Public Assessment Report

Decentralised Procedure

CARVEDILOL 3.125MG TABLETS
CARVEDILOL 6.25MG TABLETS
CARVEDILOL 12.5MG TABLETS
CARVEDILOL 25MG TABLETS

Procedure No: UK/H/1170/001-4/DC

UK Licence No: PL 32256/0004-7

Aurobindo Pharma (Malta) Limited
LAY SUMMARY

On 29th April 2010, the MHRA granted Aurobindo Pharma (Malta) Limited Marketing Authorisations (licences) for the medicinal products Carvedilol Tablets.

These medicines are available on prescription from your doctor and used in treatment of the following conditions:

- For the treatment of high blood pressure (hypertension)
- For the treatment of chest pain that occurs when the arteries that supply your heart with blood carrying oxygen are narrowed, which results in less oxygen reaching your heart muscles (angina)
- For the treatment of weakening of the heart muscle (heart failure), in combination with other medicines.

The active ingredient carvedilol belongs to a group of medicines called beta-blockers that work by relaxing and widening the blood vessels. This makes it easier for your heart to pump blood around the body and reduces blood pressure and strain on the heart.

The tablets are available in four different strengths, containing carvedilol 3.125, 6.25, 12.5 and 25mg, respectively.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Carvedilol Tablets outweigh the risks, hence Marketing Authorisations have been granted.
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# Module 1

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<td><strong>MA Holder</strong></td>
<td>Aurobindo Pharma (Malta) Limited, Vault 14, Level 2, Valletta Waterfront, Floriana, FRN 1913, Malta.</td>
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Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Carvedilol 3.125 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Carvedilol 3.125 mg film-coated tablets:
Each tablet contains 3.125 mg carvedilol.
Excipients: Each tablet contains 28.625 mg lactose monohydrate and 0.625 mg sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Carvedilol 3.125 mg film-coated tablets:
White to off-white, oval shaped, film-coated tablets, debossed with ‘E’ on one side and ‘01’ on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Essential hypertension
Chronic stable angina pectoris
Adjunctive treatment of moderate to severe stable chronic heart failure

4.2 Posology and method of administration
Oral use.

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

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

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

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

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

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

Elderly
The recommended initial dose is 12.5 mg twice daily for two days. Thereafter, the treatment is continued at the dose 25 mg twice daily, which is the recommended maximum daily dose.
Heart failure:
Carvedilol is given in moderate to severe heart failure in addition to conventional basic therapy with diuretics, ACE inhibitors, digitalis, and/or vasodilators. The patient should be clinically stable (no change in NYHA-class, no hospitalisation due to heart failure) and the basic therapy must be stabilized for at least 4 weeks prior to treatment. Additionally the patient should have a reduced left ventricular ejection fraction and heart rate should be > 50 bpm and systolic blood pressure > 85 mm Hg (see section 4.3).

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

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

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

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

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

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

Moderate hepatic dysfunction
Dose adjustment may be required.

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

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

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

Methods of administration
The tablets should be taken with the adequate supply of fluid. It is recommended that heart failure patients take their carvedilol medication with food to allow the absorption to be slower and the risk of orthostatic hypotension to be reduced.
4.3 Contraindications
- Hypersensitivity to the carvedilol or to any of the excipients of Carvedilol.
- Heart failure belonging to NYHA Class IV of the heart failure classification with marked fluid retention or overload requiring intravenous inotropic treatment.
- Chronic obstructive pulmonary disease with bronchial obstruction (see section 4.4).
- Clinically significant hepatic dysfunction.
- Bronchial asthma.
- AV block, degree II or III (unless a permanent pacemaker is in place).
- Severe bradycardia (<50 bpm).
- Sick sinus syndrome (incl. sino-arial block).
- Cardiogenic shock.
- Severe hypotension (systolic blood pressure below 85 mmHg).
- Prinzmetal’s angina.
- Untreated phaeochromocytoma.
- Metabolic acidosis.
- Severe peripheral arterial circulatory disturbances.
- Concomitant intravenous treatment with verapamil or diltiazem (see section 4.5).

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

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

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

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

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

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

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

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

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

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

Care should be taken in 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.

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

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

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

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

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Antiarrhythmics.

Isolated cases of conduction disturbance (rarely compromised haemodynamics) have been reported, if oral carvedilol and oral diltiazem verapamil and/or amiodarone are given concomitantly. As with other beta-blockers, ECG and blood pressure should be monitored closely when concomitantly administering calcium-channel-blockers of the verapamil and diltiazem type due to the risk of AV conduction disorder or risk of cardiac failure (synergetic effect). Close monitoring should be done in case of co-administration of carvedilol, and amiodarone therapy (oral) or class I antiarrhythmics. Bradycardia, cardiac arrest, and ventricular fibrillation have been reported shortly after initiation of beta-blocker treatment in patients receiving amiodarone. There is a risk of cardiac failure in case of class Ia or Ic antiarrhythmics concomitant intravenous therapy.
Concomitant treatment with reserpine, guanethidine, methyldopa, guanfacine and monoamine oxidase inhibitors (exception MAO-B inhibitors) can lead to additional decrease in heart rate. And hypotension Monitoring of vital signs is recommended.

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

**Nitrites.**
Increased hypotensive effects.

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

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

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

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

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

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

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

**Medicines inducing or inhibiting cytochrome P450 enzymes.**
Patients receiving medicines that induce (e.g. rifampicin and barbiturates) or inhibit (e.g. cimetidine, ketoconazole, fluoxetine, haloperidol, verapamil, 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

**Pregnancy**
There are no adequate data from the use of carvedilol in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
Beta-blockers reduce placental perfusion which may result in intrauterine fetal death and immature and premature deliveries. In addition, adverse reactions (especially hypoglycaemia, hypotension, bradycardia, respiratory depression and hypothermia) may occur in the fetus and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Carvedilol should not be used during pregnancy unless clearly necessary (that is if the potential benefit for the mother outweighs the potential risk for the fetus/neonate). The treatment should be stopped 2-3 days before expected birth. If this is not possible the new-born has to be monitored for the first 2-3 days of life.

**Lactation**

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

### 4.7 Effects on ability to drive and use machines

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

### 4.8 Undesirable effects

The following terminologies have been used in order to classify the occurrence of undesirable effects.

- **Very common** (≥ 1/10)
- **Common** (≥ 1/100 to <1/10)
- **Uncommon** (≥ 1/1,000 to <1/100)
- **Rare** (≥ 1/10,000 to <1/1,000)
- **Very rare** (<1/10,000), not known (cannot be established from the available data).

Adverse reactions occur mainly at the beginning of treatment.

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

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

**Cardiac disorders**

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

**Blood and lymphatic system disorder**

- **Rare**: thrombocytopenia.
- **Very rare**: leucopenia.

**Nervous system disorders**

- **Very common**: dizziness*, headache* (usually mild), asthenia (including fatigue).

**Eye disorders**

- **Common**: vision abnormalities.

**Gastrointestinal disorders**

- **Common**: nausea, diarrhoea, and vomiting.

**Renal and Urinary disorders**

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

**Metabolism and nutrition disorders**

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

* Occurring particularly at the start of treatment.

The frequency of adverse reactions is not dose dependent, with the exception of dizziness, visual disturbance, bradycardia and aggravation of heart insufficiency.
Cardiac contractility may be decreased during dose titration, but this is rare.

Adverse reactions in patients with hypertension and angina pectoris reported from clinical studies

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

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

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

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

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

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

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

Renal and urinary disorders
Rare: disturbances of micturition

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

Musculoskeletal and connective tissue disorders
Common: pain in the extremeties

General disorders and administration site conditions
Isolated cases of allergic reactions

Reproductive system and breast disorders
Uncommon: impotence

Psychiatric disorder
Uncommon: sleep disturbance, depression, hallucination, confusion
Very rare: psychosis
* Occurring particularly at the start of treatment.

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

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

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

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

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

If peripheral vasodilatation is the dominant symptom of overdose, the patient has to be given 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: C07A G02

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

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

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

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

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

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

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

*General description:*
The absolute bioavailability of orally administered carvedilol is approximately 25%. Plasma levels peak at approximately 1 hour after dosing. There is a linear correlation between the dose and plasma concentrations. In patients with slow hydroxylation of debrisoquine plasma carvedilol concentrations increased up to 2-3-fold compared to rapid debrisoquine metabolisers. Food does not affect bioavailability although the time to reach maximum plasma concentration is delayed. Carvedilol is a highly lipophilic compound. Approximately 98% to 99% of carvedilol is bound to plasma proteins. Its volume of distribution is approximately 21/kg. The first pass effect after oral administration is approximately 60-75%.

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

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

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

5.3 **Preclinical safety data**
Carvedilol demonstrated no mutagenic or carcinogenic potential.

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

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

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

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

6.2 **Incompatibilities**
Not applicable.
6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Aurobindo Pharma (Malta) Limited,
Vault 14, Level 2,
Valletta Waterfront, Floriana,
FRN 1913,
Malta.

8 MARKETING AUTHORISATION NUMBER(S)
PL 32256 / 0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/04/2010

10 DATE OF REVISION OF THE TEXT
29/04/2010
1 NAME OF THE MEDICINAL PRODUCT
Carvedilol 6.25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Carvedilol 6.25 mg film-coated tablets:
Each tablet contains 6.25 mg carvedilol.
Excipients: Each tablet contains 57.25 mg lactose monohydrate and 1.250 mg sucrose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Carvedilol 6.25 mg film-coated tablets:
White to off-white, oval shaped, film-coated tablets, debossed with ‘F57’ on one side and a deep break line on the other side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Essential hypertension
Chronic stable angina pectoris
Adjunctive treatment of moderate to severe stable chronic heart failure

4.2 Posology and method of administration
Oral use.

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

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

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

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

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

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

Elderly
The recommended initial dose is 12.5 mg twice daily for two days. Thereafter, the treatment is continued at the dose 25 mg twice daily, which is the recommended maximum daily dose.
Heart failure:
Carvedilol is given in moderate to severe heart failure in addition to conventional basic therapy with diuretics, ACE inhibitors, digitalis, and/or vasodilators. The patient should be clinically stable (no change in NYHA-class, no hospitalisation due to heart failure) and the basic therapy must be stabilized for at least 4 weeks prior to treatment. Additionally the patient should have a reduced left ventricular ejection fraction and heart rate should be > 50 bpm and systolic blood pressure > 85 mm Hg (see section 4.3).

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

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

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

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

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

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

Moderate hepatic dysfunction
Dose adjustment may be required.

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

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

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

Methods of administration
The tablets should be taken with the adequate supply of fluid. It is recommended that heart failure patients take their carvedilol medication with food to allow the absorption to be slower and the risk of orthostatic hypotension to be reduced.
4.3 Contraindications
- Hypersensitivity to the carvedilol or to any of the excipients of Carvedilol.
- Heart failure belonging to NYHA Class IV of the heart failure classification with marked fluid retention or overload requiring intravenous inotropic treatment.
- Chronic obstructive pulmonary disease with bronchial obstruction (see section 4.4).
- Clinically significant hepatic dysfunction.
- Bronchial asthma.
- AV block, degree II or III (unless a permanent pacemaker is in place).
- Severe bradycardia (<50 bpm).
- Sick sinus syndrome (incl. sino-atrial block).
- Cardiogenic shock.
- Severe hypotension (systolic blood pressure below 85 mmHg).
- Prinzmetal’s angina.
- Untreated phaeochromocytoma.
- Metabolic acidosis.
- Severe peripheral arterial circulatory disturbances.
- Concomitant intravenous treatment with verapamil or diltiazem (see section 4.5).

4.4 Special warnings and precautions for use

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

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

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

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

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

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

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

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

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

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

Care should be taken in 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.

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

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

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

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

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Antiarrhythmics.

Isolated cases of conduction disturbance (rarely compromised haemodynamics) have been reported, if oral carvedilol and oral diltiazem verapamil and/or amiodarone are given concomitantly. As with other beta-blockers, ECG and blood pressure should be monitored closely when concomitantly administering calcium-channel-blockers of the verapamil and diltiazem type due to the risk of AV conduction disorder or risk of cardiac failure (synergetic effect). Close monitoring should be done in case of co-administration of carvedilol, and amiodarone therapy (oral) or class I antiarrhythmics. Bradycardia, cardiac arrest, and ventricular fibrillation have been reported shortly after initiation of beta-blocker treatment in patients receiving amiodarone. There is a risk of cardiac failure in case of class Ia or Ic antiarrhythmics concomitant intravenous therapy.
Concomitant treatment with reserpine, guanethidine, methyldopa, guanfacine and monoamine oxidase inhibitors (exception MAO-B inhibitors) can lead to additional decrease in heart rate. And hypotension Monitoring of vital signs is recommended.

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

**Nitrates.**
Increased hypotensive effects.

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

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

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

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

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

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

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

**Medicines inducing or inhibiting cytochrome P450 enzymes.**
Patients receiving medicines that induce (e.g. rifampicin and barbiturates) or inhibit (e.g. cimetidine, ketoconazole, fluoxetine, haloperidol, verapamil, 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

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

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

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

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

4.8 Undesirable effects
The following terminologies have been used in order to classify the occurrence of undesirable effects.

Very common (≥ 1/10)
Common (≥ 1/100 to <1/10)
Uncommon (≥ 1/1,000 to <1/100)
Rare (≥ 1/10,000 to <1/1,000)
Very rare (<1/10,000), not known (cannot be established from the available data).

Adverse reactions occur mainly at the beginning of treatment.

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

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

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

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

Eye disorders
Common: vision abnormalities.

Gastrointestinal disorders
Common: nausea, diarrhoea, and vomiting.

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

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

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

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

**Adverse reactions in patients with hypertension and angina pectoris reported from clinical studies**

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

**Cardiac disorders**

**Common:** bradycardia*, postural hypotension*

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

**Blood and lymphatic system disorders**

*Very rare:* Increase of ALAT, ASAT and gamma-GT, thrombocytopenia, leucopenia.

**Nervous system disorder**

**Common:** dizziness*, headaches* and fatigue*

**Uncommon:** paraesthesia

**Eye disorder**

**Common:** reduced lacrimation (in particular in patients wearing contact lenses), eye irritation

**Uncommon:** disturbed vision.

**Respiratory disorders:**

**Common:** asthma and dyspnoea in predisposed patients.

**Rare:** stuffy nose.

**Gastrointestinal disorders**

**Common:** nausea, abdominal pain, diarrhoea

**Uncommon:** constipation and vomiting.

**Rare:** dryness of the mouth

**Renal and urinary disorders**

**Rare:** disturbances of micturition

**Skin and subcutaneous disorders**

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

**Musculoskeletal and connective tissue disorders**

**Common:** pain in the extremeties

**General disorders and administration site conditions**

Isolated cases of allergic reactions

**Reproductive system and breast disorders**

**Uncommon:** impotence

**Psychiatric disorder**

**Uncommon:** sleep disturbance, depression, hallucination, confusion

*Very rare:* psychosis

* Occuring particularly at the start of treatment.

Non-selective beta-blockers in particular may also result in latent diabetes mellitus becoming manifest, manifest diabetes being aggravated and blood glucose control being disturbed. Mild disturbances of glucose balance are possible, however not common, also during treatment with carvedilol.
The frequency of adverse reactions is not dose dependent, with the exception of dizziness, visual disturbance, bradycardia and aggravation of heart insufficiency.

4.9 Overdose

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

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

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

If peripheral vasodilatation is the dominant symptom of overdose, the patient has to be given 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: C07A G02

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

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

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

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

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

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

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

5.2 Pharmacokinetic properties

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

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

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

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

5.3 Preclinical safety data

Carvedilol demonstrated no mutagenic or carcinogenic potential.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Film-coating
Macrogol 400
Polysorbate 80
Titanium dioxide (E171)
Hyپromellose
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Aurobindo Pharma (Malta) Limited,
Vault 14, Level 2,
Valletta Waterfront, Floriana,
FRN 1913,
Malta.

8 MARKETING AUTHORISATION NUMBER(S)
PL 32256 / 0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/04/2010

10 DATE OF REVISION OF THE TEXT
29/04/2010
1 NAME OF THE MEDICINAL PRODUCT
Carvedilol 12.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Carvedilol 12.5 mg film-coated tablets:
Each tablet contains 12.5 mg carvedilol.
Excipients: Each tablet contains 114.5 mg lactose monohydrate and 2.5 mg sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Carvedilol 12.5 mg film-coated tablets:
White to off-white, oval shaped, film-coated tablets, debossed with ‘F58’ on one side and a deep break line on the other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Essential hypertension
Chronic stable angina pectoris
Adjunctive treatment of moderate to severe stable chronic heart failure

4.2 Posology and method of administration
Oral use.

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

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

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

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

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

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

Elderly
The recommended initial dose is 12.5 mg twice daily for two days. Thereafter, the treatment is continued at the dose 25 mg twice daily, which is the recommended maximum daily dose.
Heart failure:
Carvedilol is given in moderate to severe heart failure in addition to conventional basic therapy with diuretics, ACE inhibitors, digitalis, and/or vasodilators. The patient should be clinically stable (no change in NYHA-class, no hospitalisation due to heart failure) and the basic therapy must be stabilized for at least 4 weeks prior to treatment. Additionally the patient should have a reduced left ventricular ejection fraction and heart rate should be > 50 bpm and systolic blood pressure > 85 mm Hg (see section 4.3).

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

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

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

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

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

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

Moderate hepatic dysfunction
Dose adjustment may be required.

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

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

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

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

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

4.4 Special warnings and precautions for use

Warnings to be considered particularly in heart failure patients

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

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

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

Other warnings as regards carvedilol and beta-blockers in general

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

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

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

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

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

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

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

Care should be taken in 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.

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

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

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

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

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Antiarrhythmics.

Isolated cases of conduction disturbance (rarely compromised haemodynamics) have been reported, if oral carvedilol and oral diltiazem verapamil and/or amiodarone are given concomitantly. As with other beta-blockers, ECG and blood pressure should be monitored closely when concomitantly administering calcium-channel-blockers of the verapamil and diltiazem type due to the risk of AV conduction disorder or risk of cardiac failure (synergetic effect). Close monitoring should be done in case of co-administration of carvedilol, and amiodarone therapy (oral) or class I antiarrhythmics. Bradycardia, cardiac arrest, and ventricular fibrillation have been reported shortly after initiation of beta-blocker treatment in patients receiving amiodarone. There is a risk of cardiac failure in case of class Ia or Ic antiarrhythmics concomitant intravenous therapy.
Concomitant treatment with reserpine, guanethidine, methyldopa, guanfacine and monoamine oxidase inhibitors (exception MAO-B inhibitors) can lead to additional decrease in heart rate. And hypotension Monitoring of vital signs is recommended.

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

**Nitrites.**
Increased hypotensive effects.

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

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

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

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

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

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

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

**Medicines inducing or inhibiting cytochrome P450 enzymes.**
Patients receiving medicines that induce (e.g. rifampicin and barbiturates) or inhibit (e.g. cimetidine, ketoconazole, fluoxetine, haloperidol, verapamil, 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

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

Beta-blockers reduce placental perfusion which may result in intrauterine fetal death and immature and premature deliveries. In addition, adverse reactions (especially hypoglycaemia, hypotension, bradycardia, respiratory depression and hypothermia) may occur in the fetus and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period.

Carvedilol should not be used during pregnancy unless clearly necessary (that is if the potential benefit for the mother outweighs the potential risk for the fetus/neonate). The treatment should be stopped 2-3 days before expected birth. If this is not possible the new-born has to be monitored for the first 2-3 days of life.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following terminologies have been used in order to classify the occurrence of undesirable effects.

- **Very common** (≥ 1/10)
- **Common** (≥ 1/100 to <1/10)
- **Uncommon** (≥ 1/1,000 to <1/100)
- **Rare** (≥ 1/10,000 to <1/1,000)
- **Very rare** (<1/10,000), not known (cannot be established from the available data).

Adverse reactions occur mainly at the beginning of treatment.

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

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

**Cardiac disorders**

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

**Blood and lymphatic system disorder**

- **Rare**: thrombocytopenia.
- **Very rare**: leucopenia.

**Nervous system disorders**

- **Very common**: dizziness*, headache* (usually mild), asthenia (including fatigue).

**Eye disorders**

**Common**: vision abnormalities.

**Gastrointestinal disorders**

- **Common**: nausea, diarrhoea, and vomiting.

**Renal and Urinary disorders**

- **Rare**: acute renal failure and renal function abnormalities in patients with diffuse vascular disease and/or impaired renal function (see section 4.4).
Metabolism and nutrition disorders
Common: weight increase, hypercholesterolemia, hyperglycaemia, hypoglycaemia and worsening control of blood glucose (in patients with pre-existing diabetes mellitus) (see section 4.4).
* Occurring particularly at the start of treatment.

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

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

Adverse reactions in patients with hypertension and angina pectoris reported from clinical studies

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

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

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

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

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

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

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

Renal and urinary disorders
Rare: disturbances of micturition

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

Musculoskeletal and connective tissue disorders
Common: pain in the extremeties

General disorders and administration site conditions
Isolated cases of allergic reactions

Reproductive system and breast disorders
Uncommon: impotence

Psychiatric disorder
Uncommon: sleep disturbance, depression, hallucination, confusion
Very rare: psychosis
* Occurring particularly at the start of treatment.
Non-selective beta-blockers in particular may result in latent diabetes mellitus becoming manifest, manifest diabetes being aggravated and blood glucose control being disturbed. Mild disturbances of glucose balance are possible, however not common, also during treatment with carvedilol.

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

4.9 Overdose

Symptoms

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

Treatment

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

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

If peripheral vasodilatation is the dominant symptom of overdose, the patient has to be given 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: C07A G02

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

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

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

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

In hypertensive patients, a reduction in blood pressure is not associated with a concomitant increase in peripheral resistance, as observed with pure beta-blocking agents. Heart rate is slightly decreased. Stroke volume remains unchanged. Renal blood flow and renal function remain normal, as does peripheral blood flow, therefore, cold extremities, often observed with beta-blockers, are rarely seen. In hypertensive patients carvedilol increases the plasma norepinephrine concentration.
In prolonged treatment of patients with angina, carvedilol has been seen to have an anti-ischaemic effect and to alleviate pain. Haemodynamic studies demonstrated that carvedilol reduces ventricular pre- and after-load. In patients with left ventricular dysfunction or congestive heart failure, carvedilol has a favourable effect on haemodynamics and left ventricular ejection fraction and dimensions.

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

5.2 Pharmacokinetic properties

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

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

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

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

5.3 Preclinical safety data
Carvedilol demonstrated no mutagenic or carcinogenic potential.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Lactose monohydrate
Silica Colloidal anhydrous
Crospovidone (Type A)
Crospovidone (Type B)
Povidone 30
Sucrose
Magnesium stearate
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Aurobindo Pharma (Malta) Limited,
Vault 14, Level 2,
Valletta Waterfront, Floriana,
FRN 1913,
Malta.

8 MARKETING AUTHORISATION NUMBER(S)
PL 32256 / 0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/04/2010

10 DATE OF REVISION OF THE TEXT
29/04/2010
1 NAME OF THE MEDICINAL PRODUCT
Carvedilol 25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Carvedilol 25 mg film-coated tablets:
Each tablet contains 25 mg carvedilol.
Excipients: Each tablet contains 229 mg lactose monohydrate and 5 mg sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Carvedilol 25 mg film-coated tablets:
White to off-white, oval shaped, film-coated tablets, debossed with ‘F59’ on one side and deep break line on the other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Essential hypertension
Chronic stable angina pectoris
Adjunctive treatment of moderate to severe stable chronic heart failure

4.2 Posology and method of administration
Oral use.

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

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

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

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

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

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

Elderly
The recommended initial dose is 12.5 mg twice daily for two days. Thereafter, the treatment is continued at the dose 25 mg twice daily, which is the recommended maximum daily dose.
**Heart failure:**
Carvedilol is given in moderate to severe heart failure in addition to conventional basic therapy with diuretics, ACE inhibitors, digitalis, and/or vasodilators. The patient should be clinically stable (no change in NYHA-class, no hospitalisation due to heart failure) and the basic therapy must be stabilized for at least 4 weeks prior to treatment. Additionally the patient should have a reduced left ventricular ejection fraction and heart rate should be > 50 bpm and systolic blood pressure > 85 mm Hg (see section 4.3).

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

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

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

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

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

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

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

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

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

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

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

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

4.4 Special warnings and precautions for use

Warnings to be considered particularly in heart failure patients

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

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

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

Other warnings as regards carvedilol and beta-blockers in general

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Antiarrhythmics.

Isolated cases of conduction disturbance (rarely compromised haemodynamics) have been reported, if oral carvedilol and oral diltiazem verapamil and/or amiodarone are given concomitantly. As with other beta-blockers, ECG and blood pressure should be monitored closely when concomitantly administering calcium-channel-blockers of the verapamil and diltiazem type due to the risk of AV conduction disorder or risk of cardiac failure (synergetic effect). Close monitoring should be done in case of co-administration of carvedilol, and amiodarone therapy (oral) or class I antiarrhythmics. Bradycardia, cardiac arrest, and ventricular fibrillation have been reported shortly after initiation of beta-blocker treatment in patients receiving amiodarone. There is a risk of cardiac failure in case of class Ia or Ic antiarrhythmics concomitant intravenous therapy.
Concomitant treatment with reserpine, guanethidine, methyldopa, guanfacine and monoamine oxidase inhibitors (exception MAO-B inhibitors) can lead to additional decrease in heart rate. And hypotension. Monitoring of vital signs is recommended.

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

**Nitrates.**
Increased hypotensive effects.

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

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

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

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

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

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

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

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

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

**Ergotamine.**
Vasoconstriction increased.

**Neuromuscular blocking agents.**
Increased neuromuscular block.
4.6 Pregnancy and lactation

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

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

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

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

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

Adverse reactions occur mainly at the beginning of treatment.

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

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

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

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

Eye disorders
Common: vision abnormalities.

Gastrointestinal disorders
Common: nausea, diarrhoea, and vomiting.

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

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

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

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

Adverse reactions in patients with hypertension and angina pectoris reported from clinical studies

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

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

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

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

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

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

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

Renal and urinary disorders
Rare: disturbances of micturition

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

Musculoskeletal and connective tissue disorders
Common: pain in the extremities

General disorders and administration site conditions
Isolated cases of allergic reactions

Reproductive system and breast disorders
Uncommon: impotence

Psychiatric disorder
Uncommon: sleep disturbance, depression, hallucination, confusion
Very rare: psychosis
* Occurring particularly at the start of treatment.

Non-selective beta-blockers in particular may also result in latent diabetes mellitus becoming manifest, manifest diabetes being aggravated and blood glucose control being disturbed. Mild disturbances of glucose balance are possible, however not common, also during treatment with carvedilol.
The frequency of adverse reactions is not dose dependent, with the exception of dizziness, visual disturbance, bradycardia and aggravation of heart insufficiency.

4.9 Overdose

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

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

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

If peripheral vasodilatation is the dominant symptom of overdose, the patient has to be given 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: C07A G02

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

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

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

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

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

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

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

5.2 **Pharmacokinetic properties**

**General description:**
The absolute bioavailability of orally administered carvedilol is approximately 25%. Plasma levels peak at approximately 1 hour after dosing. There is a linear correlation between the dose and plasma concentrations. In patients with slow hydroxylation of debrisoquine plasma carvedilol concentrations increased up to 2-3-fold compared to rapid debrisoquine metabolisers. Food does not affect bioavailability although the time to reach maximum plasma concentration is delayed. Carvedilol is a highly lipophilic compound. Approximately 98% to 99% of carvedilol is bound to plasma proteins. Its volume of distribution is approximately 21 kg. The first pass effect after oral administration is approximately 60-75%.

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

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

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

5.3 **Preclinical safety data**
Carvedilol demonstrated no mutagenic or carcinogenic potential.

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

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

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

**Film-coating**
- Macrogol 400
- Polysorbate 80
- Titanium dioxide (E171)
- Hypromellose
6.2 \textbf{Incompatibilities}
Not applicable.

6.3 \textbf{Shelf life}
2 years

6.4 \textbf{Special precautions for storage}
Store below 25°C.

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

Not all pack sizes may be marketed.

6.6 \textbf{Special precautions for disposal}
No special requirements.

7 \textbf{MARKETING AUTHORISATION HOLDER}
Aurobindo Pharma (Malta) Limited,
Vault 14, Level 2,
Valletta Waterfront, Floriana,
FRN 1913,
Malta.

8 \textbf{MARKETING AUTHORITY NUMBER(S)}
PL 32256 / 0007

9 \textbf{DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION}
29/04/2010

10 \textbf{DATE OF REVISION OF THE TEXT}
29/04/2010
Module 3

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Carvedilol is and what it is used for
2. Before you take Carvedilol
3. How to take Carvedilol
4. Possible side effects
5. How to store Carvedilol
6. Further information

1. What Carvedilol is and what it is used for

Carvedilol belongs to a group of medicines called beta-blockers that work by relaxing and widening the blood vessels. This makes it easier for your heart to pump blood around the body and reduces blood pressure and strain on your heart.

Carvedilol is used:
- for the treatment of high blood pressure (hypertension),
- for the treatment of chest pain that occurs when the arteries that supply your heart with blood carrying oxygen are narrowed, which results in less oxygen reaching your heart muscles (angina),
- for the treatment of weakening of the heart muscle (heart failure), in combination with other medicines.

2. Before you take Carvedilol

DO NOT TAKE Carvedilol
- If you are allergic (hypersensitive) to carvedilol or any of the other ingredients of Carvedilol (see section 4 “Further Information”),
- If you have a history of wheezing due to asthma or other lung diseases,
- If you have been told you have severe heart failure and you have fluid retention (swelling) which is being treated with injections of medicines into your veins (intravenously),
- If you have liver disease,
- If you have had low blood pressure,
- If you have been told you have a condition called Pheochromocytoma's angina,
- If you have phaeochromocytoma (a tumour of the adrenal gland causing high blood pressure) which is not being treated,
- If you are suffering from serious disturbances in the body's acid-base balance (metabolic acidosis),
- If you have very poor blood circulation in the hands and feet, resulting in coldness and pain in them,
- If you have a particular condition of the heart called an AV heart block (grade II or III, unless a pacemaker is fitted, or a SA block),
- If you are currently being treated with injections of verapamil or atenolol (used in the treatment of high blood pressure or heart problems).
- If any of these apply to you, do not take Carvedilol.

Take special care with Carvedilol
- It is important to tell your doctor before taking Carvedilol if you:
  - have been told you suffer from any other heart problems,
  - have or have ever had any problems with your liver, kidneys or thyroid,
  - have diabetes. Carvedilol may hide your usual symptoms of too much sugar,
  - have a skin condition known as psoriasis,
  - have poor circulation affecting the hands, feet, lower legs or Raynaud's phenomenon,
  - have or have ever had a serious allergic reaction or you are undergoing allergic desensitization therapy for any type of severe allergy,
  - wear contact lenses because Carvedilol may cause the eyes to be drier than normal.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription or herbal medicines. Take particular care and tell your doctor or pharmacist, if you are taking any of the following medicines:
- medicines used to treat an irregular heartbeat (e.g. digoxin, verapamil or amiodarone),
- nitrates medicines for angina (e.g. isosorbide mononitrate or glyceryl trinitrate),
- medicines used to treat heart failure (e.g. Digoxin),
- any other medicine used to treat high blood pressure (e.g. doxazosin, reserpine, amiodipine or indapamide),
- medicines used to treat depression or other mental health conditions (e.g. fluoxetine, tetracyclic antidepressants, bupropions, phenothiazines, haloperidol or monoamine oxidase inhibitors (MAOIs)),
- medicines used to prevent your body rejecting organs after transplant operations (e.g. ciclosporin),
- medicines to reduce blood sugar such as oral antidiabetic medicines or insulin,
- medicines used to reduce blood pressure or to treat migraine (e.g. clonidine or enalapril),
- certain painkilling agents such as non-steroidal anti-inflammatory medicines (NSAIDs) (e.g. ibuprofen or diclofenac),
- medicines used for hormone replacement therapy (e.g. estrogen),
- colestyramine used to suppress inflammatory or allergic reactions (e.g. prednisolone),
- medicines used to treat bacterial infections (e.g. Rifampicin or erythromycin),
- medicines used to treat stomach ulcers, heartburn and acid reflux (e.g. omeprazole),
- medicines used to treat fungal infections (e.g. ketoconazole),
- medicines sometimes used in decongestant cough and cold remedies (e.g. ephedrine or pseudophedrine),

If you need to have an anaesthetic for an operation, tell your hospital doctor you are taking Carvedilol.

Taking Carvedilol with food and drink
You should take Carvedilol with water.

If you are taking Carvedilol to treat heart failure, you should take this medicine with water at your meals (see section 3 ‘How to take Carvedilol’). Do not drink alcohol whilst taking carvedilol as it might worsen the effects of alcohol.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, do not take this medicine until you have told your doctor. Consult your doctor immediately if you become pregnant while taking this medicine.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
You may experience dizziness or tiredness whilst taking Carvedilol. This is more likely to occur when you first begin treatment, or when the dose is increased. If this occurs, you should not drive or operate machinery. You should avoid drinking alcohol, as it may make these symptoms worse. If you are concerned or want more information, you should talk to your doctor.

Important information about some of the ingredients of Carvedilol
Carvedilol contains lactose and these types of sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Carvedilol

Always take Carvedilol exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Carvedilol tablets should be swallowed with a drink of water.

High blood pressure
Adults: The usual starting dose is 12.5 mg once a day for the first two days. After this, the dose is increased to 25 mg once a day. If necessary, your doctor may gradually increase the dose further at intervals of two weeks or more. The maximum recommended daily dose is 50 mg (the maximum recommended single dose is 25 mg).

Elderly: Your doctor will usually start you on 12.5 mg once a day and continue with this dose for the length of your treatment. If necessary, your doctor may increase your dose gradually at intervals of two weeks or more.

Angina
Adults: The usual starting dose is 12.5 mg twice a day for the first two days. After this, the dose is increased to 25 mg twice a day. If necessary, your doctor may gradually increase the dose further at intervals of two weeks or more to a maximum of 100 mg a day in two doses.

Elderly: The recommended starting dose is 12.5 mg twice a day for two days. After this, the dose may be increased to 25 mg twice a day, which is the recommended maximum daily dose.

Heart failure
Adults and elderly: For the treatment of stable heart failure, the tablets should be taken twice a day, in the morning and in the evening, and should be taken with food in order to reduce the risk of side effects.

The starting dose is 12.5 mg twice a day for two weeks. Your doctor will then gradually increase the strength of tablets you take at intervals of two weeks or more until you receive the dose that suits you best. If you weigh less than 85 kg, the maximum recommended dose of Carvedilol is 25 mg twice a day. If you weigh more than 85 kg, your doctor may increase your dose to 50 mg twice a day.

For the treatment of heart failure, it is recommended that your treatment with Carvedilol is started and carefully monitored by a hospital specialist. If you have stopped taking carvedilol for more than two weeks, you will need to return to the starting dose and increase the dose gradually again.

Sometimes, your heart failure may worsen while taking Carvedilol, particularly at the start of your treatment. This may result in increased symptoms (e.g. tiredness, shortness of breath) and signs of fluid retention (e.g. weight gain and swelling of the legs).

If your symptoms or condition worsen whilst taking Carvedilol you should tell your doctor, as he or she may need to change the dose of your other medications or of Carvedilol.
While taking Carvedilol, make sure that you continue with your other treatments for heart failure as advised by your doctor.

Patients with liver problems
Depending on your condition, your doctor may reduce your dose compared to those recommended above.

Children and adolescents (under 16 years old)
Carvedilol tablets are not recommended in this age group.

If you take more Carvedilol than you should
If you accidentally take too many tablets, contact your doctor immediately or go to the nearest hospital casualty department. You may feel dizzy, sick, faint, breathless/wheezy, very drowsy, or experience convulsions.

If you forget to take Carvedilol
If you forget to take a dose, do not worry. Take another as soon as you remember, provided it is not nearly time for your next dose. Take your next tablet at the normal time, but do not take a double dose to make up for a forgotten tablet.

If you stop taking Carvedilol
Do not suddenly stop taking Carvedilol before you have spoken to your doctor about it. You may have side effects if you suddenly stop the tablets. Your doctor will tell you how to reduce the dosage gradually and then stop this medicine. If you are also taking a medicine called comedone, never stop either treatment unless told to by your doctor. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects
Like all medicines, Carvedilol can cause side effects, although not everybody gets them.

The frequency of possible side effects is shown in the table below.

Very common: Occur in more than 1 in 10 users.
Common: Occur in less than 1 in 10, but more than 1 in 100 users.
Uncommon: Occur in less than 1 in 100 users but more than 1 in 1,000 users.
Rare: Occur in less than 1 in 1,000, but more than 1 in 10,000 users.

Very rare: Occur in less than 1 in 10,000 users, including isolated cases.

The majority of side effects are dose-related and disappear when the dose is reduced or the treatment discontinued. Some side effects can occur at the beginning of treatment and resolve spontaneously as the treatment continues.

Side effects in patients with heart failure:

Very common:
- Dizziness
- Headache
- Tiredness

Common:
- Increase in weight
- Elevated cholesterol levels
- Loss of control of blood sugar in people with diabetes
- Slow heart rate
- Low blood pressure. Signs include dizziness (e.g. when standing up quickly)
- Odema (including swelling of the body or parts of the body, for example hand and feet, genital odema), fluid overload, increased volume of blood in the body
- Visual disturbance
- Diarrhoea
- Malaise, sweating

Uncommon:
- Fainting
- Disturbances in the heart’s conduction system
- Worsening of heart failure at the beginning of treatment

Rare:
- Lowered blood platelet count (thrombocytopenia)
- Acute renal insufficiency and disturbances in renal function in patients with hardening of the arteries and/or impaired renal function

Very rare:
- Low numbers of white blood cells

Side effects in patients with raised blood pressure or chest pain:

Common:
- Slow heart rate in particular at the beginning of treatment (bradycardia)
- Dizziness (e.g. when standing up suddenly)
- Headache
- Tiredness
- Reduced lacrimation, eye irritation
- Asthma and breathing problems
- Malaise, stomach pain
- Diarrhoea
- Pains in the arms and legs

Uncommon:
- Abnormal sensation
- Fainting
- Problems with blood circulation (signs include cold hands and feet), worsening of symptoms in patients with Raynaud’s disease (fingers or toes turn first blue, then white, and then reddish together with pain) or claudication (pain in the legs which worsens when walking)
- Disturbances in the heart’s conduction system, angina pectoris (including chest pain), symptoms of heart failure and odema (swelling of more than one part of the body)
- Visual disturbance
- Depression
- Hallucinations
- Confusion
- Impotence

Rare:
- Mouth dryness (dryness of the mouth)
- Stuffy nose
- Difficulty in passing urine

Very rare:
- Psychosis
- Altered blood picture (thrombocytopenia, leucopenia)

Isolated cases of allergic reactions.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Carvedilol
Keep out of the reach and sight of children.

Do not use Carvedilol after the expiry date, which is stated on the carton after 3Y. The expiry date refers to the last date of that month.

Store below 25°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information

What Carvedilol contains:
- The active substance is carvedilol. Each film-coated tablet contains 3.125 mg, 6.25 mg, 12.5 mg or 25 mg carvedilol.
- The other ingredients are: lactose monohydrate, silica colloidal anhydrous, crospovidone (types A & B), povidone-30, sucrose, magnesium stearate, microcrystalline 400, polyacrylate 80, titanium dioxide (E171) and hypromellose.

What Carvedilol looks like and contents of the pack

Film-coated tablet.

Carvedilol 3.125 mg film-coated tablets:
- White to off-white, oval shaped, film-coated tablets, debossed with “3125” on one side and “01” on the other side.

Carvedilol 6.25 mg film-coated tablets:
- White to off-white, oval shaped, film-coated tablets, debossed with “625” on one side and “02” on the other side.

The tablet can be divided into equal halves.

Carvedilol 12.5 mg film-coated tablets:
- White to off-white, oval shaped, film-coated tablets, debossed with “58” on one side and deep break line on the other side. The tablet can be divided into equal halves.

Carvedilol 25 mg film-coated tablets:
- White to off-white, oval shaped, film-coated tablets, debossed with “59” on one side and deep break line on the other side. The tablet can be divided into equal halves.

Carvedilol film-coated tablets are available in PVC/PVF/PAD-Aluminium blister packs: 10, 14, 28, 30, 50, 60, 90 and 100 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Aurobindo Pharma (Malta) Limited, Unit 14, Level 2, Valletta Waterfront, Floriana, HWW 1913, Malta.

Manufacturer
Pfizer Service Company, Hohe Wieh 10, B-1930, Zaventem, Belgium, or Pfizer P gems Zone Industrielle, ZA route des Industries, 33750 Poitou-sur-Clise, France.

This leaflet was last approved in MM / YYYY
Ref: CVL 0 UK
Carvedilol 25 mg
film-coated tablets

Each film-coated tablet contains 25 mg carvedilol.
Also contains lactose and sucrose.
For oral use only.
Read the package leaflet before use.
Keep out of the reach of children.
Store below 30°C.
Module 5
Scientific discussion during initial procedure

1 INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Carvedilol 3.125, 6.25, 12.5 and 25mg Tablets (PL 32256/0004-7; UK/H/1170/001-4/DC) could be approved. These applications were submitted by the decentralised procedure, with the UK as reference member state (RMS) and Austria, Belgium, Denmark, Germany, Greece, Finland, Hungary, Ireland, Italy, the Netherlands, Norway, Poland, Portugal, Romania, and Spain as concerned member states (CMS).

The products are prescription-only medicines indicated in the treatment of:
- Essential hypertension
- Chronic stable angina pectoris
- Adjunctive treatment of moderate to severe stable chronic heart failure

These are applications made under the decentralised procedure (DCP), according to Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Dimitone Tablets, which were originally granted licences to Hoffman La Roche (Denmark) in 1993.

Carvedilol is a vasodilating non-selective beta-blocking agent with antioxidant properties. Vasodilation is predominantly mediated through alpha1 receptor antagonism. It reduces the peripheral vascular resistance through vasodilation and suppresses the renin-angiotensin-aldosterone system through beta-blockade. The activity of plasma renin is reduced and fluid retention is rare.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 12th April 2010. After a subsequent national phase, the licences were granted in the UK on 29th April 2010.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Carvedilol 3.125, 6.25, 12.5 and 25mg Tablets |
| Name(s) of the active substance(s) (INN) | Carvedilol |
| Pharmacotherapeutic classification (ATC code) | Alpha and beta blocking agents (C07A G02) |
| Pharmaceutical form and strength(s) | 3.125, 6.25, 12.5 and 25mg Tablets |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1170/001-4/DC |
| Reference Member State | United Kingdom |
| Member States concerned | Austria, Belgium, Denmark, Germany, Greece, Finland, Hungary, Ireland, Italy, the Netherlands, Norway, Poland, Portugal, Romania, and Spain |
| Marketing Authorisation Number(s) | PL 32256/0004-7 |
| Name and address of the authorisation holder | Aurobindo Pharma (Malta) Limited, Vault 14, Level 2, Valletta Waterfront, Floriana, FRN 1913, Malta. |
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

S. Active substance

INN: Carvedilol
Chemical Name: (2RS)-1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol.

Molecular Formula: C_{24}H_{26}N_{2}O_{4}
Chemical Structure:

Molecular Weight: 406.5
Appearance: White or almost white, crystalline powder, practically insoluble in water, slightly soluble in alcohol and practically insoluble in dilute acids.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, silica colloidal anhydrous, crospovidone (Type A and B), povidone 30, sucrose, magnesium stearate, macrogol 400, polysorbate 80, titanium dioxide and hypromellose.

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.
With the exception of lactose monohydrate, none of the excipients are sourced from animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals, under the same conditions as milk for human consumption. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to formulate robust, stable tablets that were containing qualitatively and quantitatively the same active ingredient as Dimitone Tablets (Hoffman La Roche, Denmark), and exhibiting the same bioavailability in order to comply with the regulations pertaining to generic medicinal product applications.

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed for all strengths are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
All strengths of tablets are packaged in either

1. polyvinylchloride/aluminium/polyvinylidene chloride/polyethylene blisters in pack sizes of 10, 14, 28, 30, 50, 56, 60 and 100 film-coated tablets.
2. high-density polyethylene bottles with white opaque polypropylene stock ribbed closure, in pack sizes of 30 and 1000 film-coated tablets

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with the storage instructions “Store below 25°C”.

Suitable post approval stability commitments have been provided.
Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet 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.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these products.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of carvedilol are well-known, no further preclinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a preclinical viewpoint.
III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Carvedilol 25mg Tablets versus the reference product Eucardic 25 (Roche Products Limited, UK) in healthy volunteers under fed conditions.

Volunteers underwent an overnight fast of at least 10 hours followed by a high-fat meal. They were dosed with either treatment 30 minutes after the high-fat meal. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 48 hours post dose. The two treatment arms were separated by a 12-day washout period.

The non-transformed pharmacokinetic results for carvedilol and 4-hydroxyphenyl-carvedilol are presented below:

### Carvedilol:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC(_{0-t}) ng/ml/h</th>
<th>AUC(_{0-\infty}) ng/ml/h</th>
<th>C(_{\text{max}}) ng/ml</th>
<th>t(_{\text{max}}) h</th>
<th>T(_{1/2}) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>374.85 (191.826)</td>
<td>382.19 (192.851)</td>
<td>78.28 (37.155)</td>
<td>1.75 (0.5-5.0)</td>
<td>6.65 (1.9)</td>
</tr>
<tr>
<td>Reference</td>
<td>413.27 (252.959)</td>
<td>423.20 (255.022)</td>
<td>87.90 (45.499)</td>
<td>2.13 (0.5-5.0)</td>
<td>6.63 (2.8)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>93.65 (88.28-99.34)</td>
<td>93.18 (87.89-98.79)</td>
<td>90.65 (83.36-98.54)</td>
<td>93.18 (87.89-98.79)</td>
<td>90.65 (83.36-98.54)</td>
</tr>
<tr>
<td>CV (%)</td>
<td>14.89%</td>
<td>14.75%</td>
<td>21.17%</td>
<td></td>
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</tbody>
</table>

*AUC\(_{0-\infty}\)* area under the plasma concentration-time curve from time zero to infinity  
*AUC\(_{0-t}\)* area under the plasma concentration-time curve from time zero to t hours  
*C\(_{\text{max}}\)* maximum plasma concentration  
*t\(_{\text{max}}\)* time for maximum concentration  
*T\(_{1/2}\)* half-life

### 4-hydroxyphenyl-carvedilol:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC(_{0-t}) ng/ml/h</th>
<th>AUC(_{0-\infty}) ng/ml/h</th>
<th>C(_{\text{max}}) ng/ml</th>
<th>t(_{\text{max}}) h</th>
<th>T(_{1/2}) h</th>
</tr>
</thead>
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<tr>
<td>Test</td>
<td>53.18 (18.006)</td>
<td>56.94 (17.926)</td>
<td>13.60 (5.639)</td>
<td>1.75 (0.5-5.0)</td>
<td>8.87 (3.3)</td>
</tr>
<tr>
<td>Reference</td>
<td>56.47 (17.666)</td>
<td>60.54 (18.153)</td>
<td>14.20 (5.194)</td>
<td>1.75 (0.5-5.0)</td>
<td>9.16 (3.4)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>94.02 (87.55-100.97)</td>
<td>94.05 (87.91-100.68)</td>
<td>94.08 (86.23-102.64)</td>
<td>94.08 (87.91-100.68)</td>
<td>94.08 (86.23-102.64)</td>
</tr>
<tr>
<td>CV (%)</td>
<td>18.03%</td>
<td>17.14%</td>
<td>22.12%</td>
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</tr>
</tbody>
</table>

*AUC\(_{0-\infty}\)* area under the plasma concentration-time curve from time zero to infinity  
*AUC\(_{0-t}\)* area under the plasma concentration-time curve from time zero to t hours  
*C\(_{\text{max}}\)* maximum plasma concentration  
*t\(_{\text{max}}\)* time for maximum concentration  
*T\(_{1/2}\)* half-life

*ln-transformed values*

The 90% confidence intervals for C\(_{\text{max}}\) and AUC for test versus reference products are within predefined acceptance criteria. The data support the claim that the test product is bioequivalent to the reference product.
As the 3.125, 6.25, 12.5 and 25mg strengths of the product meet the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the extrapolation of results and conclusions from the bioequivalence study on the 25mg strength to the other presentations is justified.

**Efficacy**
No new data on the efficacy have been submitted and none are required for these types of applications.

**Safety**
No new or unexpected safety issues were raised by the bioequivalence data.

**SPC, PIL, Labels**
The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products.

**Clinical Expert Report**
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Conclusion**
The grant of marketing authorisations is recommended.

**IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT**

**QUALITY**
The important quality characteristics of Carvedilol 3.125, 6.25, 12.5 and 25mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk-benefit balance.

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

**EFFICACY**
Bioequivalence has been demonstrated between the applicant’s Carvedilol 25mg Tablets and its respective reference product. As the 3.125, 6.25 and 12.5mg strengths of the product meet the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 25mg strength can be extrapolated to the other strengths of tablet.

No new or unexpected safety concerns arise from these applications.

The SPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

**RISK-BENEFIT ASSESSMENT**
The quality of the products is acceptable, and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. 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.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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