Carvedilol 3.125mg, 6.25mg, 12.5mg and 25mg Tablets

PL 32019/0001-4

UKPAR

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Carvedilol 3.125mg, 6.25mg, 12.5mg and 25mg Tablets

PL 32019/0001-4

LAY SUMMARY

The MHRA granted Roger Oakes Limited Marketing Authorisations (licences) for the medicinal products Carvedilol 3.125mg, 6.25, 12.5mg and 25mg Tablets (PL 32019/0001-4) on 2nd December 2009. These are Prescription-only medicines (POM).

Carvedilol tablets are beta-blockers used for the treatment of high blood pressure, the prevention of chest pain and the treatment of heart failure. Carvedilol acts by dilating blood vessels and decreasing heart rate.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking Carvedilol Tablets outweigh the risks, hence Marketing Authorisations have been granted.
Carvedilol 3.125mg, 6.25mg, 12.5mg and 25mg Tablets

PL 32019/0001-4

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisations for the medicinal products Carvedilol 3.125mg, 6.25mg, 12.5mg and 25mg Tablets (PL 32019/0001-4) to Roger Oakes Limited on 2nd December 2009. The products are Prescription-only medicines (POM).

The applications were submitted as simple abridged applications according to Article 10c of Directive 2001/83/EC. The application makes reference to marketing authorisations held by Tillomed Laboratories Ltd (PL 11311/0221-4) for Carvedilol 3.125 mg, 6.25 mg, 12.5 mg & 25 mg Tablets. A letter of access has been provided from Tillomed Laboratories Ltd.

Carvedilol is used for the treatment of essential hypertension, chronic stable angina pectoris and adjunctive treatment in moderate to severe stable heart failure.

No new data was submitted nor was it necessary for these simple applications, as the data is identical to that of the previously granted cross-reference products. As the cross-reference products were granted prior to the introduction of current legislation, no PARs were generated.
PHARMACEUTICAL ASSESSMENT

LICENSE NO: PL 32019/0001-4
PROPRIETARY NAME: Carvedilol 3.125mg, 6.25mg, 12.5mg and 25mg Tablets
ACTIVE(S): Carvedilol
COMPANY NAME: Roger Oakes Limited
E.C. ARTICLE: Article 10(c) of Directive 2001/83/EC
LEGAL STATUS: POM

1. INTRODUCTION
These are simple abridged applications for Carvedilol 3.125mg, 6.25mg, 12.5mg and 25mg Tablets submitted under Article 10(c) of Directive 2001/83/EC. The proposed MA holder is “Roger Oakes Limited, Allstoe House, Church Lane, Greetham, Oakham, LE15 7NF, UK”.

The application makes reference to marketing authorisations held by Tillomed Laboratories Ltd (PL 11311/0221-4) for Carvedilol 3.125 mg, 6.25 mg, 12.5 mg & 25 mg Tablets. It has been indicated in the application form that the invented names, Carvedilol 3.125 mg, 6.25 mg, 12.5 mg & 25 mg Tablets are being applied for, the names are acceptable.

A letter of access has been provided from Tillomed Labs authorising the MHRA to refer to PLs 11311/0221-4 as the reference products for the purpose of these informed consent applications. Signed declarations by Roger Oakes Limited, stating that they have the relevant Quality dossiers in their possession, have been provided.

Preclinical, pharmaceutical and clinical expert statements have been provided together with CVs showing the experts are appropriately qualified. The experts confirm that the products are identical in composition, manufacture and pharmaceutical characteristics to the respective reference product and that there are no toxicological or clinical issues.

2. MARKETING AUTHORISATION APPLICATION FORMS
2.1 Name(s)
The proposed names of the product are Carvedilol 3.125 mg, 6.25 mg, 12.5 mg & 25 mg Tablets. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The products contain carvedilol equivalent to 3.125, 6.25, 12.5 & 25mg Carvedilol respectively. They will be packaged into Polyethylene (PE-HD) containers and Blister (Al/PVC) packs. The packaging is identical to the packaging used for the reference products.

The respective SPCs have indicated that Carvedilol tablets will be packed into Polyethylene (PE-HD) containers with pack sizes of 28, 30, 60, 100, 250 and 500 tablets and blister (Al/PVC) packs with pack sizes of 14, 20, 28, 30, 50, 50x1, 56, 60, 98, 98x1 and 100 tablets.
The same pack sizes are stated in the reference products. The proposed shelf life of 4 years is identical to the reference products. The proposed storage condition for the container closure systems are also consistent with the details registered for the cross-reference products.

2.3 Legal status
The products are Prescription Only Medicines (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
The proposed Marketing Authorisation holder is Roger Oakes Limited, Allstoe House, Church Lane, Greetham, Rutland, LE15 7NF, United Kingdom.

The QP responsible for pharmacovigilance is stated and a CV is included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with that registered for the cross-reference products and evidence of GMP compliance has been provided.

A flow diagram showing the sequence and activities of the different sites involved in the manufacturing process has been provided.

2.6 Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specifications are in-line with the details registered for the cross-reference products.

2.9 Drug substance specification
The proposed drug substance specification conformed to in house specification for carvedilol and was consistent with that of the reference products.

The manufacturer of the active substance is in-line with the reference products.

2.10 TSE Compliance
TSE declaration has been provided for the excipients lactose monohydrate.

2.11 Bioequivalence / Bioavailability
No bioavailability and bioequivalence data are required to support these informed consent applications as the proposed product is manufactured to the same formula utilising the same process as the cross-referenced products. The finished product manufacturing site is also identical to that used by the reference products.
3. EXPERT REPORTS
The applicant has included detailed expert reports of the applications. Signed declarations and copies of the experts’ CVs are enclosed for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearances of the products are identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed SmPCs are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET/BLISTER
PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference products.

PIL user testing has been submitted and the results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The proposed artwork complies with the relevant statutory requirements. In-line with current legislation, the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS
The data submitted with these applications are acceptable. The grant of marketing authorisations is recommended.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

No new clinical data have been supplied with these applications and none are required for applications of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications are consistent with that previously assessed for the cross-reference products and as such have been judged to be satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Carvedilol is a well known drug and has been used for many years. These applications are identical to previously granted applications for Carvedilol 3.125 mg, 6.25 mg, 12.5 mg & 25 mg Tablets PL (11311/0221-4).

Preclinical, pharmaceutical and clinical expert statements have been provided together with CVs showing the experts are appropriately qualified. The experts confirm that the products are identical in composition, manufacture and pharmaceutical characteristics to the respective reference product and that there are no toxicological or clinical issues.

No new or unexpected safety concerns arise from these applications.

The SPCs, PILs and labelling are satisfactory and consistent with that for the cross-reference products.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. Extensive clinical experience with carvedilol is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is therefore considered to be positive.
### STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
<th>1</th>
<th>The MHRA received the marketing authorisation applications on 08/10/2007</th>
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<tbody>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 28/11/2007</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information on 01/07/2008 and 14/03/2008, 14/03/2008 and 18/11/2009</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 22/09/2008, 11/03/2009 and 23/11/2009</td>
</tr>
<tr>
<td>7</td>
<td>The applications were determined on 02/12/2009</td>
</tr>
</tbody>
</table>
### STEPS TAKEN AFTER ASSESSMENT

<table>
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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Carvedilol 3.125mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains 3.125mg carvedilol.
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Tablet.
Light red, round, convex, bisected tablet with a pressure sensitive scoring notch, encoded C1.

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

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 25mg and the recommended maximum daily dose is 50mg.

Adults: The recommended initial dose is 12.5mg once daily for two days. Thereafter, the treatment is continued at the dose 25mg/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 12.5mg once daily, 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 12.5mg twice daily for two days. Thereafter, the treatment is continued at the dose 25mg 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 100mg in divided doses (twice daily).

Elderly: The recommended initial dose is 12.5mg twice daily for two days. Thereafter, the treatment is continued at the dose 25mg 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 4.3 “Contraindications”).
The initial dose is 3.125mg twice daily 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 6.25mg twice daily, then 12.5mg twice daily followed by 25mg twice daily. It is recommended that the dose is increased to the highest level tolerated by the patient.

The recommended maximum dose is 25mg given twice daily in patients weighing less than 85 kg and 50mg twice daily in patients weighing more than 85 kg, provided that the heart failure is not severe. A dose increase to 50mg 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 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 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 3.125mg 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 heart failure is necessary.

Moderate hepatic dysfunction. Dose adjustment may be required.

Children and adolescents (< 18 years). There is insufficient data of 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 betablockers and especially in coronary patients, the withdrawal of carvedilol should be done gradually (see 4.4 “Special warning and special precautions for use”).

Methods 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
Heart failure belonging to NYHA Class IV of the heart failure classification requiring intravenous inotropic treatment.
Chronic obstructive pulmonary disease with bronchial obstruction (see 4.4 “Special warning and special precautions for use”).
Clinically significant hepatic dysfunction.
Asthma bronchiale.
Second or third degree AV block.
Severe bradycardia (< 50 bpm).
Cardiogenic shock
Sick sinus syndrome (including sinoatrial blocks).
Severe hypotension (systolic blood pressure below 85 mmHg).
Hypersensitivity to carvedilol or to any of the excipients.
Metabolic acidosis.
Prinzmetal’s angina.
Untreated phaeochromocytoma.
Severe peripheral arterial circulatory disturbances.
Concomitant intravenous treatment with verapamil or diltiazem (see 4.5 “Interaction with other medicinal products and other forms of interaction”).

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.

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.

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 4.5 “Interaction with other medicinal products and other forms of interaction”).

Other warnings as regards carvedilol and beta-blockers in general. Subjects with chronic obstructive pulmonary disease using no oral or inhaled medication should not use carvedilol unless the benefit outweighs the potential risks of use. If carvedilol is given to these patients, they have to be monitored carefully when carvedilol therapy is initiated and during dose titration. The carvedilol dose must be reduced if the patient exhibits signs of bronchial obstruction during treatment.

Carvedilol may mask symptoms and signs of acute hypoglycaemia. Impaired blood glucose control may occasionally occur in patients with diabetes mellitus and heart failure in connection with the use of carvedilol. Therefore, close monitoring of diabetic patients receiving carvedilol is required by means of regular blood glucose measurements and adjustment of antidiabetic medication as necessary (see 4.5 “Interaction with other medicinal products and other forms of interaction”).

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

When carvedilol is used concomitantly with calcium channel blocking agents such as verapamil and diltiazem or with other antiarrhythmics, specifically amiodarone, the patient’s blood pressure and ECG have to be monitored. Intravenous co-administration should be avoided (see 4.5 “Interaction with other medicinal products and other forms of interaction”).

Cimetidine should be administered only with caution concomitantly as effects of carvedilol may be increased (see 4.5 “Interaction with other medicinal products and other forms of interaction”).

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

Since carvedilol is a vasodilatory beta-blocker, the aggravation of peripheral vascular disease is more unlikely than with conventional beta-blockers. However, there is little clinical experience in this patient group so far. The same also applies to those with Raynaud’s syndrome, but there may be exacerbation of symptoms.

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

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

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

Betablockers reduce the risk of arrhythmias at anaesthesia, however the risk of hypotension may be increased as well. Caution should therefore be observed with the use of certain anaesthetic drugs. Newer studies suggest however, a benefit of betablockers in preventing perioperative cardiac morbidity and reduction of the incidence of cardiovascular complications.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

**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 risk of AV conduction disorder or risk of cardiac failure is increased (synergistic effect). Close monitoring should be done in case of co-administration of carvedilol, and class I antiarrhythmics or amiodarone therapy (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 lc antiarrhythmics concomitant intravenous therapy.

Concomitant treatment with reserpine, guanethidine, methyldopa, guanfacin and monoamine-oxidase inhibitors (exception MAO-B-inhibitors) 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.
**Cardiac glycosides.** An increase of steady state digoxin levels by approximately 16% and of digitoxin by approximately 13% has been seen in hypertensive patients in connection with the concomitant use of carvedilol and digoxin. Monitoring of plasma digoxin concentrations is recommended when initiating, discontinuing or adjusting treatment with carvedilol.

**Other antihypertensive 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.

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

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

**Clonidine.** When combination treatment with carvedilol and clonidine is discontinued, carvedilol should be withdrawn several days before gradually decreasing the dose of clonidine.

**Inhalational anaesthetics.** Attention should be paid to the potential negative inotropic and hypotensive interactions of carvedilol and anaesthetics in association with anaesthesia.

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

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

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

**Ergotamine.** Vasoconstriction increased.

**Neuromuscular blocking agents.** Increased neuromuscular block.

### 4.6 Pregnancy and lactation

Use of carvedilol is not recommended during pregnancy and lactation.

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 "Preclinical safety data").

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 foetal and neonate). There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Carvedilol should only be used for pregnant women, if the potential benefit for the mother outweighs the potential risk for the foetal/neonate. The treatment should be stopped 2-3 days before expected birth. If this is not possible the new-born has to be monitored for the first 2-3 days of life.

Carvedilol is lipophilic and according to results from studies with lactating animals, carvedilol and its metabolites are excreted in breast milk and, therefore, mothers receiving carvedilol should not breast-feed.
4.7 **Effects on ability to drive and use machines**

Some individuals may have reduced alertness especially on initiation and adjustment of medication. Under good therapeutic control, carvedilol is not known to reduce the ability to drive or use machines.

4.8 **Undesirable effects**

Adverse reactions occur mainly at the beginning of treatment.

*Adverse reactions in heart failure patients reported from clinical studies.*

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>VERY COMMON (&gt;1/10)</th>
<th>COMMON (&gt;1/100)</th>
<th>UNCOMMON (&gt;1/1000, &lt;1/100)</th>
<th>RARE (&lt;1/1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Mild thrombocytopenia</td>
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<tr>
<td>Metabolism and nutrition Disorders</td>
<td>Hyperglycaemia*</td>
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<td></td>
<td>Oedema peripheral</td>
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<td>Hypervolaemia</td>
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<td>Fluid retention</td>
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<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
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<td>Syncope</td>
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<td>Eye disorders</td>
<td>Visual disturbance</td>
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<td>Cardiac disorders</td>
<td>Oedematous feet</td>
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<td>Total atrio-ventricular block</td>
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<td></td>
<td>Bradycardia</td>
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<td>Aggravation of heart failure</td>
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<tr>
<td>Renal and urinary Disorders</td>
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<td>Aggravation of renal function</td>
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<td>Vascular disorders</td>
<td>Hypotension</td>
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<td></td>
<td>orthostatic</td>
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<td>Gastrointestinal Disorders</td>
<td>Nausea</td>
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<td>Constipation</td>
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<td></td>
<td>Diarrhoea</td>
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<td></td>
<td>Vomiting</td>
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</table>
Reproductive system and breast disorders

Genital oedema

General disorders and administration site conditions

Oedema

*Hyperglycaemia (in patients with diabetes mellitus), (see 4.4 “Special warning and special precautions for use”).

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.

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

<table>
<thead>
<tr>
<th>Blood and Lymphatic system disorders</th>
<th>VERY COMMON (&gt;1/10)</th>
<th>COMMON (&gt;1/100)</th>
<th>UNCOMMON (&gt;1/1000, &lt;1/100)</th>
<th>RARE (&lt;1/1000)</th>
<th>VERY RARE (&lt;1/10 000)</th>
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<td>Metabolism and nutrition disorder</td>
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<td>Hypercholesterolaemia</td>
<td>Oedema peripheral</td>
<td>Mild thrombocytopenia Leukopenia</td>
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<td>Psychiatric disorders</td>
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<td></td>
<td>Sleep disorders Depression</td>
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<tr>
<td>Nervous system disorders</td>
<td>Dizziness* Headache*</td>
<td>Paraesthesia Syncope*</td>
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<td>Eye disorders</td>
<td>Lacrimation Decreased</td>
<td>Visual disturbance Eye irritation</td>
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<tr>
<td>Cardiac disorders</td>
<td>Bradycardia*</td>
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<tr>
<td>Vascular disorders</td>
<td>Hypotension orthostatic*</td>
<td>Peripheral circulatory failure</td>
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<tr>
<td>Respiratory, thoracic and mediastinal</td>
<td></td>
<td>Nasal congestion</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea Abdominal pain Diarrhoea</td>
<td>Constipation Vomiting Dry mouth</td>
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<tr>
<td>Musculoskeletal, Connective tissue and bone disorders</td>
<td>Pain in limb</td>
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<td>Renal and urinary disorders</td>
<td></td>
<td>Aggravation of renal function Difficulty in micturition</td>
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<td>Reproductive system and breast disorders</td>
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<td>Impotence</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue*</td>
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<tr>
<td>Investigations</td>
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<td>Serum transaminase</td>
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</table>
* These reactions occur in particular at the beginning of treatment.

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

Respiratory, thoracic and mediastinal disorders. Asthmatic dyspnoea has been observed commonly in predisposed patients.

Skin and subcutaneous tissue disorders. Various skin reactions have been reported rarely (e.g. allergic exanthema, urticaria, pruritus and lichen planus-like reaction). Psoriatic skin lesions may occur or existing lesions may be aggravated.

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.

4.9 Overdose

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

Treatment. In addition to normal treatment procedures, vital signs must be monitored and, if necessary, corrected at an intensive care unit. The following supportive measures may be taken:

Atropine: 0.5 - 2mg intravenously (for treatment of severe bradycardia).

Glucagon: initially 1 - 10mg intravenously followed if necessary by a slow infusion of 2 – 5mg/hour (in order to maintain cardiovascular function).

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

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

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

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

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

Duration of the antidote treatment depends on the seriousness of the overdose; supportive treatment must be continued until the patient stabilises.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: alpha- and beta-blocking agents
ATC code: C07AG02

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 through non-selective beta-blockade. Plasma rennin activity is reduced and fluid retention is rare.

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

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

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

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

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

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

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

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

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

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

5.3 Preclinical safety data
Studies on rats and mice revealed no carcinogenic potential of carvedilol at doses of 75mg/kg and 200mg/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 (≥ 200mg/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 ≥ 60mg/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 200mg/kg and 75mg/kg, respectively (38 – 100 time the human maximum daily dose).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate.
Cellulose, microcrystalline.
Crospovidone.
Povidone K30.
Silica, colloidal anhydrous.
Magnesium stearate.
Colouring agents:
Ferric oxide, red (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
4 years

6.4 Special precautions for storage
Polyethylene (PE-HD) containers and closures: Store in the original container.
Blister (Al/PVC): Store in the original package.

6.5 Nature and contents of container
Polyethylene (PE/HD) containers and closures: 28, 30, 60, 100, 250 and 500 tablets.
Blister (Al/PVC): 14, 20, 28, 30, 50, 50x1, 56, 60, 98, 98x1 and 100 tablets.

Not all pack size and pack types may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Roger A Okes Limited,
Allstoe House, Church Lane,
Greetham, Rutland,
LE15 7NF, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 32019/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/12/2009

10 DATE OF REVISION OF THE TEXT
02/12/2009
UKPAR Carvedilol 3.125mg, 6.25mg, 12.5mg and 25mg Tablets  
PL 32019/0001-4

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Carvedilol 6.25mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains 6.25mg carvedilol.  
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Tablet.  
Yellow, round, convex, bisected tablet with a pressure sensitive scoring notch, encoded C2.

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

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 25mg and the recommended maximum daily dose is 50mg.

Adults: The recommended initial dose is 12.5mg once daily for two days. Thereafter, the treatment is continued at the dose 25mg/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 12.5mg once daily, 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 12.5mg twice daily for two days. Thereafter, the treatment is continued at the dose 25mg 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 100mg in divided doses (twice daily).

Elderly: The recommended initial dose is 12.5mg twice daily for two days. Thereafter, the treatment is continued at the dose 25mg 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 4.3 "Contraindications").

The initial dose is 3.125mg twice daily 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 6.25mg twice daily, then 12.5mg twice daily followed by 25mg twice daily. It is recommended that the dose is increased to the highest level tolerated by the patient.
The recommended maximum dose is 25mg given twice daily in patients weighing less than 85 kg and 50mg twice daily in patients weighing more than 85 kg, provided that the heart failure is not severe. A dose increase to 50mg 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 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 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 3.125mg 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 heart failure is necessary.

Moderate hepatic dysfunction. Dose adjustment may be required.

Children and adolescents (< 18 years). There is insufficient data of 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 betablockers and especially in coronary patients, the withdrawal of carvedilol should be done gradually (see 4.4 “Special warning and special precautions for use”).

Methods 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

Heart failure belonging to NYHA Class IV of the heart failure classification requiring intravenous inotropic treatment.

Chronic obstructive pulmonary disease with bronchial obstruction (see 4.4 “Special warning and special precautions for use”).

Clinically significant hepatic dysfunction.

Asthma bronchiale.

Second or third degree AV block.

Severe bradycardia (< 50 bpm).

Cardiogenic shock.

Sick sinus syndrome (including sinoatrial blocks).

Severe hypotension (systolic blood pressure below 85 mmHg).

Hypersensitivity to carvedilol or to any of the excipients.

Metabolic acidosis.

Prinzmetal’s angina.

Untreated phaeochromocytoma.

Severe peripheral arterial circulatory disturbances.

Concomitant intravenous treatment with verapamil or diltiazem (see 4.5 “Interaction with other medicinal products and other forms of interaction”).
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.

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.

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 4.5 “Interaction with other medicinal products and other forms of interaction”).

Other warnings as regards carvedilol and beta-blockers in general. Subjects with chronic obstructive pulmonary disease using no oral or inhaled medication should not use carvedilol unless the benefit outweighs the potential risks of use. If carvedilol is given to these patients, they have to be monitored carefully when carvedilol therapy is initiated and during dose titration. The carvedilol dose must be reduced if the patient exhibits signs of bronchial obstruction during treatment.

Carvedilol may mask symptoms and signs of acute hypoglycaemia. Impaired blood glucose control may occasionally occur in patients with diabetes mellitus and heart failure in connection with the use of carvedilol. Therefore, close monitoring of diabetic patients receiving carvedilol is required by means of regular blood glucose measurements and adjustment of antidiabetic medication as necessary (see 4.5 “Interaction with other medicinal products and other forms of interaction”).

Carvedilol may mask symptoms and signs of thyrotoxicosis.

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

When carvedilol is used concomitantly with calcium channel blocking agents such as verapamil and diltiazem or with other antiarrhythmics, specifically amiodarone, the patient’s blood pressure and ECG have to be monitored. Intravenous co-administration should be avoided (see 4.5 “Interaction with other medicinal products and other forms of interaction”).

Cimetidine should be administered only with caution concomitantly as effects of carvedilol may be increased (see 4.5 “Interaction with other medicinal products and other forms of interaction”).

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

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. Cautions should be exercised when prescribing beta-blockers to patients with psoriasis since skin reactions may be aggravated.
Since carvedilol is a vasodilatory beta-blocker, the aggravation of peripheral vascular disease is more unlikely than with conventional beta-blockers. However, there is little clinical experience in this patient group so far. The same also applies to those with Raynaud’s syndrome, but there may be exacerbation of symptoms.

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

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

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

Betablockers reduce the risk of arrhythmias at anaesthesia, however the risk of hypotension may be increased as well. Caution should therefore be observed with the use of certain anaesthetic drugs. Newer studies suggest however, a benefit of betablockers in preventing perioperative cardiac morbidity and reduction of the incidence of cardiovascular complications.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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 risk of AV conduction disorder or risk of cardiac failure is increased (synergistic effect). Close monitoring should be done in case of co-administration of carvedilol, and class I antiarrhythmics or amiodarone therapy (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.

Concomitant treatment with reserpine, guanethidine, methyldopa, guanfacin and monoamine-oxidase inhibitors (exception MAO-B-inhibitors) 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.

Cardiac glycosides. An increase of steady state digoxin levels by approximately 16% and of digitoxin by approximately 13% has been seen in hypertensive patients in connection with the concomitant use of carvedilol and digoxin. Monitoring of plasma digoxin concentrations is recommended when initiating, discontinuing or adjusting treatment with carvedilol.
Other antihypertensive drugs. Carvedilol may potentiate the effects of other concomitantly administered antihypertensives (e.g. α₁-receptor antagonists) and drugs with antihypertensive side effects such as barbiturates, phenothiazines, tricyclic antidepressants, vasodilating agents and alcohol.

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

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

Clonidine. When combination treatment with carvedilol and clonidine is discontinued, carvedilol should be withdrawn several days before gradually decreasing the dose of clonidine.

Inhalational anaesthetics. Attention should be paid to the potential negative inotropic and hypotensive interactions of carvedilol and anaesthetics in association with anaesthesia.

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

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

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

Ergotamine. Vasoconstriction increased.

Neuromuscular blocking agents. Increased neuromuscular block.

4.6 Pregnancy and lactation
Use of carvedilol is not recommended during pregnancy and lactation.

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 "Preclinical safety data"). 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 foetal and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Carvedilol should only be used for pregnant women, if the potential benefit for the mother outweighs the potential risk for the foetal/neonate. The treatment should be stopped 2-3 days before expected birth. If this is not possible the new-born has to be monitored for the first 2-3 days of life.

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

4.7 Effects on ability to drive and use machines
Some individuals may have reduced alertness especially on initiation and adjustment of medication. Under good therapeutic control, carvedilol is not known to reduce the ability to drive or use machines.
4.8 Undesirable effects
Adverse reactions occur mainly at the beginning of treatment.

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

<table>
<thead>
<tr>
<th>System</th>
<th>Very Common (&gt;1/10)</th>
<th>Common (&gt;1/100)</th>
<th>Uncommon (&gt;1/1000, &lt;1/100)</th>
<th>Rare (&lt;1/1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Mild thrombocytopenia</td>
<td></td>
<td></td>
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<tr>
<td>Metabolism and nutrition Disorders</td>
<td>Hyperglycaemia* Oedema peripheral Hypervolaemia Fluid retention</td>
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<td></td>
<td></td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Dizziness</td>
<td></td>
<td>Syncope</td>
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<tr>
<td>Eye disorders</td>
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<td>Visual disturbance</td>
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<tr>
<td>Cardiac disorders</td>
<td>Oedematous feet Bradycardia</td>
<td>Total atrio-ventricular block Aggravation of heart failure</td>
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<tr>
<td>Renal and urinary Disorders</td>
<td></td>
<td>Aggravation of renal function</td>
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<tr>
<td>Vascular disorders</td>
<td>Hypotension orthostatic</td>
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<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea Diarrhoea Vomiting</td>
<td>Constipation</td>
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<tr>
<td>Reproductive system and</td>
<td>Genital oedema</td>
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breast disorders

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<tr>
<th>General disorders and administration site conditions</th>
<th>Oedema</th>
</tr>
</thead>
</table>

*Hyperglycaemia (in patients with diabetes mellitus), (see 4.4 “Special warning and special precautions for use”).

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.

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

<table>
<thead>
<tr>
<th>Blood and Lymphatic system disorders</th>
<th>VERY COMMON (&gt;1/10)</th>
<th>COMMON (&gt;1/100)</th>
<th>UNCOMMON (&gt;1/1000, &lt;1/100)</th>
<th>RARE (&lt;1/1000)</th>
<th>VERY RARE (&lt;1/10000)</th>
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<tbody>
<tr>
<td>Blood and Lymphatic system disorders</td>
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<td>Depression</td>
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<td>Nervous system disorder</td>
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<td>Paraesthesia</td>
<td>Syncope*</td>
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</tr>
<tr>
<td>Cardiac disorders</td>
<td>Bradycardia*</td>
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<tr>
<td>Vascular disorders</td>
<td>Hypotension orthostatic*</td>
<td></td>
<td>Peripheral circulatory failure</td>
<td></td>
<td></td>
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<tr>
<td>Respiratory, thoracic and mediastinal</td>
<td></td>
<td></td>
<td>Nasal congestion</td>
<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea Abdominal pain Diarrhoea</td>
<td>Constipation Vomiting</td>
<td>Dry mouth</td>
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</tr>
<tr>
<td>Musculoskeletal, Connective tissue and bone disorder</td>
<td>Pain in limb</td>
<td></td>
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<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td>Aggravation of renal function</td>
<td>Difficulty in micturition</td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
<td></td>
<td>Impotence</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td>Serum transaminase increased</td>
<td></td>
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</tr>
</tbody>
</table>

* These reactions occur in particular at the beginning of treatment.
Very rare adverse reactions include angina, AV block and exacerbation of symptoms in patients suffering from intermittent claudication or Raynaud's phenomenon.

*Respiratory, thoracic and mediastinal disorders.* Asthmatic dyspnoea has been observed commonly in predisposed patients.

*Skin and subcutaneous tissue disorders.* Various skin reactions have been reported rarely (*e.g.* allergic exanthema, urticaria, pruritus and lichen planus-like reaction). Psoriatic skin lesions may occur or existing lesions may be aggravated.

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.

### 4.9 Overdose

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

**Treatment.** In addition to normal treatment procedures, vital signs must be monitored and, if necessary, corrected at an intensive care unit. The following supportive measures may be taken:

- **Atropine:** 0.5 - 2mg intravenously (for treatment of severe bradycardia).
- **Glucagon:** initially 1 - 10mg intravenously followed if necessary by a slow infusion of 2 – 5mg/hour (in order to maintain cardiovascular function).
- **Sympathomimetics** according to their efficacy and the patient’s weight: dobutamine, isoprenaline or adrenaline.

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

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

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

**Important!** In cases of severe overdose when the patient is in shock, supportive treatment should be continued for a sufficiently long period of time, since the elimination and redistribution of carvedilol are likely to be slower than normal.

Duration of the antidote treatment depends on the seriousness of the overdose; supportive treatment must be continued until the patient stabilises.

### 5 Pharmacological Properties

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: *alpha- and beta-blocking agents*

ATC code: C07AG02

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
through non-selective beta-blockade. Plasma rennin activity is reduced and fluid retention is rare.

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

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

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

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

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

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

5.2 Pharmacokinetic properties

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

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

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

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

5.3 Preclinical safety data

Studies on rats and mice revealed no carcinogenic potential of carvedilol at doses of 75mg/kg and 200mg/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 (≥ 200mg/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 ≥ 60mg/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 200mg/kg and 75mg/kg, respectively (38 – 100 time the human maximum daily dose).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate.
Cellulose, microcrystalline.
Crospovidone.
Povidone K30.
Silica, colloidal anhydrous.
Magnesium stearate.
Colouring agents:
Ferric oxide, yellow (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

Polyethylene (PE-HD) containers and closures: Store in the original container.
Blister (Al/PVC): Store in the original package.

6.5 Nature and contents of container

Polyethylene (PE/HD) containers and closures: 28, 30, 60, 100, 250 and 500 tablets.
Blister (Al/PVC): 14, 20, 28, 30, 50, 50x1, 56, 60, 98, 98x1 and 100 tablets.

Not all pack size and pack types may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORIZATION HOLDER

Roger A Oakes Limited,
Allstoe House, Church Lane,
Greetham, Rutland,
LE15 7NF, United Kingdom

8 MARKETING AUTHORIZATION NUMBER(S)

PL 32019/0002

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
UKPAR Carvedilol 3.125mg, 6.25mg, 12.5mg and 25mg Tablets

02/12/2009

10 DATE OF REVISION OF THE TEXT

02/12/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Carvedilol 12.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains 12.5mg carvedilol.
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Tablet.
Red/brown, round, convex, bisected tablet with a pressure sensitive scoring notch, encoded C3.

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

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 25mg and the recommended maximum daily dose is 50mg.

Adults: The recommended initial dose is 12.5mg once daily for two days. Thereafter, the treatment is continued at the dose 25mg/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 12.5mg once daily, 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 12.5mg twice daily for two days. Thereafter, the treatment is continued at the dose 25mg 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 100mg in divided doses (twice daily).

Elderly: The recommended initial dose is 12.5mg twice daily for two days. Thereafter, the treatment is continued at the dose 25mg 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 4.3 “Contraindications”).

The initial dose is 3.125mg twice daily 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 6.25mg twice daily, then 12.5mg twice daily followed by 25mg twice daily. It is recommended that the dose is increased to the highest level tolerated by the patient.
The recommended maximum dose is 25mg given twice daily in patients weighing less than 85 kg and 50mg twice daily in patients weighing more than 85 kg, provided that the heart failure is not severe. A dose increase to 50mg 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 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 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 3.125mg 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 heart failure is necessary.

Moderate hepatic dysfunction. Dose adjustment may be required.

Children and adolescents (< 18 years). There is insufficient data of 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 betablockers and especially in coronary patients, the withdrawal of carvedilol should be done gradually (see 4.4 “Special warning and special precautions for use”).

Methods 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
Heart failure belonging to NYHA Class IV of the heart failure classification requiring intravenous inotropic treatment.
Chronic obstructive pulmonary disease with bronchial obstruction (see 4.4 “Special warning and special precautions for use”).
Clinically significant hepatic dysfunction.
Asthma bronchiale.
Second or third degree AV block.
Severe bradycardia (< 50 bpm).
Cardiogenic shock
Sick sinus syndrome (including sinoatrial blocks).
Severe hypotension (systolic blood pressure below 85 mmHg).
Hypersensitivity to carvedilol or to any of the excipients.
Metabolic acidosis.
Prinzmetal’s angina.
Untreated phaeochromocytoma.
Severe peripheral arterial circulatory disturbances.
Concomitant intravenous treatment with verapamil or diltiazem (see 4.5 “Interaction with other medicinal products and other forms of interaction”).

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.

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.

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 4.5 “Interaction with other medicinal products and other forms of interaction”).

Other warnings as regards carvedilol and beta-blockers in general. Subjects with chronic obstructive pulmonary disease using no oral or inhaled medication should not use carvedilol unless the benefit outweighs the potential risks of use. If carvedilol is given to these patients, they have to be monitored carefully when carvedilol therapy is initiated and during dose titration. The carvedilol dose must be reduced if the patient exhibits signs of bronchial obstruction during treatment.

Carvedilol may mask symptoms and signs of acute hypoglycaemia. Impaired blood glucose control may occasionally occur in patients with diabetes mellitus and heart failure in connection with the use of carvedilol. Therefore, close monitoring of diabetic patients receiving carvedilol is required by means of regular blood glucose measurements and adjustment of antidiabetic medication as necessary (see 4.5 “Interaction with other medicinal products and other forms of interaction”).

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

When carvedilol is used concomitantly with calcium channel blocking agents such as verapamil and diltiazem or with other antiarrhythmics, specifically amiodarone, the patient’s blood pressure and ECG have to be monitored. Intravenous co-administration should be avoided (see 4.5 “Interaction with other medicinal products and other forms of interaction”).

Cimetidine should be administered only with caution concomitantly as effects of carvedilol may be increased (see 4.5 “Interaction with other medicinal products and other forms of interaction”).

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

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. Cautions should be exercised when prescribing beta-blockers to patients with psoriasis since skin reactions may be aggravated.

Since carvedilol is a vasodilatory beta-blocker, the aggravation of peripheral vascular disease is more unlikely than with conventional beta-blockers. However, there is little clinical experience in this patient group so far. The same also applies to those with Raynaud’s syndrome, but there may be exacerbation of symptoms.

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

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

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

Betablockers reduce the risk of arrhythmias at anaesthesia, however the risk of hypotension may be increased as well. Caution should therefore be observed with the use of certain anaesthetic drugs. Newer studies suggest however, a benefit of betablockers in preventing perioperative cardiac morbidity and reduction of the incidence of cardiovascular complications.

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

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

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

#### 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 risk of AV conduction disorder or risk of cardiac failure is increased (synergistic effect). Close monitoring should be done in case of co-administration of carvedilol, and class I antiarrhythmics or amiodarone therapy (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.

Concomitant treatment with reserpine, guanethidine, methyldopa, guanfacin and monoamine-oxidase inhibitors (exception MAO-B-inhibitors) 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.

Cardiac glycosides. An increase of steady state digoxin levels by approximately 16% and of digitoxin by approximately 13% has been seen in hypertensive patients in connection with the concomitant use of carvedilol and digoxin. Monitoring of plasma digoxin concentrations is recommended when initiating, discontinuing or adjusting treatment with carvedilol.
Other antihypertensive drugs. Carvedilol may potentiate the effects of other concomitantly administered antihypertensives (e.g. \( \alpha \)-receptor antagonists) and drugs with antihypertensive side effects such as barbiturates, phenothiazines, tricyclic antidepressants, vasodilating agents and alcohol.

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

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

Clonidine. When combination treatment with carvedilol and clonidine is discontinued, carvedilol should be withdrawn several days before gradually decreasing the dose of clonidine.

Inhalational anaesthetics. Attention should be paid to the potential negative inotropic and hypotensive interactions of carvedilol and anaesthetics in association with anaesthesia.

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

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

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

Ergotamine. Vasoconstriction increased.

Neuromuscular blocking agents. Increased neuromuscular block.

4.6 Pregnancy and lactation

Use of carvedilol is not recommended during pregnancy and lactation. 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 "Preclinical safety data").

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 foetal and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Carvedilol should only be used for pregnant women, if the potential benefit for the mother outweighs the potential risk for the foetal/neonate. The treatment should be stopped 2-3 days before expected birth. If this is not possible the new-born has to be monitored for the first 2-3 days of life.

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

4.7 Effects on ability to drive and use machines

Some individuals may have reduced alertness especially on initiation and adjustment of medication. Under good therapeutic control, carvedilol is not known to reduce the ability to drive or use machines.
4.8 Undesirable effects

Adverse reactions occur mainly at the beginning of treatment.

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

<table>
<thead>
<tr>
<th>Category</th>
<th>VERY COMMON (&gt;1/10)</th>
<th>COMMON (&gt;1/100)</th>
<th>UNCOMMON (&gt;1/1000, &lt;1/100)</th>
<th>RARE (&lt;1/1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Mild thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition Disorders</td>
<td>Hyperglycaemia*</td>
<td>Oedema peripheral</td>
<td>Hypervolaemia</td>
<td>Fluid retention</td>
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<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
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<td>Eye disorders</td>
<td>Visual disturbance</td>
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<td>Cardiac disorders</td>
<td>Oedematous feet</td>
<td>Bradycardia</td>
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<td>Renal and urinary Disorders</td>
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<td>Aggravation of renal function</td>
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<td>Vascular disorders</td>
<td>Hypotension orthostatic</td>
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<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea</td>
<td>Diarrhoea</td>
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<td>Constipation</td>
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<tr>
<td>Reproductive</td>
<td>Genital oedema</td>
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system and breast disorders

| General disorders and administration site conditions | Oedema |

*Hyperglycaemia (in patients with diabetes mellitus), (see 4.4 “Special warning and special precautions for use”).

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.

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

<table>
<thead>
<tr>
<th>Blood and Lymphatic system disorders</th>
<th>VERY COMMON (&gt;1/10)</th>
<th>COMMON (&gt;1/100)</th>
<th>UNCOMMON (&gt;1/1000, &lt;1/100)</th>
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<td>Metabolism and nutrition disorder</td>
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<td>Psychiatric disorders</td>
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<tr>
<td>Nervous system disorder</td>
<td>Dizziness*</td>
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<td></td>
<td>Headache*</td>
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Decreased Visual disturbance
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<th>Effect</th>
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</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
<td>Bradycardia*</td>
<td></td>
<td>Eye irritation</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension orthostatic*</td>
<td>Peripheral circulatory failure</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal</td>
<td></td>
<td>Nasal congestion</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, Abdominal pain, Diarrhoea</td>
<td>Constipation, Vomiting</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Musculoskeletal, Connective tissue and bone disorder</td>
<td>Pain in limb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>Aggravation of renal function</td>
<td>Difficulty in micturition</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
<td>Impotence</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td>Serum transaminase increased</td>
<td></td>
</tr>
</tbody>
</table>

* These reactions occur in particular at the beginning of treatment.

Very rare adverse reactions include angina, AV block and exacerbation of symptoms in patients suffering from intermittent claudication or Raynaud's phenomenon.
Respiratory, thoracic and mediastinal disorders. Asthmatic dyspnoea has been observed commonly in predisposed patients.

Skin and subcutaneous tissue disorders. Various skin reactions have been reported rarely (e.g. allergic exanthema, urticaria, pruritus and lichen planus-like reaction). Psoriatic skin lesions may occur or existing lesions may be aggravated.

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.

4.9 Overdose

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

Treatment. In addition to normal treatment procedures, vital signs must be monitored and, if necessary, corrected at an intensive care unit. The following supportive measures may be taken:

Atropine: 0.5 - 2mg intravenously (for treatment of severe bradycardia).

Glucagon: initially 1 - 10mg intravenously followed if necessary by a slow infusion of 2 – 5mg/hour (in order to maintain cardiovascular function).

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

If peripheral vasodilation is the dominant symptom of overdose, the patient has to be given norepinephrine or etilefrine. The patient’s circulation must be monitored continuously.

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

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

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

Duration of the antidote treatment depends on the seriousness of the overdose; supportive treatment must be continued until the patient stabilises.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: alpha- and beta-blocking agents

ATC code: C07AG02

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 rennin activity is reduced and fluid retention is rare.

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

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

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

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

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

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

5.2 Pharmacokinetic properties

**General description.** The absolute bioavailability of orally administered carvedilol is approximately 25 %. Plasma levels peak at approximately 1 hour after dosing. There is linear correlation between the dose and plasma concentrations. In patients with slow hydroxylation of debrisoquine plasma carvedilol concentrations increased up to 2 - 3-fold compared to rapid debrisoquine metabolisers. Food does not affect bioavailability although the time to reach maximum plasma concentration is delayed. Carvedilol is a highly lipophilic compound.

Approximately 98 % to 99 % of carvedilol is bound to plasma proteins. Its volume of distribution is approximately 2 l/kg. The first pass effect after oral administration is approximately 60 – 75 %.

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

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

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

5.3 Preclinical safety data
Studies on rats and mice revealed no carcinogenic potential of carvedilol at doses of 75mg/kg and 200mg/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 (≥ 200mg/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 ≥ 60mg/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 200mg/kg and 75mg/kg, respectively (38 – 100 time the human maximum daily dose).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate.
Cellulose, microcrystalline.
Crospovidone.
Povidone K30.
Silica, colloidal anhydrous.
Magnesium stearate.
Colouring agents:
Ferric oxide, red (E172)
Ferric oxide, yellow (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
4 years

6.4 Special precautions for storage
Polyethylene (PE-HD) containers and closures: Store in the original container.
Blister (Al/PVC): Store in the original package.

6.5 Nature and contents of container
Polyethylene (PE/HD) containers and closures: 28, 30, 60, 100, 250 and 500 tablets.
Blister (Al/PVC): 14, 20, 28, 30, 50, 50x1, 56, 60, 98, 98x1 and 100 tablets.

Not all pack size and pack types may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Roger A Oakes Limited,
Allstoe House, Church Lane,
Greetham, Rutland,
LE15 7NF, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 32019/0003
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/12/2009

10 DATE OF REVISION OF THE TEXT
02/12/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Carvedilol 25mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains 25mg carvedilol.
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Tablet.
White, round, convex, bisected tablet with a pressure sensitive scoring notch, encoded C4.

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

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 25mg and the recommended maximum daily dose is 50mg.

Adults: The recommended initial dose is 12.5mg once daily for two days. Thereafter, the treatment is continued at the dose 25mg/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 12.5mg once daily, 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 12.5mg twice daily for two days. Thereafter, the treatment is continued at the dose 25mg 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 100mg in divided doses (twice daily).

Elderly: The recommended initial dose is 12.5mg twice daily for two days. Thereafter, the treatment is continued at the dose 25mg 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 4.3 “Contraindications”).

The initial dose is 3.125mg twice daily 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 6.25mg
twice daily, then 12.5mg twice daily followed by 25mg twice daily. It is recommended that the dose is increased to the highest level tolerated by the patient.

The recommended maximum dose is 25mg given twice daily in patients weighing less than 85 kg and 50mg twice daily in patients weighing more than 85 kg, provided that the heart failure is not severe. A dose increase to 50mg 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 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 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 3.125mg 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 heart failure is necessary.

Moderate hepatic dysfunction. Dose adjustment may be required.

Children and adolescents (<18 years). There is insufficient data of 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 coronary patients, the withdrawal of carvedilol should be done gradually (see 4.4 “Special warning and special precautions for use”).

Methods 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
Heart failure belonging to NYHA Class IV of the heart failure classification requiring intravenous inotropic treatment.
Chronic obstructive pulmonary disease with bronchial obstruction (see 4.4 “Special warning and special precautions for use”).
Clinically significant hepatic dysfunction.
Asthma bronchiale.
Second or third degree AV block.
Severe bradycardia (< 50 bpm).
Cardiogenic shock
Sick sinus syndrome (including sinoatrial blocks).
Severe hypotension (systolic blood pressure below 85 mmHg).
Hypersensitivity to carvedilol or to any of the excipients.
Metabolic acidosis.
Prinzmetal’s angina.
Untreated phaeochromocytoma.
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.

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.

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 4.5 "Interaction with other medicinal products and other forms of interaction").

Other warnings as regards carvedilol and beta-blockers in general. Subjects with chronic obstructive pulmonary disease using no oral or inhaled medication should not use carvedilol unless the benefit outweighs the potential risks of use. If carvedilol is given to these patients, they have to be monitored carefully when carvedilol therapy is initiated and during dose titration. The carvedilol dose must be reduced if the patient exhibits signs of bronchial obstruction during treatment.

Carvedilol may mask symptoms and signs of acute hypoglycaemia. Impaired blood glucose control may occasionally occur in patients with diabetes mellitus and heart failure in connection with the use of carvedilol. Therefore, close monitoring of diabetic patients receiving carvedilol is required by means of regular blood glucose measurements and adjustment of antidiabetic medication as necessary (see 4.5 "Interaction with other medicinal products and other forms of interaction").

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

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

Cimetidine should be administered only with caution concomitantly as effects of carvedilol may be increased (see 4.5 "Interaction with other medicinal products and other forms of interaction").

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

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

Since carvedilol is a vasodilatory beta-blocker, the aggravation of peripheral vascular disease is more unlikely than with conventional beta-blockers. However, there is little clinical experience in this patient group so far. The same also applies to those with Raynaud’s syndrome, but there may be exacerbation of symptoms.

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

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

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

Betablockers reduce the risk of arrhythmias at anaesthesia, however the risk of hypotension may be increased as well. Caution should therefore be observed with the use of certain anaesthetic drugs. Newer studies suggest however, a benefit of betablockers in preventing perioperative cardiac morbidity and reduction of the incidence of cardiovascular complications.

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

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

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

**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 risk of AV conduction disorder or risk of cardiac failure is increased (synergistic effect). Close monitoring should be done in case of co-administration of carvedilol, and class I antiarrhythmics or amiodarone therapy (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.

Concomitant treatment with reserpine, guanethidine, methylodopa, guanfacin and monoamine-oxidase inhibitors (exception MAO-B-inhibitors) 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.

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

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

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

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

*Clonidine.* When combination treatment with carvedilol and clonidine is discontinued, carvedilol should be withdrawn several days before gradually decreasing the dose of clonidine.

*Inhalational anaesthetics.* Attention should be paid to the potential negative inotropic and hypotensive interactions of carvedilol and anaesthetics in association with anaesthesia.

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

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

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

*Ergotamine.* Vasoconstriction increased.

*Neuromuscular blocking agents.* Increased neuromuscular block.

### 4.6 Pregnancy and lactation

Use of carvedilol is not recommended during pregnancy and lactation.

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 "Preclinical safety data").

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 foetal and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Carvedilol should only be used for pregnant women, if the potential benefit for the mother outweighs the potential risk for the foetal/neonate. The treatment should be stopped 2-3 days before expected birth. If this is not possible the new-born has to be monitored for the first 2-3 days of life.

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

### 4.7 Effects on ability to drive and use machines
Some individuals may have reduced alertness especially on initiation and adjustment of medication. Under good therapeutic control, carvedilol is not known to reduce the ability to drive or use machines.

4.8 Undesirable effects

Adverse reactions occur mainly at the beginning of treatment.

*Adverse reactions in heart failure patients reported from clinical studies.*

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

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>VERY COMMON (&gt;1/10)</th>
<th>COMMON (&gt;1/100)</th>
<th>UNCOMMON (&gt;1/1000, &lt;1/100)</th>
<th>RARE (&lt;1/1000)</th>
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<tbody>
<tr>
<td></td>
<td>Mild thrombocytopenia</td>
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<thead>
<tr>
<th>Metabolism and nutrition Disorders</th>
<th>Common (&gt;1/100)</th>
<th>Uncommon (&gt;1/1000, &lt;1/100)</th>
<th>Rare (&lt;1/1000)</th>
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<tbody>
<tr>
<td>Hyperglycaemia*</td>
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<td>Oedema peripheral</td>
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<tr>
<td>Hyperoalaemia</td>
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<td>Fluid retention</td>
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<tr>
<th>Nervous system disorders</th>
<th>Very Common (&gt;1/100)</th>
<th>Common (&gt;1/100)</th>
<th>Uncommon (&gt;1/1000, &lt;1/100)</th>
<th>Rare (&lt;1/1000)</th>
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<tbody>
<tr>
<td>Dizziness</td>
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<tr>
<th>Eye disorders</th>
<th>Very Common (&gt;1/100)</th>
<th>Common (&gt;1/100)</th>
<th>Uncommon (&gt;1/1000, &lt;1/100)</th>
<th>Rare (&lt;1/1000)</th>
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<td>Visual disturbance</td>
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<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th>Very Common (&gt;1/100)</th>
<th>Common (&gt;1/100)</th>
<th>Uncommon (&gt;1/1000, &lt;1/100)</th>
<th>Rare (&lt;1/1000)</th>
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<tbody>
<tr>
<td>Oedematous feet</td>
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<tr>
<td>Bradycardia</td>
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<thead>
<tr>
<th>Renal and urinary Disorders</th>
<th>Very Common (&gt;1/100)</th>
<th>Common (&gt;1/100)</th>
<th>Uncommon (&gt;1/1000, &lt;1/100)</th>
<th>Rare (&lt;1/1000)</th>
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<tbody>
<tr>
<td>Aggravation of renal function</td>
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<tr>
<th>Vascular disorders</th>
<th>Very Common (&gt;1/100)</th>
<th>Common (&gt;1/100)</th>
<th>Uncommon (&gt;1/1000, &lt;1/100)</th>
<th>Rare (&lt;1/1000)</th>
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<tr>
<td>Hypotension</td>
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<td>Orthostatic</td>
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<th>Common (&gt;1/100)</th>
<th>Uncommon (&gt;1/1000, &lt;1/100)</th>
<th>Rare (&lt;1/1000)</th>
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<td>Diarrhoea</td>
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<td>Vomiting</td>
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<td>Constipation</td>
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Reproductive system and breast disorders | Genital oedema |  |
---|---|---
General disorders and administration site conditions | Oedema |  |

*Hyperglycaemia (in patients with diabetes mellitus), (see 4.4 “Special warning and special precautions for use”).

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.

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

<table>
<thead>
<tr>
<th>VERY COMMON (&gt;1/10)</th>
<th>COMMON (&gt;1/100)</th>
<th>UNCOMMON (&gt;1/1000, &lt;1/100)</th>
<th>RARE (&lt;1/1000)</th>
<th>VERY RARE (&lt;1/10 000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic system disorders</td>
<td></td>
<td></td>
<td>Mild thrombocytopenia Leukopenia</td>
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<tr>
<td>Metabolism and nutrition disorder</td>
<td></td>
<td>Hypercholesterolaemia</td>
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<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td>Sleep disorders Depression</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td>Dizziness*</td>
<td>Headache*</td>
<td></td>
<td>Paraesthesia Syncope*</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Lacrimation Decreased</td>
<td>Cardiac disorders</td>
<td>Bradycardia*</td>
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<tr>
<td>Vascular disorders</td>
<td>Hypotension orthostatic*</td>
<td></td>
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<tr>
<td>Respiratory, thoracic and mediastinal</td>
<td></td>
<td></td>
<td>Nasal congestion</td>
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</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea Abdominal pain Diarrhoea</td>
<td>Constipation Vomiting</td>
<td>Dry mouth</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal, Connective tissue and bone disorder</td>
<td>Pain in limb</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>Aggravation of renal function</td>
<td>Difficulty in micturition</td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
<td>Impotence</td>
<td></td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td>Serum transaminase increased</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* These reactions occur in particular at the beginning of treatment.

Very rare adverse reactions include angina, AV block and exacerbation of symptoms in patients suffering from intermittent claudication or Raynaud's phenomenon.
Respiratory, thoracic and mediastinal disorders. Asthmatic dyspnoea has been observed commonly in predisposed patients.

Skin and subcutaneous tissue disorders. Various skin reactions have been reported rarely (e.g. allergic exanthema, urticaria, pruritus and lichen planus-like reaction). Psoriatic skin lesions may occur or existing lesions may be aggravated.

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.

4.9 Overdose

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

Treatment. In addition to normal treatment procedures, vital signs must be monitored and, if necessary, corrected at an intensive care unit. The following supportive measures may be taken:

- Atropine: 0.5 - 2mg intravenously (for treatment of severe bradycardia).
- Glucagon: initially 1 - 10mg intravenously followed if necessary by a slow infusion of 2 – 5mg/hour (in order to maintain cardiovascular function).
- Sympathomimetics according to their efficacy and the patient’s weight: dobutamine, isoprenalin or adrenaline.

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

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

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

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

Duration of the antidote treatment depends on the seriousness of the overdose; supportive treatment must be continued until the patient stabilises.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: alpha- and beta-blocking agents
ATC code: C07AG02
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 through non-selective beta-blockade. Plasma rennin activity is reduced and fluid retention is rare.

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

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

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

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

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

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

### 5.2 Pharmacokinetic properties

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

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

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

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

5.3 Preclinical safety data
Studies on rats and mice revealed no carcinogenic potential of carvedilol at doses of 75mg/kg and 200mg/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 (≥ 200mg/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 ≥ 60mg/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 200mg/kg and 75mg/kg, respectively (38 – 100 time the human maximum daily dose).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate.
Cellulose, microcrystalline.
Crospovidone.
Povidone K30.
Silica, colloidal anhydrous.
Magnesium stearate.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
4 years

6.4 Special precautions for storage
Polyethylene (PE-HD) containers and closures: Store in the original container.
Blister (Al/PVC): Store in the original package.

6.5 Nature and contents of container
Polyethylene (PE/HD) containers and closures: 28, 30, 60, 100, 250 and 500 tablets.
Blister (Al/PVC): 14, 20, 28, 30, 50, 50x1, 56, 60, 98, 98x1 and 100 tablets.

Not all pack size and pack types may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Roger A Oakes Limited,
Allstoe House, Church Lane,
Greetham, Rutland,
LE15 7NF,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/12/2009

10 DATE OF REVISION OF THE TEXT
02/12/2009
PATIENT INFORMATION LEAFLET

Carvedilol 3.125mg, 6.25mg, 12.5mg and 25mg Tablets

Please read this leaflet before you start to take your medicine and, in addition, follow the advice given to you by your doctor. If there is anything you do not understand, please ask your doctor or pharmacist (chemist).

Keep this leaflet while you are taking Carvedilol Tablets; you may want to read it again.

What are Carvedilol Tablets and what are they used for?
Carvedilol Tablets are available in packs of 28 tablets. Other pack sizes of 14, 20, 30, 50, 60, 88 and 100 tablets may also become available.

Carvedilol Tablets contain the active ingredient carvedilol. They are available in 4 strengths containing 3.125mg, 6.25mg, 12.5mg and 25mg carvedilol respectively.

The other ingredients in the tablets are lactose monohydrate, microcrystalline cellulose, cross-povidone, povidone K90, colloidal silicon dioxide, magnesium stearate and two colouring agents. These are ferrous oxide red (E172), found in 3.125mg or 12.5mg tablets and ferrous oxide yellow (E172), only in 6.25mg tablets and 12.5mg tablets.

Marketing Authorisation Holder / Distributor
Roger A Case Limited,
Altlea House, Church Lane,
Greetland, Rotton,
LE137NF, United Kingdom

Manufacturer:
Solus Pharmaco GmbH
Otto-von-Guericke-Allee 1, 39179, Barleben
Germany

Carvedilol Tablets are beta-blockers used for the treatment of high blood pressure, the prevention of chest pain and the treatment of heart failure. Carvedilol acts by dilating blood vessels and decreasing heart rate.

Before taking Carvedilol Tablets
Do not use Carvedilol Tablets
- If you have severe heart failure
- If you have a conduction defect of the heart
- If you have a liver disease
- If you have asthma or other lung diseases
- If you have a very slow pulse
- If you have any low blood pressure
- If you have had an allergic reaction to carvedilol or any of the other ingredients listed above
- If you are pregnant or breast-feeding

Please note: This product contains lactose, so any patients who are lactose intolerant or suffer from any other medical condition associated with lactose should not take this medicine unless told to do so by a doctor.

Take special care with Carvedilol Tablets:
- If you have diabetes, regular blood glucose measurements and adjustment of anti-diabetic medication may be necessary. Carvedilol Tablets can hide the symptoms of hypoglycaemia (low blood sugar).
- If you suffer from heart failure with low blood pressure, insufficient blood and oxygen supply in the heart (ischaemic heart disease) and hardening of the arteries (generalised arteriosclerosis).
- If you suffer from kidney problems. Your doctor may monitor your kidney function and if necessary reduce your dosage.
- If you are taking other heart medicines such as digoxin.
- If you have a very slow heart beat.
- If you suffer from a condition called Prinzmetal’s angina (heart disease).
- If you have phaeochromocytoma (a growth of the adrenal gland causing high blood pressure).
- If you use contact lenses, there is a possibility your eyes may become dry.
- If you have a circulation disorder called Raynaud’s phenomenon (cold hands or feet).
- If you suffer from psoriasis, skin reactions may become aggravated.
- If you have a history of severe allergies.
- Carvedilol Tablets may hide the symptoms of thyrotoxicosis (overactivity of the thyroid gland).

Please tell your doctor if you are taking, or have recently taken any other medicines.

Please remember that all medicines can sometimes cause unwanted side effects. There is more information about this later in the leaflet.

Pregnancy and breast-feeding
Carvedilol Tablets should not be used if you are pregnant (or think you may be) or if you are breast-feeding.

Driving or operating machinery
Some people may suffer from reduced alertness, especially in the beginning and on adjustment of medication, but under good therapeutic control Carvedilol Tablets are not known to affect the ability to drive or use machines. If you suffer from dizziness or impaired vision you should seek advice from your doctor before driving or operating machinery.

Taking other medicines
Certain other medicines may influence the effect of, or be influenced by, Carvedilol Tablets. Some of the medicines in question are listed below:
- Heart medication such as those containing diuretics, verapamil and/or amiodarone, class I antiarrhythmic drugs (such as flecainide) and cardiac glycosides (such as digoxin and digitoxin).
- Medicines such as reserpine, guanethidine, methyldopa, guanfacine and a group of drugs known as monoamine oxidase inhibitors (e.g. Modocynide).
- Dihydropyridines (such as nifedipine).
- Carvedilol may react with nitrates (drugs used to treat angina – chest pain).
- Drugs used to treat high blood pressure or those with similar side effects such as barbiturates, phenothiazines (such as chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), vasodilating agents and alcohol.
- Blood levels of cyclosporin are increased when carvedilol is used, so if you are taking cyclosporin your doctor may alter your dose.
- Drugs used to treat diabetes such as insulin and anti-diabetic tablets.
- When carvedilol and clonidine are being used together, withdrawal from this medication would require carvedilol to be stopped several days before slowly lowering the dose of clonidine.
• Medicines containing clonidine, ritampicin, cimetidine, ketocazole, fluoxetine, haloperidol, verapamil or erythromycin.
• Inhalation anasthetics (used at surgery)
• Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, estrogens and corticosteroids (such as dexamethasone)
• Ergotamine (used to treat migraine or pain)
• Neuromuscular blocking agents (such as suxamethonium)
• Drugs belonging to the sympathomimetic family of drugs such as ephedrine.

You should therefore consult your doctor before you take other medicines, self-medication products including natural products and herbal remedies together with this medicine.

Taking your medicine
Your doctor will tell you how much and when to take this medicine, depending on your age, weight and the reason for giving you this medicine.

Your doctor may change the dose of medicine you are taking, depending on how you respond to it. The dispensing label on the pack will tell you how many tablets to take and how often to take them.

The tablets do not need to be taken with a meal. However, heart failure patients should take their Carvedilol Tablets medication with food.

Carvedilol Tablets should not be used for children under 18 years.

What to do if you miss a dose?
If you miss a dose, do not worry. Do not take the missed tablet(s) - just take the next dose when it is due.

What to do if you take too many tablets?
If you have accidentally taken too many Carvedilol Tablets contact your doctor or nearest hospital casualty department immediately. If you go to the doctor or hospital take Carvedilol Tablets or this leaflet with you.

After taking your medicine – Possible side effects
Like all medicines, Carvedilol Tablets can have side effects. These mainly occur at the beginning of treatment. In connection with heart failure they include:

Very common:
• Disturbances in glucose control
• Fluid retention around the body/towelling
• Disturbed vision
• Swollen/puffy feet or ankles
• Slow pulse
• Low blood pressure
• Nausea, diarrhoea, vomiting

Common:
• Bruising
• Dizziness

In connection with high blood pressure and chest pain, they include:

Very common:
• Dizziness
• Headache
• Dry eyes
• Slow pulse
• Low blood pressure
• Pain in limb
• Tiredness

Common:
• Nausea
• Abdominal pain
• Diarrhoea
• Increased cholesterol levels in the blood

Asthma-related symptoms and breathing difficulties may be enhanced during carvedilol treatment.

As with other beta-blockers, mild disturbances of blood glucose level may occur.

You may rarely suffer symptoms such as:
• Constipation
• Heart failure
• Kidney problems
• Skin rashes (which may be infectious)
• Itchiness
• Sleep disorders
• Depression
• Nasal congestion
• Difficulty in passing urine (very rare)

Carvedilol may cause insomnia and agitation in some patients, just as other beta-blockers.

If you experience any disturbing or unusual effects, which you think may have been caused by Carvedilol Tablets, you should contact your doctor. You should not stop taking Carvedilol Tablets, unless your doctor tells you to.

Storing your medicine
Keep out of reach of sight of children.

Store in the original packaging.

If your doctor tells you to stop taking your medicine you should return any remaining tablets to the pharmacist, unless the doctor tells you to keep them at home. Do not use Carvedilol Tablets after the expiry date on the package.

REMEMBER
This medicine is for YOU. Only a doctor can prescribe it, so never offer it to anybody else, even if their symptoms seem to be the same as yours. It may harm them.

Carvedilol 3.125mg Tablets: PL 32019/0001
Carvedilol 6.25mg Tablets: PL 32019/0002
Carvedilol 12.5mg Tablets: PL 32019/0003
Carvedilol 25mg Tablets: PL 32019/0004

This leaflet was prepared in September 2007
Carvedilol 12.5mg Tablets
Each tablet contains 12.5mg Carvedilol

Date:
Expiry:

Attach dispensing label here

Product licence holder:
Roger A Oakes Limited,
Allstoe House, Church Lane,
Grestham, Rutland,
LE15 7NF, United Kingdom

PL 32019/0003