SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Carvedilol 25mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 25 mg of carvedilol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White to off-white, round flat tablet. Scored on one side, debossed on the other side with “CVL” on top and “T4” on bottom. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic heart failure

Carvedilol is adjunctive therapy for the treatment of moderate to severe stable chronic heart failure.

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

The tablets should be taken with fluid.

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.

Adults
The recommended dose for initiation of therapy is 12.5 mg once a day for the first two days. Thereafter the recommended dosage is 25 mg once a day. Although this is an adequate dose in most patients, if necessary the dose may be titrated up to a recommended daily maximum dose of 50 mg given once a day or in divided doses.
Dose titration should occur at intervals of at least two weeks.

Elderly
An initial dose of 12.5 mg daily is recommended. This has provided satisfactory control in some cases. If the response is inadequate the dose may be titrated up to the recommended daily maximum dose of 50 mg given once a day or in divided doses.

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

Angina
A twice-daily regimen is recommended.

Adults
The recommended dose for initiation of therapy is 12.5 mg twice a day for the first two days. Thereafter, the recommended dosage is 25 mg twice a day.

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

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

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.

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

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

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 active substance or to any of the excipients listed in section 6.1.

- Carvedilol is contra-indicated in patients with marked fluid retention or overload requiring intravenous inotropic support.

- Patients with obstructive airways disease, unstable/decompensated heart failure, clinically manifested liver dysfunction.

- *As with other beta-blocking agents:* History of bronchospasm or asthma, 2nd and 3rd degree A-V heart block (unless a permanent pacemaker is in place), severe bradycardia (< 50 bpm), cardiogenic shock, sick sinus syndrome (including sino-atrial block), severe hypotension (systolic blood pressure < 85 mmHg), metabolic acidosis and phaeochromocytoma (unless adequately controlled by alpha blockade).

- Prinzmetal's angina.

- Severe peripheral arterial circulatory disturbances.

- Concomitant intravenous treatment with verapamil or diltiazem (see section 4.5).

- Unsuitable for patients with lactase insufficiency, galactosaemia or glucose/galactose malabsorption syndrome.

4.4 Special warnings and precautions for use

Chronic Heart Failure

In chronic 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 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 (see section 4.5).

In hypertensive patients who have chronic heart failure controlled with digoxin, diuretics and/or an ACE inhibitor, carvedilol should be used with caution since both digoxin and carvedilol may slow A-V conduction.

Renal function in Chronic Heart Failure

Reversible deterioration of renal function has been observed with carvedilol therapy in chronic heart failure patients with low blood pressure (systolic BP < 100 mmHg), ischaemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency. In 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.

Chronic obstructive pulmonary disease

Carvedilol should be used with caution, in patients with chronic obstructive pulmonary disease (COPD) with a bronchospastic component who are not receiving oral or inhaled medication, and only if the potential benefit outweighs the potential risk.

In patients with a tendency to bronchospasm, respiratory distress can occur as a result of a possible increase in airway resistance. Patients should be closely monitored during initiation and up-titration of carvedilol and the dose of 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.Alternatives to beta-blocking agents are generally preferred in insulin-dependent patients. In chronic heart failure patients with diabetes, the use of carvedilol may be associated with worsening control of blood glucose. Therefore, regular monitoring of blood glucose is required in diabetics when carvedilol is initiated or up-titrated and hypoglycaemic therapy adjusted accordingly.

Peripheral vascular disease

Carvedilol should be used with caution in patients with peripheral vascular disease as beta-blockers can precipitate or aggravate symptoms of arterial insufficiency. However as carvedilol also has alpha-blocking properties this effect is largely counterbalanced.

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.

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

Thyrotoxicosis

Carvedilol may obscure the symptoms of thyrotoxicosis.

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.

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.

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

Patients with a history of psoriasis associated with beta-blocker therapy should be given carvedilol only after consideration of the risk-benefit ratio.

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.

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. However, caution should be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.

Contact lenses

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

Withdrawal syndrome

Although angina has not been reported on stopping treatment, carvedilol treatment should not be discontinued abruptly, particularly in patients suffering from ischaemic heart disease. The withdrawal of carvedilol should be gradual (over a period of two weeks).

Lactose

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

In patients with a tendency to bronchospastic reactions, respiratory distress can occur as a result of a possible increase in airway resistance. 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. Consult your doctor or pharmacist first.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Digoxin and cardiac glycosides

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

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

Mixed function oxidase inducers or inhibitors

Inducers and inhibitors of hepatic metabolism: In a study in 12 healthy subjects, Rifampicin reduced plasma concentrations of carvedilol *by* about 70%, most likely by induction of P-glycoprotein leading to a decrease of the intestinal absorption of carvedilol. 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.
These interactions arise from the extensive metabolism of carvedilol by the cytochrome P450 enzyme system. Induction or inhibition of these enzymes by drugs such as rifampicin or cimetidine, respectively, may thus affect the biotransformation of carvedilol, with consequent effects on the therapeutic response and toleration of the beta-blocker.

Cyclosporin

Two studies in renal and cardiac transplant patients receiving oral cyclosporin have shown an increase in cyclosporin plasma concentrations following initiation of carvedilol treatment. In about 30% of the 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.

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.

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.

Phenylalkylamine or benzothiazepine calcium channel blockers, class I anti-arrhythmic drugs
Verapamil. diltiazem, or other antiarrhythmics

In combination with carvedilol can increase the risk of AV conduction disturbances (see section 4.4).Isolated cases of conduction disturbance (rarely with haemodynamic disruption) have been observed when carvedilol and diltiazem were given concomitantly. Therefore, as with other drugs with beta-blocking activity, careful monitoring of ECG and blood pressure should be undertaken when co-administering calcium channel blockers of the verapamil or diltiazem type, or class I anti-arrhythmic drugs. These types of drugs should not be co-administered intravenously in patients receiving carvedilol.

Pharmacodynamic interactions

Insulin or oral hypoglycaemic drugs

Agents with beta-blocking properties may enhance the blood sugar- reducing effect of insulin and oral hypoglycemics. The signs of hypoglycaemia may be masked or attenuated (especially tachycardia).The effects of insulin or oral hypoglycaemics may be intensified. Regular monitoring of blood glucose is therefore recommended (see section 4.4).

Drugs with beta-blocking or catecholamine-depleting properties

Catecholamine-depleting agents

Patients taking an agent with beta-blocking properties and a drug that can deplete catecholamines (eg reserpine and monoamine oxidase inhibitors) should be observed closely for signs of hypotension and/severe bradycardia.

Digoxin

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

Verapamil, diltiazem, aminodarone 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 beta-blocking properties may potentiate blood-pressure and heart-rate lowering effects. When concomitant treatment with agents with beta-blocking properties and clonidine is to be terminated, the beta-blocking agent should be discontinued first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage.

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 beta-blocking properties, if carvedilol is to be administered orally with calcium channel blockers of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored.

Anti-hypertensive drugs

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.

Other antihypertensive medicine

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.

Anaesthetic agents

Careful monitoring of vital signs must be paid during general anaesthesia 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.

Estrogens and corticosteroids

The antihypertensive effect of carvedilol is decreased due to water and sodium retention.

Beta-agonist bronchodilators

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

Ergotamine

Vasoconstriction increased.

Neuromuscular blocking agent.

Increased neuromuscular block.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development (see section 5.3). The potential risk for humans is unknown.

Carvedilol should not be used during pregnancy unless the potential benefit outweighs the potential risk.

Beta blockers reduce placental perfusion, which may result in intrauterine foetal death, and immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia) may occur in the foetus and neonate. There may be an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Animal studies have not shown substantive evidence of teratogenicity with carvedilol (see section 5.3).

Breast-feeding
Animal studies demonstrated that carvedilol or its metabolites are excreted in breast milk. It is not known whether carvedilol is excreted in human 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:Adverse drug reactions are listed below by system organ class and frequency.

Frequencies are defined as:

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

In patients with chronic heart failure

Frequency	***System organ class***	***Adverse events***
Very common (> 1/10)	*Nervous system disorders*	Asthenia (including fatigue); dizziness, headache: usually mild, occur particularly at the start of treatment
	Cardiac disorders *Vascular disorders*	Cardiac failure Hypotension
Common (>1/100, <1/10)	*Infections and infestations*	Bronchitis, pneumonia, upper respiratory tract infection, urinary tract infection
	Blood and lymphatic system disorders	Anaemia
	Metabolism and nutrition disorders	Hypercholesterolemia, hyperglycaemia*, hypoglycaemia*, weight increase, impaired control of blood glucose*
	Psychiatric disorder	Depression and depressed mood
	Eye disorders	Vision abnormalities, visual impairment
	Cardiac disorders *Vascular disorders*	Bradycardia, oedema (including generalised, peripheral, dependent and genital oedema, oedema of the legs, hypervolaemia and fluid overload) Orthostatic hypotension

Frequency	***System organ class***	***Adverse events***
	Respiratory, thoracic and mediastinal disorders	Pulmonary oedema
	General disorder	Pain
	Gastro-intestinal disorders	Diarrhoea, dyspepsia, nausea, vomiting
	Renal and urinary disorders	Acute renal failure and renal function abnormalities in patients with diffuse vascular disease and/or impaired renal function (see section 4.4)
Uncommon (>1/1000, <1/100)	*Cardiac disorders*	Atrioventricular-block, angina pectoris
	Skin and subcutaneous tissue disorder	Dermatitis, increased sweating, alopecia
	Nervous system disorders	Presyncope, syncope
Rare (>1/10000, <1/1000)	*Blood and lymphatic system disorders*	Thrombocytopenia
Very rare (incl. isolated cases) (< 1/10000)	*Blood and lymphatic system disorders*	Leucopenia
	Immune system disorder	Hypersensitivity (Allergic reaction)
	Hepatobiliary disorder	Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gammaglutamyltransferase (GGT) increased
	Renal and urinary disorders	Urinary incontinence in women
	Skin and subcutaneous tissue disorders	Severe cutaneous adverse reactions (e.g. Erythema mulitforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis)

* common in patients with pre-existing diabetes mellitus (see section 4.5)

In patients with hypertension and angina

The profile is similar to that observed in chronic heart failure although the incidence of events is generally lower in patients with hypertension or angina treated with carvedilol.

Frequency	***System organ class***	***Adverse events***

Frequency	***System organ class***	***Adverse events***
Very common (> 1/10)	*Cardiac disorders* *Vascular disorders*	Cardiac failure Hypotension
Common (>1/100, <1/10)	*Infections and infestations*	Bronchitis, pneumonia, upper respiratory tract infection, urinary tract infection
	Blood and lymphatic system disorders	Anaemia
	Psychiatric disorder	Depression and depressed mood
	Nervous system disorders	Dizziness, fatigue, headache: usually mild, occur particularly at the start of treatment
	Eye disorders	Lacrimation decreased (dry eye), visual impairment, eye irritation
	Cardiac disorders *Vascular disorders*	Bradycardia, postural hypotension, especially at the beginning of treatment. Orthostatic hypotension, disturbances of peripheral circulation (cold extremities, peripheral vascular disease, exacerbation of intermittent claudication and Raynaud's phenomenon)
	Respiratory, thoracic and mediastinal disorders	Dyspnea, pulmonary oedema and asthma in predisposed patients
	Gastro-intestinal disorders	Gastro-intestinal upset (with symptoms such as abdominal pain, dyspepsia, diarrhoea, nausea)
	Musculoskeletal and connective tissue disorder	Pain in the extremities
	Renal and urinary disorders	Micturition disorder
	General disorder	Pain
Uncommon (>1/1000, <1/100)	*Nervous system disorders*	Asthenia, syncope, paraesthesia
	Psychiatric disorder	Sleep disorder
	Eye disorders	Disturbed vision
	Cardiovascular system	Angina pectoris (including chest pain), AV-block, symptoms of heart failure and peripheral oedema.
	Gastro-intestinal disorders	Constipation, vomiting
	Skin and subcutaneous tissue disorder	Skin reactions (eg allergic exanthema, dermatitis, increased sweating, lichen planus-like skin lesions, pruritus, urticaria). Psoriatic skin lesions may occur

Frequency	***System organ class***	***Adverse events***
		or existing lesions exacerbated. Alopecia
	Reproductive system	Sexual impotence, erectile dysfunction
Rare (>1/10000, <1/1000)	*Respiratory, thoracic and mediastinal disorders*	Flu-like symptoms, nasal congestion, wheezing
	Gastro-intestinal disorders	Dryness of the mouth
Very rare (incl. isolated cases) (< 1/10000)	*Blood and lymphatic system disorders*	Changes in serum transaminases, leucopenia, thrombocytopenia
	Immune system disorder	Hypersensitivity (Allergic reaction)
	Hepatobiliary disorder	Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gammaglutamyltransferase (GGT) increased
	Renal and urinary disorders	Urinary incontinence in women
	Skin and subcutaneous tissue disorders	Severe cutaneous adverse reactions (e.g. Erythema mulitforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis)

(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 chronic 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.

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 professional are asked to report any suspected adverse reactions via the Yellow Card Scheme at: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, beta-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. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code:
C07A G02 (Cardiovascular system – Beta-blocking agents – Alpha- and beta-blocking agents)

Mechanism of action
Carvedilol is a vasodilating non-selective beta blocking agent with antioxidant properties. It has antagonist activity at both $alpha_1$- and beta-adrenoceptors, with a higher affinity for the latter.

Pharmacodynamic effects

Vasodilation is predominantly mediated through alpha$_1$ receptor antagonism.

Carvedilol reduces the peripheral vascular resistance through vasodilation and suppresses the renin-angiotensin-aldosterone system through beta blockade. The activity of plasma renin is reduced and fluid retention is rare.

Carvedilol has no intrinsic sympathomimetic activity and like propranolol, it has membrane stabilising properties.

Carvedilol is a racemate of two stereoisomers. Beta-blockade is attributed to the S(-) enantiomer; in contrast, both enantiomers exhibit the same α_1-blocking activity.

Carvedilol is a potent antioxidant, a scavenger of reactive oxygen radicals and an anti-proliferative agent. The 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.

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

- In hypertensive patients, a reduction in blood pressure is not associated with a concomitant increase in total peripheral resistance, as observed with pure beta-blocking agents. Heart rate is slightly decreased. Renal blood flow and renal function are maintained. Peripheral blood flow is maintained, therefore, cold extremities, often observed with drugs possessing beta-blocking activity, are rarely seen.

- In patients with stable angina, carvedilol has demonstrated anti-ischaemic and anti-anginal properties. Acute haemodynamic studies demonstrated that carvedilol reduces ventricular pre- and after-load.

Serum lipid profile and electrolytes are not affected.

5.2 Pharmacokinetic properties

The absolute bioavailability of carvedilol is approximately 25% in humans. Bioavailability is stereo-selective, 30% for the R-form and 15% for the S-form. Serum levels peak at approximately 1 hour after an oral dose. There is a linear relationship between the dose and serum concentrations. Food does not affect bioavailability or the maximum serum concentration although the time to reach maximum serum concentration is delayed. Carvedilol is highly lipophilic, approximately 98% to 99% is bound to plasma proteins. The distribution volume is approximately 2 l/kg and increased in patients with liver cirrhosis. The first pass effect after oral administration is approximately 60 - 75%; enterohepatic circulation of the parent substance has been shown in animals.

Carvedilol exhibits a considerable first pass effect. The metabolite pattern reveals intensive metabolism with glucuronidation as one of the major steps. Demethylation and hydroxylation at the phenol ring produce three metabolites with beta-receptor blocking activity.

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

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 cirrhotic liver disease, the bioavailability of carvedilol was four times greater and the peak plasma level five times higher than in healthy subjects. Since carvedilol is primarily excreted via the faeces, significant accumulation in patients with renal impairment is unlikely. In patients with impaired liver function, bioavailability is raised to as much as 80% due to a reduced first pass effect.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Povidone
Crospovidone
Colloidal silica anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

White opaque PVC/PVdC aluminium blisters.

Pack sizes : 14, 28, 30, 50, 56 & 100 tablets. Hospital packs of 50 and 100 tablets.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited
Ridings Point,
Whistler Drive,
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8. MARKETING AUTHORISATION NUMBER

PL 00289/0549

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 February 2004

10 DATE OF REVISION OF THE TEXT

24/02/2022