional experienced in the management of heart failure to ensure that the clinical status has remained stable. The dose of carvedilol should not be increased in any patient with deteriorating heart failure since last visit or with signs of decompensated or unstable chronic 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 Carvedilol treatment.

Adults

The recommended dose for the initiation of therapy is 3.125mg 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 6.25mg twice daily, followed by 12.5mg 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 25mg given twice daily for all patients with severe CHF and for patients with mild to moderate CHF weighing less than 85kg (187lbs). In patients with mild or moderate CHF weighing more than 85kg, the recommended maximum dose is 50mg twice daily.

During up-titration of the dose in patients with systolic blood pressure < 100mmHg, 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 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 is discontinued for more than two weeks, therapy should be recommended at 3.125mg twice daily and up-titrated in line with the above dosing recommendation.

Older people

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 12.5mg once a day for the first two days. Thereafter the recommended dosage is 25mg 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.

Older people
An initial dose of 12.5mg 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 50mg given once a day or in divided doses.

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

Angina
Adults
The recommended dose for initiation of therapy is 12.5mg twice a day for the first two days. Thereafter, the recommended dosage is 25mg twice a day. If necessary, the dose may be titrated up to 50 mg twice a day.
Dose titration should occur at intervals of at least two weeks.

Older people
The recommended maximum daily dose is 50mg given in divided doses.

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

Special dosage instructions
As with all beta-blockers, treatment should not be stopped abruptly but rather gradually reduced at weekly intervals. This is particularly important in the case of patients with concomitant coronary heart disease.

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

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

Method of administration

The tablets should be taken with fluid. For 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
- Marked fluid retention or overload requiring intravenous support
- Obstructive airways disease
- 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 < 85mmHg)
- Metabolic acidosis
- Phaeochromocytoma (unless adequately controlled by alpha blockade).

4.4 Special warnings and precautions for use

Chronic Congestive Heart Failure

In chronic congestive heart failure patients, worsening cardiac failure or fluid retention may occur during up-titration of Carvedilol. If such symptoms occur, the dose of 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 should be used with caution in combination with digitalis glycosides since both drugs may slow A -V conduction (see section-4.5)

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).

Renal function in Congestive Heart Failure
Reversible deterioration of renal function has been observed with Carvedilol therapy in chronic heart failure patients with low blood pressure (systolic BP < 100mmHg), 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 drug 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 the preceding 48 hours, and the dose of the ACE inhibitor should have been stable for at least the preceding 24 hours.

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

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 patients 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 drugs (e.g., digoxin, ciclosporin, rifampicin, anaesthetic drugs, anti-arrhythmic drug. 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.

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 Carvedilol may prevent such symptoms. Caution should be taken in the administration of Carvedilol to patients suspected of having Prinzmetal's variant angina.

Withdrawal syndrome

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

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.

The following warnings will be included on the outer packaging and leaflet.

Packaging
Do not take this medicine if you have a history of wheezing due to asthma or other lung diseases.
Leaflet
Do not take this medicine if you have a history of wheezing due to asthma or other lung diseases. If you are not sure, talk to your doctor or pharmacist before taking carvedilol.

Important information regarding the ingredients of Carvedilol tablet
Lactose: This product contains the excipient lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium: This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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 and tacrolimus:
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. Furthermore, there is evidence that CYP3A4 is involved in the metabolism of carvedilol. As tacrolimus is a substrate of P-glycoprotein and CYP3A4, its pharmacokinetics may also be affected by carvedilol through these interaction mechanisms.

Inducers and inhibitors of hepatic metabolism:

Rifampicin reduced plasma concentrations of carvedilol by about 70% Cimetidine increased AUC by about 30% but caused no change in Cmax. Care may be required in those 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.

Effects of other medicinal products and substances on the pharmacokinetics of Carvedilol:

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.

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 AUC 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.

Alcohol:
Alcohol intake is shown to have acute hypotensive effects which may augment the blood pressure reduction caused by carvedilol. As carvedilol is soluble in ethanol, the presence of alcohol could affect the rate and/or extent of intestinal absorption of carvedilol. Also, carvedilol is partly metabolized by CYP2E1, an enzyme known to be induced and inhibited by alcohol.

Grapefruit juice:
Consumption of a single dose of 300 ml grapefruit juice results in a 1.2-fold increase of the AUC of carvedilol in comparison to water. While clinical relevance is unclear, patients should avoid concomitant intake of grapefruit juice at least until a stable dose-response relationship is established.

Pharmacodynamic interactions
Insulin or oral hypoglycaemics:
Agents with beta-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 (see section 4.4).

Catecholamine-depleting agents:
Patients taking both agents with beta-blocking properties and a medicinal product 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:
The combined use of non-dihydropyridine calcium channel blockers, amiodarone or other antiarrhythmics 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.

Antihypertensives:
As with other agents with beta-blocking activity, Carvedilol may potentiate the effect of other concomitantly administered drugs that are anti-hypertensive in action (e.g. $alpha_1$-receptor antagonists) or have hypotension as part of their adverse effect profile.

Clonidine:
Concomitant administration of clonidine with agents with β-blocking properties may potentiate blood pressure and heart rate lowering effects. When concomitant treatment with agents with Beta-blockers and clonidine together is to be terminated, Carvedilol should be withdrawn first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage.

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

Non-steroidal anti-inflammatory drugs (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**.** Careful monitoring of patients is recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Animal studies demonstrated effects on pregnancy, embryonal/foetal development, parturition, reproductive toxicity 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)

Breast-feeding:

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 during the 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, after dose increases and in conjunction with alcohol

4.8 Undesirable effects

(a) Summary of the safety profile

The frequency of adverse reactions is not dose-dependent except for dizziness, visual disturbances and bradycardia.

(b) Table of adverse reactions
The risk of most adverse reactions associated with carvedilol is similar for all indications. The exceptions are described in subsection (c).

The following undesirable effects have been reported (e.g. from clinical trials, post-authorisation safety studies or spontaneous reporting) 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**
Infections and Infestations	Pneumonia	Common
	Bronchitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
Blood and Lymphatic System Disorders	Anaemia	Common
	Thrombocytopenia	Rare
	Leukopenia	Very rare
Immune System Disorders	Hypersensitivity (allergic reactions)	Very rare
Metabolism and Nutrition Disorders	Weight increase	Common
	Hypercholesterolaemia	Common
	Impaired blood glucose control (hyperglycaemia, hypoglycaemia) in patients with pre-existing diabetes	Common
Psychiatric Disorders	Depression, depressed mood	Common
	Sleep disorders	Uncommon

Nervous System Disorders	Dizziness	Very common
	Headache	Very Common
	Syncope, presyncope	Common
	Paraesthesia	Uncommon
Eye Disorders	Visual impairment	Common
	Lacrimation decreased (dry eye)	Common
	Eye irritation	Common
Cardiac Disorders	Cardiac failure	Very common
	Bradycardia	Common
	Hypervolaemia (Fluid overload)	Common
	Atrioventricular block	Uncommon
	Angina pectoris	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
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	Common
	Pulmonary oedema	Common
	Asthma in predisposed patients	Common
	Nasal congestion, flu-like symptoms	Rare
Gastrointestinal Disorders	Nausea	Common
	Diarrhoea	Common
	Vomiting	Common
	Dyspepsia	Common
	Abdominal pain	Common
	Constipation	Uncommon
	Dry mouth	Rare
Hepatobiliary disorders	Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT)	Very rare

	increased	
Skin and Subcutaneous Disorders	Skin reactions (e.g. allergic exanthema, dermatitis, urticaria, pruritus, psoriatic and lichen planus like skin lesions), alopecia	Uncommon
Musculoskeletal and Connective Tissue Disorders	Pain in extremities	Common
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
General Disorders and Administration Site Conditions	Asthenia (fatigue)	Very common
	Oedema	Common
	Pain	Common

c) 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 congestive heart failure patients, 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 (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).

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 medicinal product exposure:

Metabolism and nutrition disorder
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.

Psychiatric disorders
Carvedilol may cause hallucinations.

Cardiac disorders
Sinus arrest may occur in predisposed patients (e.g. elderly patients or patients with pre-existing bradycardia, sinus node dysfunction or atrioventricular block).

Skin and subcutaneous tissue disorders
Severe cutaneous adverse reactions (Toxic epidermal necrolysis, Stevens-Johnson syndrome (see section 4.4). Hyperhidrosis

Renal and urinary disorders
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 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, sinus arrest 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

Mechanism of action

Carvedilol, a racemic mixture of two enantiomers (R- and S-carvedilol), is a multiple action alpha- and beta-adrenergic receptor blocker. The beta-adrenergic receptor blockade is associated with the S-enantiomer and non-selective for beta1- and beta2-adrenoceptors, while both enantiomers have the same blocking properties specific for alpha1-adrenergic receptors. At higher concentrations, carvedilol also has a weak to moderate calcium-channel blocking activity. It has no intrinsic sympathomimetic activity and (like propranolol) it has membrane-stabilising properties.

Pharmacodynamic effects
Carvedilol reduces peripheral vascular resistance by selective blockade of alpha1-adrenoreceptors. Through its beta-blocking action, carvedilol suppresses the renin-angiotensin-aldosterone system, reducing the release of renin and making fluid retention rare. It attenuates the increase in blood pressure induced by phenylephrine, an alpha1-adrenoceptor agonist, but not that induced by angiotensin II. Carvedilol's calcium-channel blocking activity may increase blood flow in specific vascular beds such as the cutaneous circulation.

Carvedilol has organ-protective effects likely resulting at least in part from additional properties beyond its adrenergic receptor blockade action. It has potent antioxidant properties associated with both enantiomers, is a scavenger of reactive oxygen radicals and has antiproliferative effects on human vascular smooth muscle cells. Carvedilol has no adverse effect on the lipid profile.

Clinical efficacy and safety

Clinical studies have shown that the balance of vasodilation and beta-blockade provided by carvedilol results in the following effects:

Hypertension
Carvedilol lowers blood pressure in hypertensive patients by beta-blockade and alpha1-mediated vasodilation, without 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. Carvedilol has been shown to maintain stroke volume and reduce total peripheral resistance, without compromising blood supply to distinct organs and vascular beds e.g. kidneys, skeletal muscles, forearms, legs, skin, brain or the carotid artery. There is a reduced incidence of cold extremities and early fatigue during physical activity.

Hypertensive patients with 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.

Stable Angina pectoris
In patients with stable angina, carvedilol has demonstrated anti-ischaemic (improved total exercise time, time to 1 mm ST segment depression and time to angina) and anti-anginal properties that were maintained during long-term treatment. Acute haemodynamic studies demonstrated that carvedilol significantly decreases myocardial oxygen demand and sympathetic over-activity, and reduces both cardiac pre-load (pulmonary artery pressure and pulmonary capillary wedge pressure) and after-load (total peripheral resistance) with consequent improvement in left ventricular systolic and diastolic function without substantial changes in the cardiac output.

Carvedilol has no adverse affects on the metabolic risk factors of coronary heart disease. It does not impair the normal serum lipid profile and in hypertensive patients with dyslipidaemia favourable effects on the serum lipids have been reported after six months of oral therapy.

In two studies, carvedilol 25 mg b.i.d. was compared with other anti-anginal medicinal products 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 (120 mg t.i.d.)	126/122	12 weeks
061	ISDN s.r. (40 mg 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.

Chronic Heart Failure

Carvedilol significantly reduces mortality and hospitalisations and improves symptoms and left ventricular function in patients with ischaemic or non-ischaemic chronic heart failure. The effect of carvedilol is dose dependent.

Chronic Heart Failure patients with renal impairment
Carvedilol reduces morbidity and mortality in dialysis patients with dilated cardiomyopathy, as well as all-cause mortality, cardiovascular mortality and heart failure mortality or first hospitalization in heart failure patients with mild to moderate non-dialysis-dependent chronic kidney disease. 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.

Paediatric population
The safety and efficacy of carvedilol in children and adolescents has not been established due to limited number and size of studies. Available studies focus on treatment of paediatric heart failure which differs from the disease in adults regarding characteristics and aetiology. Because of the small number of

participants compared to studies in adults and a general lack of an optimal dosing scheme for children and adolescents, available data is not sufficient to establish a paediatric safety profile for carvedilol.

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.

Biotransformation
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.

Demethylation and hydroxylation at the phenol ring produce three metabolites with beta-adrenergic receptor blocking activity. Based on pre-clinical studies, the 4'-hydroxy-phenol metabolite is approximately 13 times more potent than carvedilol for beta-blockade. Compared to carvedilol, the three active metabolites exhibit weak vasodilating activity. In humans, the concentrations of the three active metabolites are about 10 times lower than that of the parent substance. Two of the hydroxy-carbazole metabolites of carvedilol are extremely potent antioxidants, demonstrating a 30 to 80-fold greater potency than carvedilol.

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.

Paediatric population*:* The weight-adjusted clearance in children and adolescents is significantly larger than in 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.

In patients with hypertension and renal insufficiency, the area under plasma level-time curve, elimination half-life and maximum plasma concentration does not change significantly. Renal excretion of the unchanged drug decreases in the patients with renal insufficiency; however, changes in pharmacokinetic parameters are modest. Carvedilol is not eliminated during dialysis because it does not cross the dialysis membrane, probably due to its high plasma protein binding.

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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Impairment of fertility
Administration of carvedilol to adult female rats at toxic doses (≥ 200 mg/kg, ≥ 100 times MRHD) resulted in impairment of fertility (poor mating, fewer corpora lutea and fewer implants).

Teratogenicity
There is no evidence from animal studies that Carvedilol has any teratogenic effects.

Embryotoxicity
Embryotoxicity was observed only after large doses in rabbits. Embryotoxicity was observed only after large doses in rabbits. Doses > 60 mg/kg (> 30 times MRHD) caused delays in physical growth/development of offspring. There was embryotoxicity (increased post-implantation deaths) but no malformations in rats and rabbits at doses of 200 mg/kg and 75 mg/kg, respectively (38 to 100 times MRHD). 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 (also see section 4.6).

In summary, effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use (see section 4.6).

6.1 List of excipients

PL 17907/0097

Maize starch
Lactose monohydrate
Sodium starch glycollate
Microcrystalline cellulose
Colloidal silicon dioxide
Magnesium stearate
Polysorbate –80
Colourant:
Red ferric oxide (E172)

PL 17907/0098

Maize starch
Lactose monohydrate
Sodium starch glycollate
Microcrystalline cellulose
Colloidal silicon dioxide
Magnesium stearate
Polysorbate –80
Colourant:
Yellow ferric oxide (E172)

PL 17907/0099

Maize starch
Lactose monohydrate
Sodium starch glycollate
Microcrystalline cellulose
Colloidal silicon dioxide
Magnesium stearate
Polysorbate –80
Colourant:
Yellow ferric oxide (E172) and Red ferric oxide (E172)

PL 17907/0100

Maize starch
Lactose monohydrate
Sodium starch glycollate
Microcrystalline cellulose
Colloidal silicon dioxide
Magnesium stearate
Polysorbate - 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PL 17907/0097

2 years

PL 17907/0098-0099-0100

3 years

6.4 Special precautions for storage

Do not store above 25ºC.

Store in the original package to protect from moisture.

Keep blister in outer carton to protect from light.

6.5 Nature and contents of container

Al / PVC/PVDC blister, pack sizes of 14, 28, 56, 84 tablets.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

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