# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Carvedilol 3.125 mg tablet

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 3.125 mg carvedilol.

Excipient with known effect: Each tablet contains 12.5mg lactose monohydrate
For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet

White, oval, smooth on both sides.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Essential hypertension.
Chronic stable angina pectoris
Adjunctive treatment in moderate to severe stable heart failure.

### *4.2 Posology and method of administration*

Posology
Carvedilol is available in 4 strengths: 3.125 mg, 6.25 mg, 12.5 mg and 25 mg

*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*

*Adults*
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. If necessary, the dose may be further increased gradually at intervals of two weeks or more rarely. The recommended maximum daily dose is 100 mg in divided doses (50mg 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*
Treatment of 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 stabilised for at least 4 weeks prior to treatment. Additionally the patient should have a reduced left ventricular ejection fraction and heart frequency 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 the initial dose is well tolerated, the carvedilol dose can be increased at intervals of two weeks or more rarely, first to 6.25 mg twice daily, then 12.5 mg twice daily followed by 25 mg twice daily. It is recommended that the dose is increased to the highest level tolerated by the patient.

The recommended maximum dose is 25 mg given twice daily in patients weighing less than 85 kg and 50 mg twice daily in patients weighing more than 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 the dose should not be increased. The patient should be monitored by a physician/cardiologist after starting carvedilol 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 heart 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 stabilised. 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.

If carvedilol therapy is discontinued for more than two weeks, it should be reinitiated at 3.125 mg twice daily and increased gradually in accordance with the above recommendation.

*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 failure is necessary.

*Moderate hepatic dysfunction.*
Dose adjustment may be required.

*Paediatric population (< 18 years)*
The safety and efficacy of carvedilol in children and adolescents aged below 18 years has not been established.

*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 coronary patients, the withdrawal of carvedilol should be done gradually (see section 4.4).

Method of administration.
The tablets do not need to be taken with a meal. However, 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 carvedilol or to any of the excipients listed in section 6.1.
Unstable/decompensated heart failure
Heart failure belonging to NYHA Class IV of the heart failure classification requiring intravenous inotropic treatment.
Clinically significant hepatic dysfunction.
History of bronchospasm or asthma.
Second or third degree AV block (unless a permanent pacemaker is in place).
Severe bradycardia (<50 bpm).
Cardiogenic shock.
Sick sinus syndrome (including sinoatrial blocks).
Severe hypotension (systolic blood pressure below 85 mmHg).
Metabolic acidosis.
Patients with phaeochromocytoma that are not receiving alpha blockade treatment.
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.**

Carvedilol should be administered principally in addition to diuretics, ACE inhibitors, digitalis and/or vasodilators. Therapy should only be initiated, if the patient is stabilized on conventional basic therapy for at least 4 weeks. Decompensated patients have to be re-compensated. 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. The carvedilol dose may be further reduced or temporarily discontinued, if necessary. The carvedilol dose should not be increased again before symptoms due to the worsening of heart failure or vasodilatation are under control.

*Chronic congestive heart failure*
In congestive heart failure patients, worsening cardiac failure or fluid retention may occur during up-titration of carvedilol. If such symptoms occur, diuretics should be increased and the carvedilol dose should not be advanced 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 titration of carvedilol. Carvedilol should be used with caution in combination with digitalis glycosides, as both drugs slow AV conduction.

*Renal function in congestive heart failure*
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 generalised 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.

*Concomitant use of digitalis*
During concomitant administration of carvedilol and digitalis, it has to be kept in mind that both digitalis and carvedilol lengthen the atrioventricular conduction time (see section 4.5).

**Other warnings as regards carvedilol and beta-blockers in general.**

*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.

*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 oral or inhaled medication, and only if the potential benefit outweighs the potential risk.

In patients with a tendency to bronchospasm, respiratory distress can occur as a result of a possible increase in airway resistance. Patients should be closely monitored during initiation and up-titration of carvedilol and the dose of carvedilol should be reduced if any evidence of bronchospasm is observed during treatment.

## Diabetes

***Care should be taken in the administration of carvedilol to patients with diabetes mellitus, as the early signs and symptoms of acute hypoglycaemia may be masked or attenuated. . In chronic heart failure patients with diabetes, the use of carvedilol may be associated with worsening control of blood glucose. Therefore, close monitoring of diabetic patients receiving carvedilol is required by means of regular blood glucose measurements and adjustment of antidiabetic medication as necessary (see section 4.5).***

*Thyrotoxicosis*
Carvedilol may mask the symptoms and signs of thyrotoxicosis.

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

*Concomitant use of calcium channel blockers*
Careful monitoring of ECG and blood pressure is necessary in patients receiving concomitant therapy with calcium channel blockers of the verapamil or diltiazem type or other antiarrhythmic drugs. Intravenous co-administration should be avoided (see section 4.5).

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

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

*Hypersensitivity*
Care should be taken in administering 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.

*Psoriasis*
Caution should be exercised when prescribing beta-blockers to patients with psoriasis since skin reactions may be aggravated.
Patients with a history of psoriasis associated with b-blocker therapy should take carvedilol only after consideration of the risk-benefit ratio.

*Peripheral vascular disease*
Carvedilol should be used with caution in patients with peripheral vascular disease as β-blockers can precipitate or aggravate symptoms of arterial insufficiency.
*Raynaud's phenomenon*

Carvedilol should be used with caution in patients suffering from peripheral circulatory disorders (eg Raynaud's phenomenon) as there may be exacerbation of symptoms.

*Poor metabolisers of debrisoquine*
Patients who are known as poor metabolisers of debrisoquine, should be closely monitored during initiation of therapy (see 5.2 “Pharmacokinetic properties”).

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

*Anesthesia and major surgery*
Caution should be exercised in patients undergoing general surgery, because of the synergistic negative inotropic effects of carvedilol and anaesthetic drugs. Caution should therefore be observed with the use of certain anaesthetic drugs. Newer studies suggest however, a benefit of beta-blocker in preventing perioperative cardiac morbidity and reduction of the incidence of cardiovascular complications.

*Withdrawal syndrome*
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.

*Prinzmetal's variant angina*
Agents with non-selective b-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 a-blocking activity of carvedilol may prevent such symptoms. Caution should, however, be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.

*Phaeochromocytoma*
In patients with pheochromocytoma, an a-blocking agent should be initiated prior to the use of any b-blocking agent. Although carvedilol has both a- and b-blocking pharmacological activities, there is no experience with its use in this condition. Caution should therefore be taken in the administration of carvedilol to patients suspected of having pheochromocytoma.

Since there is limited clinical experience, carvedilol should not be administered in patients with labile or secondary hypertension, orthostasis, acute inflammatory heart disease, haemodynamically relevant obstruction of heart valves or outflow tract, end-stage peripheral arterial disease, concomitant treatment with $\alpha_1$-receptor antagonist or $\alpha_2$-receptor agonist.

*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.

## *4.5 Interaction with other medicinal products and other forms of interaction*

*Pharmacokinetic interactions*
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.

*Antiarrhythmics.*
Isolated cases of conduction disturbance, rarely with haemodynamic disruption, have been observed in patients taking carvedilol and (oral) diltiazem, verapamil and/or amiodarone. As with other beta-blockers, careful monitoring of the ECG and blood pressure should be undertaken when co-administering calcium channel-blockers of the verapamil and diltiazem type as the risk of AV conduction disorders or risk of cardiac failure are increased (synergistic effect). Close monitoring should be done when co-administering carvedilol, and either a class I antiarrhythmics or amiodarone (oral). 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.

*Amiodarone.*
In patients with heart failure, amiodarone decreased the clearance of S-carvedilol likely by inhibition of CYP2C9. The mean R-carvedilol plasma concentration was not altered. Consequently, there is a potential risk of increased β-blockade caused by a raise of the plasma S-carvedilol concentration.

Concomitant treatment with guanethidine, methyldopa and guanfacine can lead to additional decrease in heart rate. 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.

*Digoxin*
Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Both digoxin and carvedilol slow AV conduction. Monitoring of plasma digoxin concentrations is recommended when initiating, discontinuing or adjusting treatment with carvedilol (see section 4.4).

*Other antihypertensive drugs*

Carvedilol may potentiate the effects of other concomitantly administered antihypertensives (e.g. $\alpha_1$-receptor antagonists) and drugs with antihypertensive side effects such as barbiturates, phenothiazines, tricyclic antidepressants, vasodilating agents and alcohol.

*Ciclosporin*
Two studies in renal and cardiac transplant patients receiving oral cyclosporin have shown an increase in cyclosporin plasma concentrations following initiation of carvedilol treatment. In about 30% of patients, the dose of cyclosporin had to be reduced in order to maintain cyclosporin concentrations within the therapeutic range, while in the remainder no adjustment was needed. On average, the dose of cyclosporin was reduced about 20% in these patients. 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.

*Oestrogens 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, erythromycin) cytochrome P450 enzymes have to be monitored closely during concomitant treatment with carvedilol as serum carvedilol concentrations may be reduced by enzyme inducers and increased by the enzyme inhibitors. However, based on the relatively small effect of cimetidine on carvedilol drug levels, the likelihood of any clinically important interaction is minimal.

*Rifampicin*
Rifampicin reduced plasma concentrations of carvedilol by about 70% Cimetidine increased AUC by about 30% but caused no change in Cmax. In a study in 12 healthy subjects, rifampicin administration decreased the carvedilol plasma levels by about 70%, most likely by induction of P-glycoprotein leading to a decrease of the intestinal absorption of carvedilol.

*Fluoxetine*
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 AUC. However, no difference in adverse events, blood pressure or heart rate were noted between treatment groups.

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

*Ergotamine*
Vasoconstriction increased.

*Neuromuscular blocking agents*.

Increased neuromuscular block.

***Pharmacodynamic interactions***

Insulin or oral hypoglycaemics
*Symptoms of hypoglycaemia may be masked or attenuated (especially tachycardia).*
Agents with β-blocking properties may enhance the blood-sugar-reducing effect of insulin and oral hypoglycaemics. 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.

*Verapamil, diltiazem, amiodarone or other antiarrhythmics*
In combination with carvedilol can increase the risk of AV conduction disturbances (see section 4.4).

*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 β-blocking properties and clonidine is to be terminated, the β-blocking agent should be discontinued first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage.

*Calcium channel blockers*
(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 calcium channel blockers Carvedilol of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored.

*Antihypertensives*
As with other agents with β-blocking activity, carvedilol may potentiate the effect of other concomitantly administered drugs that are anti-hypertensive in action (eg α1-receptor antagonists) or have hypotension as part of their adverse effect profile such as barbiturates, phenothiazines, tricyclic antidepressants, vasodilating agents and alcohol.

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

*NSAIDs*

The concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) and beta-adrenergic blockers may result in an increase in blood pressure and 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
Use of carvedilol is not recommended during pregnancy and lactation.

There is no adequate clinical experience with carvedilol in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development (see section 5.3). The potential risk for humans is unknown.

Carvedilol did not demonstrate any teratogenic effects in animal reproduction studies, but there is insufficient clinical evidence of its safety in pregnant women *(see 5.3).*

Beta-blockers reduce placental perfusion which may result in intrauterine foetal death and immature and premature deliveries. In addition, adverse reactions (especially hypoglycaemia, bradycardia, respiratory depression and hypothermia) may occur in the foetus 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 the potential benefit outweighs the potential risk. 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.

Breast-feeding
Carvedilol is lipophilic and according to results from studies with lactating animals, carvedilol and its metabolites are excreted in breast milk. Breast feeding is therefore not recommended during 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**

*(a) Summary of the safety profile*
The frequency of adverse reactions is not dose-dependent, with the exception of dizziness, abnormal vision and bradycardia.

*(b) Tabulated list of adverse reactions*
The risk of most adverse reactions associated with carvedilol is similar across all indications.
Exceptions are described in subsection (c).

Frequency categories are as follows:
Very common ≥ 1/10
Common ≥ 1/100 and < 1/10
Uncommon ≥ 1/1,000 and < 1/100
Rare ≥ 1/10,000 and < 1/1,000
Very rare < 1/10,000

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

*Blood and lymphatic system disorders*
Common: Anaemia, Thrombocytopenia[1]
Rare: Thrombocytopaenia[2,] Leukopenia

*Immune system disorders*
Very rare: Hypersensitivity (allergic reaction)

*Metabolism and nutrition disorders*
Very Common: Hyperglycaemia[#], peripheral oedema[1], hypovolaemia, fluid retention
Common: Weight increase, hypercholesterolaemia, impaired blood glucose control (hyperglycaemia, hypoglycaemia) in patients with pre-existing diabetes
Rare: Peripheral oedema

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

*Nervous system disorders*
Very common: Dizziness[*,2], headache[*]
Common: Dizziness[1]
Uncommon: Presyncope, syncope, paraesthesia
Rare: syncope[*]

*Eye disorders*
Very common: lacrimation decreased (dry eye), visual disturbance[1]
Common: Visual impairment, eye irritation
Very Rare: Visual disturbance[2]

*Cardiac disorders*
Very common: Bradycardia[*], cardiac failure
Common: Oedema, hypervolaemia, fluid overload
Uncommon: Atrioventricular block, angina pectoris
Rare: Aggravation of heart failure

*Vascular disorders*
Very common: Hypotension, oedematous feet, orthostatic hypotension*
Common: Orthostatic hypotension, disturbances of peripheral circulation (cold extremities, peripheral vascular disease, exacerbation of intermittent claudication and Reynaud's phenomenon)

*Respiratory, thoracic and mediastinal disorders*
Common: Dyspnoea, pulmonary oedema, asthma in predisposed patients
Rare: Nasal congestion

*Gastrointestinal disorders*
Very common:Nausea[1], diarrhoea[1], vomiting[1]
Common: Nausea[2], diarrhoea, vomiting, dyspepsia, abdominal pain
Uncommon: Constipation
Rare: Vomiting[2]
Very rare: Dry mouth

*Hepatobiliary disorders*
Very rare: Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gammaglutamyltransferase (GGT) increased

*Skin and subcutaneous tissue disorders*
Uncommon: Skin reactions (e.g. allergic exanthema, dermatitis, urticaria, pruritus, psoriatic and lichen planus like skin lesions), alopecia
Very rare: Severe cutaneous adverse reactions (e.g. Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis)
Rare: psoriatic skin lesions, existing lesions may be aggravated.

*Musculoskeletal and connective tissue disorders*
Very common: Pain in limb
Common: Pain in extremities

*Renal and urinary disorders*
Common: Renal failure and renal function abnormalities in patients with diffuse vascular disease and/or underlying renal insufficiency, micturition disorders
Very rare: Urinary incontinence in women

*Reproductive system and breast disorders*
Very common: Genital oedema
Uncommon: Erectile dysfunction

*General disorders and administration site conditions*
Very common: Asthenia (fatigue)*, oedema
Common: Pain
*These reactions occur in particular at the beginning of treatment.
# Hyperglycaemia (in patients with diabetes mellitus), (see section 4.4).
[1]in patients with heart failure
[2]in patients with hypertension and angina

*(c) Description of selected adverse reactions*
Dizziness, syncope, headache and asthenia are usually mild and are more likely to occur at the beginning of treatment.

In patients with congestive heart failure, worsening cardiac failure and fluid retention may occur during up-titration of carvedilol dose (see section 4.4).

Cardiac failure is a commonly reported adverse event in both placebo and carvedilol-treated patients (14.5% and 15.4% respectively, in patients with left ventricular dysfunction following acute myocardial infarction).

Reversible deterioration of renal function has been observed with carvedilol therapy in chronic heart failure patients with low blood pressure, ischaemic heart disease and diffuse vascular disease and/or underlying renal insufficiency (see section 4.4).

As a class, beta-adrenergic receptor blockers may cause latent diabetes to become manifest, manifest diabetes to be aggravated, and blood glucose counter-regulation to be inhibited.

Carvedilol may cause urinary incontinence in women which resolves upon discontinuation of the medication.

Acute renal insufficiency and disturbance of renal function in patients with generalised atherosclerosis and/or impaired renal function have been rare adverse reactions. 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.

Very rare adverse reactions include angina, AV block and exacerbation of symptoms in patients suffering from intermittent claudication or Raynaud's phenomenon.

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.

**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 and cardiac arrest. There may also be respiratory

problems, bronchospasm, vomiting, disturbed consciousness and generalised seizures.

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

Atropine can be used for excessive bradycardia, while to support ventricular function intravenous glucagon, or sympathomimetics (dobutamine, isoprenaline) are recommended. If positive inotropic effect is required, phosphodiesterase inhibitors (PDE) should be considered. If peripheral vasodilation dominates the intoxication profile then norfenephrine or noradrenaline should be administered with continuous monitoring of the circulation. In the case of drug-resistant bradycardia, pacemaker therapy should be initiated.

For bronchospasm, β-sympathomimetics (as aerosol or intravenous) should be given, or aminophylline may be administered intravenously by slow injection or infusion. In the event of seizures, slow intravenous injection of diazepam or clonazepam is recommended.

In cases of severe overdose with symptoms of shock, supportive treatment must be continued for a sufficiently long period, i.e. until the patient's condition has stabilised, as a prolongation of elimination half-life and redistribution of carvedilol from deeper compartments are to be expected.

## *5.1 Pharmacodynamic properties*

Pharmacotherapeutic group: beta- and alpha$_1$-receptor blocking agents
ATC code: C07AG02

*Mechanism of action*
Carvedilol is a vasodilatory non-selective beta-blocker, which reduces the peripheral vascular resistance by selective alpha 1- receptor blockade and suppresses the renin-angiotensin system through non-selective beta-blockade. Plasma renin activity is reduced and fluid retention is rare.

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

Carvedilol is a racemate of two stereoisomers. Both enantiomers were found to have alpha-adrenergic blocking activity in animal models. Non-selective beta$_1$- and beta$_2$-adrenoceptor blockade is attributed mainly to the S(-) enantiomer.

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

*Pharmacodynamic effects*

*Antihypertensive properties*

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 noradrenaline (norepinephrine) concentration.

*Heart failure*
*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*

*Absorption*
The absolute bioavailability of orally administered carvedilol is approximately 25 %. Plasma levels peak at approximately 1 hour after dosing. 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.

*Distribution*
Approximately 98 % to 99 % of carvedilol is bound to plasma proteins. Its volume of distribution is approximately 2 l/kg.

*Biotransformation*
The first pass effect after oral administration is approximately 60 – 75 %.

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.

*Elimination*
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.

*Linearity*
There is linear correlation between the dose and plasma concentrations.

*Elderly*
The pharmacokinetics of carvedilol are affected by age; plasma levels of carvedilol are approximately 50 % higher in the elderly compared to young subjects.

*Patients with hepatic impairment*
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.

*Patients with renal impairment*
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

Studies on rats and mice revealed no carcinogenic potential of carvedilol at doses of 75 mg/kg and 200 mg/kg (38 - 100 times the human maximum daily dose).
Carvedilol demonstrated no mutagenic potential in studies conducted on mammals or other animals *in vitro* or *in vivo*.
When high doses of carvedilol were administered to pregnant rats (≥ 200 mg/kg = ≥ 100 times the human maximum daily dose), undesirable effects on pregnancy and fertility were observed. Physical growth and development of the foetus were delayed at doses of ≥ 60 mg/kg (≥ 30 times the human maximum daily dose). Embryotoxicity (increased mortality after implantation of the embryo) occurred, but there were no deformations in rats or rabbits at doses of 200 mg/kg and 75 mg/kg, respectively (38 – 100 time the human maximum daily dose).

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Lactose monohydrate
Crospovidone
Povidone
Anhydrous colloidal silicon dioxide
Magnesium stearate

Tablet coat:
Hypromellose
Titanium dioxide (E 171)
Triethyl citrate
Macrogol
Polydextrose

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Store in the original package, in order to protect from light.
Do not store above 30°C.

### 6.5 Nature and contents of container

Plastic bottle (HDPE) or blister pack (PVC/Alu)
Pack sizes: 10, 14, 28, 30, 50, 56, 98 and 100 tablets

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 00142/0597

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/04/2008

## 10 DATE OF REVISION OF THE TEXT

12/11/2018