Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Carvedilol Pfizer 3.125 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 3.125 mg carvedilol.
Excipients: Each tablet contains 28.625 mg lactose monohydrate and 0.625 mg sucrose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, oval shaped, film-coated tablets, debossed with ‘E’ on one side and ‘01’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Essential hypertension
Chronic stable angina pectoris
Adjunctive treatment of moderate to severe stable chronic heart failure

4.2 Posology and method of administration

Oral use.

Essential hypertension:
Carvedilol may be used for the treatment of hypertension alone or in combination with other antihypertensives, especially thiazide diuretics. Once daily dosing is recommended, however the recommended maximum single dose is 25 mg and the recommended maximum daily dose is 50 mg.

Adults
The recommended initial dose is 12.5 mg once a day for the first two days. Thereafter, the treatment is continued at the dose 25 mg/day. If necessary, the dose may be further increased gradually at intervals of two weeks or more rarely.

Elderly
The recommended initial dose in hypertension is 12.5 mg once a day which may also be sufficient for continued treatment.

However, if the therapeutic response is inadequate at this dose, the dose may be further increased gradually at intervals of two weeks or more rarely.

Chronic stable angina pectoris:
A twice-daily regimen is recommended.

Adults
The recommended initial dosage is 12.5 mg twice a day for the first two days. Thereafter, the treatment is continued at the dose 25 mg twice a day. If necessary, the dose may be further increased gradually at intervals of two weeks or more rarely to the recommended maximum dose of 100 mg a day divided into two doses (twice daily).

Elderly
The recommended initial dose is 12.5 mg twice daily for two days. Thereafter, the treatment is continued at the dose 25 mg twice daily, which is the recommended maximum daily dose.

Heart failure:
Carvedilol is given in moderate to severe heart failure in addition to conventional basic therapy with diuretics, ACE inhibitors, digitalis, and/or vasodilators. The patient should be clinically stable (no change in NYHA-class, no hospitalisation due to heart failure) and the basic therapy must be stabilized for at least 4 weeks prior to treatment. Additionally the patient should have a reduced left ventricular ejection fraction and heart rate should be > 50 bpm and systolic blood pressure > 85 mm Hg (see section 4.3).

The initial dose is 3.125 mg twice a day for two weeks. If this dose is tolerated, the dose may be increased slowly with intervals of not less than two weeks up to 6.25 mg twice a day, then up to 12.5 mg twice a day and finally up to 25 mg twice a day. The dosage should be increased to the highest tolerable level.

The recommended maximum dosage is 25 mg twice a day for patients with a body weight of less than 85 kg, and 50 mg twice a day for patients with a body weight above 85 kg, provided that the heart failure is not severe. A dose increase to 50 mg twice daily should be performed carefully under close medical supervision of the patient.

Transient worsening of symptoms of heart failure may occur at the beginning of treatment or due to a dose increase, especially in patients with severe heart failure and/or under high dose diuretic treatment. This does usually not call for discontinuation of treatment, but dose should not be increased. The patient should be monitored by a physician/cardiologist for two hours after starting treatment or increasing the dose. Before each dose increase, an examination should be performed for potential symptoms of worsening heart failure or for symptoms of excessive vasodilatation (e.g. renal function, body weight, blood pressure, heart rate and rhythm). Worsening of heart failure or fluid retention is treated by increasing the dose of diuretic, and the dose of carvedilol should not be increased until the patient is stabilized. If bradycardia appears or in case of lengthening of AV conduction, the level of digoxin should first be monitored. Occasionally it may be necessary to reduce the carvedilol dose or temporarily discontinue treatment altogether. Even in these cases, carvedilol dose titration can often be successfully continued.

Renal function, thrombocytes and glucose (in case of NIDDM and/or IDDM) should be monitored regularly during dose titration. However, after dose titration the frequency of monitoring can be reduced.

If carvedilol has been withdrawn for more than two weeks, the therapy should be reinitiated with 3.125 mg twice a day and increased gradually according to the above recommendations.

Renal insufficiency
Dosage must be determined for each patient individually, but according to pharmacokinetic parameters there is no evidence that dose adjustment of carvedilol in patients with renal impairment is necessary.

Moderate hepatic dysfunction
Dose adjustment may be required.

Children and adolescents (< 18 years)
Carvedilol is not recommended for the use in children below 18 years of age due to insufficient data on the efficacy and safety of carvedilol.

Elderly
Elderly patients may be more susceptible to the effects of carvedilol and should be monitored more carefully.

As with other beta-blockers and especially in patients with coronary disease, the withdrawal of carvedilol should be done gradually (see section 4.4).

Methods of administration
The tablets should be taken with the adequate supply of fluid. It is recommended that heart failure patients take their carvedilol medication with food to allow the absorption to be slower and the risk of orthostatic hypotension to be reduced.

4.3 Contraindications

- Hypersensitivity to the carvedilol or to any of the excipients of Carvedilol .
- Heart failure belonging to NYHA Class IV of the heart failure classification with marked fluid retention or overload requiring intravenous inotropic treatment.
- Chronic obstructive pulmonary disease with bronchial obstruction (see section 4.4).
- Clinically significant hepatic dysfunction.
- Bronchial asthma.
- AV block, degree II or III (unless a permanent pacemaker is in place).
- Severe bradycardia (<50 bpm).
- Sick sinus syndrome (incl. sino-atrial block).
- Cardiogenic shock.
- Severe hypotension (systolic blood pressure below 85 mmHg).
- Prinzmetal's angina.
- Untreated phaeochromocytoma.
- Metabolic acidosis.
- Severe peripheral arterial circulatory disturbances.
- Concomitant intravenous treatment with verapamil or diltiazem (see section 4.5).

4.4 Special warnings and precautions for use

Warnings to be considered particularly in heart failure patients
In chronic heart failure patients carvedilol should be administered principally in addition to diuretics, ACE inhibitors, digitalis and/or vasodilators. Initiation of therapy should be under the supervision of a hospital physician. Therapy should only be initiated, if the patient is stabilized on conventional basic therapy for at least 4 weeks. Patients with severe heart failure, salt and volume depletion, elderly or patients with low basic blood pressure should be monitored for approximately 2 hours after the first dose or after dose increase as hypotension may occur. Hypotension due to excessive vasodilatation is initially treated by reducing the dose of the diuretic. If symptoms still persist, the dose of any ACE inhibitor may be reduced. At the start of therapy or during up-titration of Carvedilol worsening of heart failure or fluid retention may occur. In these cases, the dose of diuretic should be increased. However, sometimes it will be necessary to reduce or withdraw Carvedilol medication. The carvedilol dose should not be increased before symptoms due to the worsening of heart failure or hypotension due to vasodilatation are under control.

Reversible deterioration of renal function has been observed during carvedilol therapy in heart failure patients with low blood pressure (systolic < 100 mm Hg), ischaemic heart disease and generalized atherosclerosis, and/or underlying renal insufficiency. In heart failure patients with these risk factors, renal function should be monitored during dose titration of carvedilol. If significant worsening of renal function occurs, the carvedilol dose must be reduced or therapy must be discontinued.

In patients with chronic heart failure treated with digitalis, carvedilol should be given with caution, as digitalis and carvedilol both lengthen the AV conduction time (see section 4.5).

Other warnings as regards carvedilol and beta-blockers in general
Agents with non-selective beta-blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There is no clinical experience with carvedilol in these patients, although the alpha-blocking activity of carvedilol may prevent such symptoms. However, caution should be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.

Patients with a chronic obstructive pulmonary disease with a tendency towards bronchospasms who are not treated with oral or inhalation medicine should only be given carvedilol if the expected improvement outweighs the possible risk. Patients should be monitored closely in the initial phase, and titration of carvedilol and carvedilol dose should be reduced in case of bronchospasms.

Carvedilol may mask symptoms and signs of acute hypoglycaemia. Impaired blood glucose control may occasionally occur in patients with diabetes mellitus and heart failure in connection with the use of carvedilol. Therefore, close monitoring of diabetic patients receiving carvedilol is required by means of regular blood glucose measurements, especially during dose titration, and adjustment of antidiabetic medication as necessary (see section 4.5). Blood glucose levels should also be closely monitored after a longer period of fasting.

Carvedilol may mask features (symptoms and signs) of thyrotoxicosis.

Carvedilol may cause bradycardia. If there is a decrease in pulse rate to less than 55 beats per minute, and symptoms associated with bradycardia occur, the carvedilol dose should be reduced.

When carvedilol is used concomitantly with calcium channel blocking agents such as verapamil and diltiazem or with other antiarrhythmics, specifically amiodarone, the patient's blood pressure and ECG have to be monitored. Intravenous co-administration should be avoided (see section 4.5).

Cimetidine should be administered only with caution concomitantly as effects of carvedilol may be increased (see section 4.5).

Persons wearing contact lenses should be advised of a possible reduction of the secretion of lacrimal fluid.

Care should be taken in administrating carvedilol to patients with a history of serious hypersensitivity reactions and in those undergoing desensitisation therapy as beta-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions. Cautions should be exercised when prescribing beta-blockers to patients with psoriasis since skin reactions may be aggravated.

Carvedilol should be used with caution in patients with peripheral vascular diseases, as beta-blockers may aggravate symptoms of the disease. The same also applies to those with Raynaud's syndrome, as there may be exacerbation or aggravation of symptoms.

Patients who are known as poor metabolizers of debrisoquine, should be closely monitored during initiation of therapy (see section 5.2).

Since there is limited clinical experience, carvedilol should not be administered in patients with labile or secondary hypertension, orthostasis, acute inflammatory heart disease, haemodynamic relevant obstruction of heart valves or outflow tract, end-stage peripheral arterial disease, concomitant treatment with α1-receptor antagonist or α2-receptor agonist.

In patients with phaeochromocytoma, an initial treatment with alpha-blockers should be started before using any beta-blocker. Although carvedilol exercises alpha and beta blockade there is not sufficient experience in this disease, therefore caution should be advised in these patients.

Because of its negative dromotropic action, carvedilol should be given with caution to patients with first degree heart block.

Beta-blockers reduce the risk of arrhythmias at anasthesia, however the risk of hypotension may be increased as well. Caution should therefore be observed with the use of certain anaesthetic medicines. Newer studies suggest however, a benefit of beta-blockers in preventing perioperative cardiac morbidity and reduction of the incidence of cardiovascular complications.

As with other beta-blockers, carvedilol should not be discontinued abruptly. This applies in particular to patients with ischaemic heart disease. Carvedilol therapy must be discontinued gradually within two weeks, e.g. by reducing the daily dose to half every three days. If necessary, at the same time replacement therapy should be initiated to prevent exacerbation of angina pectoris.

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

4.5 Interaction with other medicinal products and other forms of interaction

Antiarrhythmics.
Isolated cases of conduction disturbance (rarely compromised haemodynamics) have been reported, if oral carvedilol and oral diltiazem verapamil and/or amiodarone are given concomitantly. As with other beta-blockers, ECG and blood pressure should be monitored closely when concomitantly administering calcium-channel-blockers of the verapamil and diltiazem type due to the risk of AV conduction disorder or risk of cardiac failure (synergetic effect). Close monitoring should be done in case of co-administration of carvedilol, and amiodarone therapy (oral) or class I antiarrhythmics. Bradycardia, cardiac arrest, and ventricular fibrillation have been reported shortly after initiation of beta-blocker treatment in patients receiving amiodarone. There is a risk of cardiac failure in case of class Ia or Ic antiarrhythmics concomitant intravenous therapy.

Concomitant treatment with reserpine, guanethidine, methyldopa, guanfacine and monoamine oxidase inhibitors (exception MAO-B inhibitors) can lead to additional decrease in heart rate. And hypotension Monitoring of vital signs is recommended.

Dihydropyridines.
The administration of dihydropyridines and carvedilol should be done under close supervision as heart failure and severe hypotension have been reported.

Nitrates.
Increased hypotensive effects.

Cardiac glycosides.
An increase of steady state digoxin levels by approximately 16% and of digitoxin by approximately 13% has been seen in hypertensive patients in connection with the concomitant use of carvedilol and digoxin. Monitoring of plasma digoxin concentrations is recommended when initiating, discontinuing or adjusting treatment with carvedilol.

Other antihypertensive medicines.
Carvedilol may potentiate the effects of other concomitantly administered antihypertensives (e.g. α1-receptor antagonists) and medicines with antihypertensive adverse reactions such as barbiturates, phenothiazines, tricyclic antidepressants, vasodilating agents and alcohol.

Cyclosporin.
The plasma level of cyclosporin is increased when carvedilol is co-administered. It is recommended that cyclosporin concentrations are carefully monitored.

Antidiabetics including insulin.
The blood sugar-lowering effect of insulin and oral diabetic medicines may be intensified. Symptoms of hypoglycaemia may be masked. In diabetic patients regular monitoring of blood glucose levels is necessary.

Clonidine.
In case of withdrawal of both carvedilol and clonidine, carvedilol should be withdrawn several days before the stepwise withdrawal of clonidine.

Inhalational anaesthetics.
Caution is advised in case of anaesthesia due to synergistic, negative inotrope and hypotensive effect of carvedilol and certain anaesthetics.

NSAIDs, estrogens and corticosteroids.
The antihypertensive effect of carvedilol is decreased due to water and sodium retention.

Medicines inducing or inhibiting cytochrome P450 enzymes.
Patients receiving medicines that induce (e.g. rifampicin and barbiturates) or inhibit (e.g. cimetidine, ketoconazole, fluoxetine, haloperidol, verapamil, erythromycine) cytochrome P450 enzymes have to be monitored closely during concomitant treatment with carvedilol as serum carvedilol concentrations may be reduced by the first agents and increased by the enzyme inhibitors.

Sympathomimetics with alpha-mimetic and beta-mimetic effects.
Risk of hypertension and excessive bradycardia.

Ergotamine.
Vasoconstriction increased.

Neuromuscular blocking agents.
Increased neuromuscular block.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of carvedilol in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Beta-blockers reduce placental perfusion which may result in intrauterine fetal death and immature and premature deliveries. In addition, adverse reactions (especially hypoglycaemia, hypotension, bradycardia, respiratory depression and hypothermia) may occur in the fetus and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Carvedilol should not be used during pregnancy unless clearly necessary (that is if the potential benefit for the mother outweighs the potential risk for the fetus/neonate). The treatment should be stopped 2-3 days before expected birth. If this is not possible the new-born has to be monitored for the first 2-3 days of life.

Lactation
Carvedilol is lipophilic and according to results from studies with lactating animals, carvedilol and its metabolites are excreted in breast milk and, therefore, mothers receiving carvedilol should not breast-feed.

4.7 Effects on ability to drive and use machines

This medicinal product has minor influence on the ability to drive and use machines. Some individuals may have reduced alertness especially on initiation and adjustment of medication.

4.8 Undesirable effects

The following terminologies have been used in order to classify the occurrence of undesirable effects.
Very common (≥ 1/10)
Common (≥ 1/100 to <1/10)
Uncommon (≥ 1/1,000 to <1/100)
Rare (≥ 1/10,000 to <1/1,000)
Very rare (<1/10,000), not known (cannot be established from the available data).

Adverse reactions occur mainly at the beginning of treatment.

Adverse reactions in heart failure patients reported from clinical studies.
Adverse reactions that occurred in heart failure patients, in clinical studies, and not seen as commonly in subjects who received placebo are listed below.

Cardiac disorders
Common: bradycardia, postural hypotension, hypotension, oedema (including generalised, peripheral, dependent and genital oedema, oedema of the legs, hypervolaemia and fluid overload).
Uncommon: syncope (including presyncope), AV-block and aggravation of heart insufficiency during up-titration.

Blood and lymphatic system disorder
Rare: thrombocytopenia.
Very rare: leucopenia.

Nervous system disorders
Very common: dizziness*, headache* (usually mild), asthenia (including fatigue).

Eye disorders
Common: vision abnormalities.

Gastrointestinal disorders
Common: nausea, diarrhoea, and vomiting.

Renal and Urinary disorders
Rare: acute renal failure and renal function abnormalities in patients with diffuse vascular disease and/or impaired renal function (see section 4.4).

Metabolism and nutrition disorders
Common: weight increase, hypercholesterolemia, hyperglycaemia, hypoglycaemia and worsening control of blood glucose (in patients with pre-existing diabetes mellitus) (see section 4.4).

* Occuring particularly at the start of treatment.

The frequency of adverse reactions is not dose dependent, with the exception of dizziness, visual disturbance, bradycardia and aggravation of heart insufficiency.

Cardiac contractility may be decreased during dose titration, but this is rare.

Adverse reactions in patients with hypertension and angina pectoris reported from clinical studies
The adverse reaction profile in patients with hypertension and angina is similar to that observed in patients with heart failure. However, the frequency of adverse reactions is lower in patients with hypertension and angina pectoris.

Cardiac disorders
Common: bradycardia*, postural hypotension*
Uncommon: syncope*, disturbances of peripheral circulation (cold extremities, PVD, exacerbation of intermittent claudication and Raynauds phenomenon). AV-block, angina pectoris (including chest pain), symptoms of heart failure and peripheral oedema.

Blood and lymphatic system disorders
Very rare: Increase of ALAT, ASAT and gamma-GT, thrombocytopenia, leucopenia.

Nervous system disorder
Common: dizziness*, headaches* and fatigue*
Uncommon: paraesthesia

Eye disorder
Common: reduced lacrimation (in particular in patients wearing contact lenses), eye irritation
Uncommon: disturbed vision.

Respiratory disorders:
Common: asthma and dyspnoea in predisposed patients.
Rare: stuffy nose.

Gastrointestinal disorders
Common: nausea, abdominal pain, diarrhoea
Uncommon: constipation and vomiting.
Rare: dryness of the mouth

Renal and urinary disorders
Rare: disturbances of micturition

Skin and subcutaneous disorders
Uncommon: skin reactions (e.g. allergic exanthema, dermatitis, urticaria, pruritus, lichen planus-like reactions, and increased sweating). Psoriatic skin lessions may occur or existing lesions exacerbated.

Musculoskeletal and connective tissue disorders
Common: pain in the extremeties

General disorders and administration site conditions
Isolated cases of allergic reactions

Reproductive system and breast disorders
Uncommon: impotence

Psychiatric disorder
Uncommon: sleep disturbance, depression, hallucination, confusion
Very rare: psychosis

* Occuring particularly at the start of treatment.

Non-selective beta-blockers in particular may also result in latent diabetes mellitus becoming manifest, manifest diabetes being aggravated and blood glucose control being disturbed. Mild disturbances of glucose balance are possible, however not common, also during treatment with carvedilol.

The frequency of adverse reactions is not dose dependent, with the exception of dizziness, visual disturbance, bradycardia and aggravation of heart insufficiency.

4.9 Overdose

Symptoms
Overdose may cause serious hypotension, bradycardia, heart failure, cardiogenic shock and cardiac arrest. There may also be respiratory problems, bronchospasm, vomiting, reduced consciousness and convulsions.

Treatment
In addition to normal treatment procedures, vital signs must be monitored and, if necessary, corrected at an intensive care unit. The following supportive measures may be taken: Atropine: 0.5 - 2 mg intravenously (for treatment of severe bradycardia). Glucagon: initially 1 - 10 mg intravenously followed if necessary by a slow infusion of 2 – 5 mg/hour (in order to maintain cardiovascular function).

Sympathomimetics according to their efficacy and the patient's weight: dobutamine, isoprenaline or adrenaline.

If peripheral vasodilatation is the dominant symptom of overdose, the patient has to be given noradneraline or etilefrine. The patient's circulation must be monitored continuously.

If the patient has bradycardia unresponsive to pharmacotherapy, pacemaker therapy should be started. For the treatment of bronchospasm, the patient must be given beta-sympathomimetics (as aerosol or intravenously, if the aerosol does not provide adequate effect) or theophylline intravenously. If the patient has convulsions, diazepam may be administered as a slow intravenous injection.

Carvedilol is highly protein-bound. Therefore, it cannot be eliminated by dialysis.

Important! In cases of severe overdose when the patient is in shock, supportive treatment should be continued for a sufficiently long period of time, since the elimination and redistribution of carvedilol are likely to be slower than normal. Duration of the antidote treatment depends on the seriousness of the overdose; supportive treatment must be continued until the patient stabilises.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha- and beta- blocking agents
ATC code: C07A G02

Carvedilol is a vasodilatory non-selective beta-blocker, which reduces the peripheral vascular resistance by selective alpha1-receptor blockade and suppresses the renin-angiotensin through non-selective beta-blockade. Plasma rennin activity is reduced and fluid retention is rare.

Carvedilol has no intrinsic sympathomimetic activity (ISA). Like propranolol, it has membrane stabilising properties.

Carvedilol is a racemate of two stereoisomers. Both enantiomers were found to have alpha-adrenergic blocking activity in animal models. Non-selective beta1-and beta2-adrenoceptor blockade is attributed mainly to the S(-) enantiomer.

The antioxidant properties of carvedilol and its metabolites have been demonstrated in *in vitro* and *in vivo* animal studies and *in vitro* in a number of human cell types.

In hypertensive patients, a reduction in blood pressure is not associated with a concomitant increase in peripheral resistance, as observed with pure beta-blocking agents. Heart rate is slightly decreased. Stroke volume remains unchanged. Renal blood flow and renal function remain normal, as does peripheral blood flow, therefore, cold extremities, often observed with beta-blockers, are rarely seen. In hypertensive patients carvedilol increases the plasma norepinephrine concentration.

In prolonged treatment of patients with angina, carvedilol has been seen to have an anti-ischaemic effect and to alleviate pain. Haemodynamic studies demonstrated that carvedilol reduces ventricular pre- and after-load. In patients with left ventricular dysfunction or congestive heart failure, carvedilol has a favourable effect on haemodynamics and left ventricular ejection fraction and dimensions.

Carvedilol has no negative effect on the serum lipid profile or electrolytes. The ratio of HDL (high-density lipoproteins) and LDL (low-density lipoproteins) remains normal.

5.2 Pharmacokinetic properties

General description:
The absolute bioavailability of orally administered carvedilol is approximately 25 %. Plasma levels peak at approximately 1 hour after dosing. There is a linear correlation between the dose and plasma concentrations. In patients with slow hydroxylation of debrisoquine plasma carvedilol concentrations increased up to 2-3-fold compared to rapid debrisoquine metabolisers. Food does not affect bioavailability although the time to reach maximum plasma concentration is delayed. Carvedilol is a highly lipophilic compound. Approximately 98% to 99% of carvedilol is bound to plasma proteins. Its volume of distribution is approximately 2l/kg. The first pass effect after oral administration is approximately 60-75%.

The average elimination half-life of carvedilol ranges from 6 to 10 hours. Plasma clearance is approximately 590 ml/min. Elimination is mainly biliary. The primary route of excretion of carvedilol is via the faeces. A minor portion is eliminated via the kidneys as metabolites.

Carvedilol is found to be extensively metabolised into various metabolites, which are mainly eliminated in bile. Carvedilol is metabolised in the liver mainly through aromatic ring oxidation and glucuronidation. Demethylation and hydroxylation at the phenol ring yield three active metabolites with beta-blocking activity. Compared to carvedilol, these three active metabolites have a weak vasodilatory effect. On the basis of preclinical studies, the 4'-hydroxyphenolmetabolite has a beta-blocking activity 13 times more potent than that of carvedilol. However, the metabolite concentrations in humans are approximately 10 times lower than those of carvedilol. Two of the hydroxycarbazole metabolites of carvedilol are highly potent antioxidants, with a 30-80-fold potency compared to carvedilol.

Properties in the patient.
The pharmacokinetics of carvedilol are affected by age; plasma levels of carvedilol are approximately 50% higher in the elderly compared to young subjects. In a study in patients with liver cirrhosis, the bioavailability of carvedilol was four times greater and the peak plasma level five times higher and the volume of distribution three times higher than in healthy subjects. In some of the hypertensive patients with moderate (creatinine clearance 20-30 ml/min) or severe (creatinine clearance < 20 ml/min) renal insufficiency, an increase in plasma carvedilol concentrations of approximately 40-55% was seen compared to patients with normal renal function. However, there was a large variation in the results.

5.3 Preclinical safety data

Carvedilol demonstrated no mutagenic or carcinogenic potential.

High doses of carvedilol impaired fertility and affected pregnancy in rats (increased resorptions). Decreased fetal weight and delayed skeletal development were also seen in rats. Embryotoxicity (increased post-implantation loss) occurred in rats and rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Lactose monohydrate
Silica Colloidal anhydrous
Crospovidone (Type A)
Crospovidone (Type B)
Povidone 30
Sucrose
Magnesium stearate

Film-coating
Macrogol 400
Polysorbate 80
Titanium dioxide (E171)
Hypromellose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

PVC/PE/PVDC –Aluminium blister packs:
Pack sizes: 10, 14, 28, 30, 50, 56, 60 and 100 film-coated tablets.
HDPE bottle with white opaque polypropylene stock ribbed closure:
Pack sizes: 30 and 1000 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 822/44/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th February 2011

10 DATE OF REVISION OF THE TEXT