

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Carvedilol 25 mg Tablets.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Carvedilol 25 mg tablet contains 25 mg carvedilol.

Excipient with known effect: Each tablet contains 125.88 mg of lactose monohydrate.  
For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Uncoated tablet.

Cream coloured, circular, biconvex tablets marked '25' on one face and plain on reverse face.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

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

#### *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**

For oral administration. The tablets should be taken with fluid. For CHF patients carvedilol should be given with food.

### *Symptomatic chronic heart failure*

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

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

The dosage must be titrated to individual requirements.

For those patients receiving diuretics and/or digoxin and/or ACE inhibitors, dosing of these other drugs should be stabilized prior to initiation of carvedilol treatment.

### *Adults*

The recommended dose for the initiation of therapy is 3.125 mg twice a day for two weeks. If this dose is tolerated, the dosage should be increased subsequently, at intervals of not less than two weeks, to 6.25 mg twice daily, followed by 12.5 mg twice daily and thereafter 25 mg twice daily. Dosing should be increased to the highest level tolerated by the patient.

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

During up-titration of the dose in patients with systolic blood pressure < 100mmHg, deterioration of renal and/or cardiac functions may occur. Therefore, before each dose increase these patients should be evaluated by the physician for renal function and symptoms of worsening heart failure or vasodilation. Transient worsening of heart failure, vasodilation or fluid retention may be treated by adjusting doses of diuretics or ACE inhibitors or by modifying or temporarily discontinuing carvedilol treatment.

Under these circumstances, the dose of carvedilol should not be increased until symptoms of worsening heart failure or vasodilation have been stabilised.

If carvedilol is discontinued for more than two weeks, therapy should be recommenced at 3.125 mg twice daily and up-titrated in line with the above dosing recommendation.

#### *Elderly*

As for adults.

#### *Children*

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

#### ***Hypertension***

Once daily dosing is recommended.

#### *Adults*

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

Dose titration should occur at intervals of at least two weeks.

#### *Elderly*

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

#### *Children*

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

#### ***Angina***

##### *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.

### *Children*

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

### ***Patients with co-existing hepatic disease***

Carvedilol is contra-indicated in patients with hepatic dysfunction (see sections 4.3 *Contra-indications* and 5.2 *Pharmacokinetic properties*).

### ***Patients with co-existing renal dysfunction***

No dose adjustment is anticipated as long as systolic blood pressure is above 100 mmHg (see also sections 4.4 *Special warnings and precautions for use* and 5.2 *Pharmacokinetic properties*).

## **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 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 (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 the peripheral circulatory disorder (e.g 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*

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the total 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 asthma or other lung diseases unless you have consulted 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 C<sub>max</sub>. 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 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 inter individual 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 can 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 beta-blockade caused by a raise of the S-carvedilol concentration

#### *Fluoxetine*

In a randomised, 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 noticed 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 hypoglycaemics*

Agents with beta-blocking properties may enhance the blood-sugar-reducing effect of insulin and oral hypoglycaemics. The signs of hypoglycaemia may be masked or attenuated (especially tachycardia). 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 (e.g. reserpine and monoamine-oxidase inhibitors) should be observed closely for signs of hypotension and/or severe bradycardia.

##### *Digoxin*

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

##### *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 beta-blocking properties may potentiate blood-pressure and heart-rate-lowering effects. When concomitant treatment with agents with beta-blocking properties and clonidine together is to be terminated, the beta-blocking agent should be withdrawn first. Clonidine therapy can 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.  $\alpha_1$ -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 also 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 the 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 experiences 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  $\geq 1/10$ ; Common  $\geq 1/100$  and  $< 1/10$ ; Uncommon  $\geq 1/1,000$  and  $< 1/100$ ; Rare  $\geq 1/10,000$  and  $< 1/1,000$ ; Very rare  $< 1/10,000$ .

*In patients with chronic heart failure*

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

<b>Frequency</b>	<b>System organ class</b>	<b>Adverse events</b>
	<i>Cardiac disorders</i>	Bradycardia, oedema (including generalised, peripheral, dependent and genital oedema, oedema of the legs, hypervolaemia and fluid overload)
	<i>Vascular disorders</i>	Orthostatic hypotension
	<i>Respiratory, thoracic and mediastinal disorders</i>	Pulmonary oedema
	<i>General disorder</i>	Pain
	<i>Gastro-intestinal disorders</i>	Diarrhoea, dyspepsia, nausea, vomiting
	<i>Renal and urinary Disorders</i>	Acute renal failure and renal function abnormalities in patients with diffuse vascular disease and/or impaired renal function (see section 4.4)
<b>Uncommon</b> (>1/1000, <1/100)	<i>Cardiac disorders</i>	Atrioventricular-block, angina pectoris
	<i>Skin and subcutaneous tissue disorder</i>	Dermatitis, increased sweating, alopecia
	<i>Nervous system disorders</i>	Presyncope, syncope
<b>Rare</b> (>1/10000, <1/1000)	<i>Blood and lymphatic system disorders</i>	Thrombocytopenia
<b>Very rare</b> (incl. isolated cases) (< 1/10000)	<i>Blood and lymphatic system disorders</i>	Leucopenia
	<i>Immune system disorder</i>	Hypersensitivity (Allergic reaction)
	<i>Hepatobiliary disorder</i>	Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT) increased
	<i>Renal and urinary disorders</i>	Urinary incontinence in women
	<i>Skin and subcutaneous tissue disorders</i>	Severe cutaneous adverse reactions (e.g. Erythema multiforme, 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.

<b>Frequency</b>	<b>System organ class</b>	<b>Adverse events</b>
<b>Very common</b> (> 1/10)	<i>Cardiac disorders</i>	Cardiac failure
	<i>Vascular disorders</i>	Hypotension

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

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

*c) Description of selected adverse reactions*

Dizziness, syncope, headache and asthenia are usually mild and 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.

#### 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 at: [www.mhra.gov.uk/yellowcard](http://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 norfenefrine 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 i.v. 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 of time, i.e. until the patient's condition is stabilised, as a prolongation of elimination half-life and redistribution of carvedilol from deeper compartments can 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 alpha1- and beta-adrenoceptors, with a higher affinity for the latter.

### *Pharmacodynamic effects*

Vasodilation is predominantly mediated through alpha1 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  $\alpha$ 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 590 ml/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).

# **6 PHARMACEUTICAL PARTICULARS**

## **6.1 List of excipients**

Lactose monohydrate  
Microcrystalline cellulose  
Low substituted hydroxypropyl cellulose  
Maize starch  
Yellow iron oxide (E172)  
Colloidal anhydrous silica  
Talc  
Magnesium stearate

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

3 years

## **6.4 Special precautions for storage**

Store in the original package.

## **6.5 Nature and contents of container**

Packs of 28 tablets.

Blister strips comprising of PVC/PVdC/Aluminium foil enclosed in an outer carton.

## **6.6 Special precautions for disposal**

Not applicable.

**7      MARKETING AUTHORISATION HOLDER**

Relonchem Limited,  
Cheshire House,  
Gorse Lane,  
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WA8 0RP,  
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