PROFESSIONAL INFORMATION

CARVETREND RANGE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CARVETREND 6,25 mg (tablets)

CARVETREND 12,5 mg (tablets)

CARVETREND 25 mg (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CARVETREND 6,25 mg tablet contains carvedilol 6,25 mg.

Each CARVETREND 12,5 mg tablet contains carvedilol 12,5 mg.

Each CARVETREND 25 mg tablet contains carvedilol 25 mg.

CARVETREND contains sugar (lactose monohydrate and sucrose) in the following quantities per tablet, respectively:

CARVETREND 6,25 mg: (72,25 mg; 5,00 mg)

CARVETREND 12,5 mg: (144,50 mg; 10,00 mg)

CARVETREND 25 mg: (85,00 mg; 60,00 mg)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

CARVETREND 6,25 mg: A white, oval, slightly biconvex tablet, one side scored, with sign S2 on the opposite side.

CARVETREND 12,5 mg: A white, oval, slightly biconvex tablet, one side scored, with sign S3 on the opposite side.

CARVETREND 25 mg: A white, round, slightly biconvex tablet, bevel-edged, one side scored.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CARVETREND is indicated for the treatment of:

- essential mild to moderate hypertension
- mild to moderate stable symptomatic congestive heart failure either of cardiomyopathic or ischaemic origin. Used as an adjunct to standard therapy. Has been used in patients that are not tolerant to angiotensin-converting-enzyme (ACE) inhibitors. Has been used in patients who may, or may not, be on digitalis therapy
- long term treatment following otherwise uncomplicated myocardial infarction, but with left ventricular dysfunction (left ventricular ejection fraction (LVEF) < 40 % or wall motion index < 1,3), in combination with ACE inhibitors and other treatments recommended in the management of patients after myocardial infarction.

4.2 Posology and method of administration

Posology

Oral use.

Treatment should be started with low doses, and gradually titrated upwards until an optimal effect is achieved.

Essential Hypertension:

Adults:

The initial recommended dose is 12,5 mg once daily for the first 2 days. Dosage is then increased to 25 mg daily thereafter. Combination with a diuretic may assist in attaining the desired clinical response.

Elderly:

The initial recommended dose is 12,5 mg once daily. If the clinical response is inadequate, the dose should be increased at 14-day intervals up to 25 mg once daily or in divided doses. The incidence of side effects increases significantly with doses higher

than 25 mg with only a slight increase in efficacy.

Symptomatic congestive heart failure:

Dosage must be individualised and closely monitored by a medical practitioner experienced in the management of heart failure, during up-titration. Patients on concomitant digitalis, diuretics and ACE inhibitors should have dosing stabilised for these medicines before initiating treatment with CARVETREND.

Treatment should be initiated with 3,125 mg twice a day for at least 14 days; if this dose is tolerated, the dosage should be increased at intervals of not less than 14 days to 6,25 mg twice a day, 12,5 mg twice a day and then 25 mg twice a day.

Maximum recommended dose for patients weighing:

- less than 85 kg is 25 mg twice a day, and
- more than 85 kg is 50 mg twice a day.

The medical practitioner should assess the patient for symptoms of worsening heart failure or vasodilation before the dose increments. The diuretic should be increased to treat the transient worsening heart failure or fluid retention; sometimes lowering the CARVETREND dose or temporarily discontinuing CARVETREND may be necessary.

When treatment of CARVETREND has been discontinued for longer than 14 days, the dosage regimen should be initiated from the starting point reflected above. Reduction of the diuretic dose may assist in the management of vasodilation symptoms (such as
dizziness, headache and postural hypotension). The ACE inhibitor dose may be reduced if symptoms continue. If necessary, the CARVETREND dose may be reduced.

CARVETREND dose should not be increased until the symptoms of worsening heart failure or vasodilation have been stabilised.

Left ventricular dysfunction following otherwise uncomplicated acute myocardial infarction:

Dosage must be individualised and closely monitored by a doctor during up-titration.

Treatment may be started as an inpatient or outpatient when the patient is haemodynamically stable and

fluid retention has been minimised.

Prior to initiating CARVETREND:

Haemodynamically stable patients should have received an ACE inhibitor for at least 48 hours, given at a stable dose during at least the preceding 24 hours. CARVETREND can then be started between day 3 and day 21 after the myocardial infarction.

First dose of CARVETREND:

The initial recommended dose is 6,25 mg. Patients should remain under close medical supervision for at least 3 hours following the initial dose (see section 4.4).

Subsequent doses of CARVETREND:

If the patient has tolerated the first dose (i.e. heart rate > 50 beats/minute, systemic blood pressure > 80mmHg, and absence of clinical signs of intolerance), the dose should be increased to 6,25 mg twice daily and maintained for 3 - 10 days. The dose should be reduced to 3,125 mg twice daily if the patient develops signs of intolerance during this period, in particular bradycardia < 50 beats/minute, systolic blood pressure < 80 mmHg or fluid retention. If this dose is not tolerated, treatment should be stopped. If it is well tolerated, it should be increased again to 6,25 mg twice daily after 3 - 10 days.

Subsequent up-titration:

If the dose of 6,25 mg twice daily is well tolerated, the dose should be increased at intervals of 3 - 10 days to 12,5 mg twice daily and then to 25 mg twice daily. The maintenance dose is the maximum dose tolerated by the patient.

The maximum recommended dose is 25 mg twice daily, irrespective of the patient's weight.

Special populations

Elderly:

Carvedilol plasma levels are approximately 50 % higher in elderly subjects when compared to young

subjects; appropriate dosage adjustment should be made.

Renal impairment:

Available pharmacokinetic data in patients with varying degrees of renal impairment (including renal failure) suggest no changes in CARVETREND dosing recommendations are warranted in patients with moderate to severe renal insufficiency.

Hepatic impairment:

CARVETREND is contraindicated in patients with clinical manifestations of liver dysfunction (see section 4.3).

Paediatric population

The safety and efficacy of CARVETREND in children and adolescents (< 18 years) has not been established.

Method of administration

Tablets should be taken after meals and swallowed with sufficient fluid. In patients with heart failure, CARVETREND should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects.

Withdrawal:

Treatment with CARVETREND is a long-term therapy. Treatment should not be stopped abruptly but rather gradually reduced at weekly intervals. This is particularly important in the case of patients with concomitant coronary heart disease.

4.3 Contraindications

CARVETREND is contraindicated in:

- hypersensitivity to carvedilol or to any of the ingredients of CARVETREND (see section 6.1)
- bronchial asthma
- chronic obstructive pulmonary disease
- severe bradycardia (< 50 bpm)

- sick sinus syndrome including sinoatrial block
- second or third-degree atrioventricular (AV) block (unless a permanent pacemaker is in place)
- decompensated heart failure (New York Heart Association (NYHA) Class IV) requiring intravenous inotropic support
- cardiogenic shock
- clinically manifest liver impairment
- severe hypotension (systolic BP < 85 mmHg)
- Prinzmetal angina
- untreated phaeochromocytoma
- metabolic acidosis
- severe peripheral arterial circulatory disturbances
- concomitant treatment with calcium channel blockers like verapamil or diltiazem (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

In chronic heart failure patients, CARVETREND 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 doctor. Therapy should only be initiated, if the patient is stabilised 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 CARVETREND 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 CARVETREND.

The CARVETREND dose should not be increased before symptoms due to the worsening of heart failure or hypotension due to vasodilatation are under control.

In patients with chronic heart failure treated with digitalis, CARVETREND should be given with caution, as

digitalis and CARVETREND both lengthen the AV conduction time (see section 4.5).

Do not use in patients with metabolic acidosis, partial heart block, or sinus bradycardia.

Interaction with clonidine:

Caution should be exercised when transferring a patient from clonidine. The withdrawal of clonidine may result in the release of large amounts of catecholamines that may give rise to a hypertensive crisis. If beta blockers are administered in these circumstances, the unopposed alpha receptor stimulation may potentiate this effect. If a beta blocker and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of the beta blocker, as severe rebound hypertension may occur (see section 4.5).

Congestive heart failure:

Use with extreme caution in patients with congestive heart failure who have previously achieved adequate clinical control.

When symptoms of worsening cardiac effects or fluid retention occur during dosage increase, the diuretic dose should be increased. CARVETREND dose should not be increased until the symptoms have been stabilised.

It may be necessary to reduce the dose of CARVETREND or temporarily discontinue its use.

As both CARVETREND and digitalis slow AV conduction, CARVETREND should be used with caution in patients who are controlled with digitalis, diuretics and/or ACE inhibitor treatment.

Left ventricular dysfunction following uncomplicated acute myocardial infarction:

Before treatment with CARVETREND is initiated, the patient must be clinically stable and should have received an ACE inhibitor for at least the preceding 48 hours, and the dose of the ACE inhibitor should have been stable for at least the preceding 24 hours (see section 4.2).

Bradycardia:

CARVETREND may cause bradycardia. If the pulse rate is below 55 beats per minute, CARVETREND dosage should be decreased.

Concomitant use of calcium channel blockers:

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

Cimetidine:

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

Ischaemic heart disease:

In these patients, treatment should not be abruptly discontinued but should instead be over a period of 7 - 14 days, e.g. by reducing the daily dose to half every three days. If required, replacement therapy should be initiated at the same time to prevent exacerbation of angina pectoris.

Renal insufficiency:

Use with caution in patients with renal impairment.

As CARVETREND is metabolised mainly by the hepatic route, no dosage adjustment is necessary.

However, in patients with congestive heart failure (CHF) having low blood pressure (systolic < 100 mmHg), diffuse vascular disease, ischaemic heart disease and/or an underlying renal insufficiency, reversible deterioration of renal function has been observed.

Given these risk factors in patients with congestive heart failure, monitoring of renal function during dosage adjustment is advised. If worsening of renal function occurs, CARVETREND treatment should be discontinued or the dosage reduced.

Diabetes mellitus:

CARVETREND should be used with care in diabetes mellitus patients as the early warning symptoms and signs of acute hypoglycaemia could be enhanced or masked.

In diabetics with CHF, worsening control of blood glucose may be accompanied with CARVETREND.

Therefore, when CARVETREND therapy is initiated or even during dosage adjustment, regular monitoring of blood glucose is essential, and hypoglycaemia treated accordingly.

On the other hand, numerous studies have demonstrated that vasodilating ß-blockers, such as carvedilol, have a more favourable effect on glucose and lipid profiles. Carvedilol has shown modest insulin-sensitizing properties and may alleviate some manifestations of metabolic syndrome.

Pulmonary:

Do not use in patients with obstructive airway diseases, bronchospasm, or allergic conditions involving the airways (example, glottis oedema, allergic rhinitis).

In patients with chronic obstructive pulmonary disease (COPD) with a bronchospastic element, CARVETREND treatment is not recommended (see section 4.3). Where the benefit outweighs the risk in patients not requiring oral or inhaled treatment for their bronchospastic disease, CARVETREND has been initiated. However, when CARVETREND therapy is initiated or even during dosage adjustment, the patient should be closely monitored. Treatment should be discontinued or even reduced if bronchospasm is observed.

Thyrotoxicosis:

Symptoms may be masked by CARVETREND.

Raynaud's phenomenon:

Symptoms of arterial insufficiency (see **Peripheral vascular disease**) may be exacerbated.

Contact lens wearers:

The possibility of reduced lacrimation should be borne in mind.

Other cardiac:

Since there is limited clinical experience, carvedilol should not be administered in patients with labile or secondary hypertension, orthostasis, acute inflammatory heart disease, haemodynamic relevant obstruction of heart valves or outflow tract, end-stage peripheral

arterial disease, concomitant treatment with alpha-1-receptor antagonist or alpha-2-receptor agonist.

Phaeochromocytoma:

Treatment should be initiated with alpha blocking agents before using any beta blocking agent.

There is currently no documented evidence with CARVETREND use in this condition, despite CARVETREND displaying pharmacological properties of alpha- and beta blockers.

Peripheral vascular disease:

As beta blockers can accelerate or exacerbate arterial insufficiency symptoms, CARVETREND should be used with caution (see Raynaud's phenomenon above). Because of its negative dromotropic action, CARVETREND should be given with caution to patients with first degree heart block.

Debrisoquine:

Patients known to be poor metabolizers of debrisoquine should be closely monitored during initiation of therapy.

Prinzmetal angina:

Medicines having nonselective beta blocking activity can aggravate chest pains in patients with Prinzmetal variant angina. Caution should be exercised when initiating CARVETREND treatment in patients suspected of having Prinzmetal angina as there is no documented evidence of its use in this condition.

Vagal influences:

Intravenous administration of 1 - 2 mg atropine can be used for protection against vagal influences. In case of severe postural hypotension, CARVETREND should be discontinued in these patients.

Anaesthesia and major surgery:

Caution should be exercised in patients undergoing general surgery, because of the synergistic negative inotropic effects of CARVETREND and anaesthetic medicines.

Beta blockers like CARVETREND may reduce the risk of arrhythmias at anaesthesia, however the risk of hypotension may also be increased. Caution is advised with the use of certain anaesthetic medicines.

Hypersensitivity:

Care should be taken in administering CARVETREND 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.

Severe cutaneous adverse reactions (SCARs):

Severe cutaneous adverse reactions like toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported during treatment with CARVETREND.

CARVETREND should be permanently discontinued in patients who experience severe cutaneous adverse reactions possibly attributable to carvedilol.

Psoriasis:

Patients with a history of psoriasis associated with beta blockers should take CARVETREND only after consideration of the risk-benefit ratio as skin reactions may be aggravated.

Information on excipients of CARVETREND

CARVETREND contains sucrose and lactose.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take CARVETREND.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take CARVETREND.

Paediatric population

Safety has not been established.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions

CARVETREND may result in the potentiation of the effect when used with other antihypertensives or medicines that result in hypotension as a side effect.

Effects of CARVETREND on the pharmacokinetics of other medicines:

CARVETREND is a substrate as well as an inhibitor of P-glycoprotein. Bioavailability of medicines transported by P-glycoprotein may therefore be increased with concomitant administration of CARVETREND. The bioavailability of CARVETREND can also be
modified by inducers or inhibitors of P-glycoprotein.

Digoxin: An increased exposure of digoxin of up to 20 % has been shown in healthy patients and patients with heart failure. Digoxin levels should be monitored when CARVETREND therapy is initiated, adjusted or discontinued (see section 4.4).

Cimetidine: May result in the increase of systemic bioavailability (approximately 30 %) of carvedilol without affecting C_{max} when administered with cimetidine.

Phenothiazines: The concurrent use of phenothiazines and beta blockers result in a rise in the plasma levels of both medicines, since phenothiazines are inhibitors of cytochrome P450 isoenzyme CYP2D6 and may inhibit the metabolism of CARVETREND, which is a substrate for this isoenzyme. Both beta blockers and

phenothiazines can cause

hypotension, and these effects could be additive.

Ciclosporin: Modest increases in mean trough ciclosporin concentrations were observed following initiation of CARVETREND treatment. Due to wide inter-individual variability of ciclosporin levels, it is recommended that ciclosporin concentrations be monitored closely

after initiation of CARVETREND therapy, and that the dose of ciclosporin be adjusted as appropriate. In case of intravenous administration of ciclosporin, no interaction with CARVETREND is expected.

Effects of other medicines on the pharmacokinetics of CARVETREND:

Inhibitors and inducers of CYP2D6 and CYP2C9 can modify the systemic and/or pre-systemic metabolism of CARVETREND, leading to increased or decreased plasma concentrations.

Rifampicin: May lead in the reduced systemic availability of carvedilol. Close monitoring of the beta blockade activity in patients receiving concomitant administration of CARVETREND and rifampicin is appropriate. Rifampicin reduces plasma concentrations of carvedilol by about 70 %.

Amiodarone: Monitoring of the beta blockade activity in patients treated with the combination of CARVETREND and amiodarone is advised. 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.

Medicines inducing or inhibiting cytochrome P450 enzymes:

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

Fluoxetine and Paroxetine: In a randomised cross-over study in 10 patients with heart failure, co-administration of fluoxetine, a strong inhibitor of CYP2D6, resulted in stereo-selective inhibition of carvedilol metabolism with a 77 % increase in mean R (+) enantiomer AUC, and a non-statistically significant 35 % increase of the S (-) enantiomer's AUC as compared to the placebo group. However, no differences in adverse events, blood pressure or heart rate were noted between treatment groups. The effect of a single

dose paroxetine, a strong CYP2D6 inhibitor, on carvedilol pharmacokinetics was investigated in 12 healthy subjects following single oral administration. Despite significant increase in R and S-carvedilol exposure, no clinical effects were observed in these healthy subjects.

Pharmacodynamic interactions

Insulin or oral hypoglycaemics: The effects of these agents may be increased. Regular blood glucose monitoring is recommended as hypoglycaemic signs and symptoms are either hidden or aggravated (see section 4.4).

Catecholamines: With medicines that lead to catecholamine depletion, e.g. reserpine, or adrenergic neuron blocking agents like guanethidine or bethanidine, methyldopa and monoamine oxidase inhibitors (exception MAO-B inhibitors) may lead to hypotension and/or severe bradycardia. These patients should be closely monitored for these signs and symptoms.

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

Clonidine: Concomitant administration of clonidine with agents with beta blocking properties may potentiate blood pressure and heart rate lowering effects. If concomitant treatment with CARVETREND and clonidine is to be withdrawn, CARVETREND should be discontinued first. Clonidine can be discontinued several days later by gradually reducing the dosage.

Alpha- and beta-adrenoreceptor stimulating agents: The effects of CARVETREND are diminished by beta-adrenoreceptor stimulating agents such as isoprenaline; the hypotensive effects of CARVETREND may be dangerously reversed and the peripheral vasoconstrictor effects enhanced by alpha-adrenoreceptor stimulating agents such as
noradrenaline or those with mixed alpha- and beta-adrenoreceptor stimulating properties such as adrenaline; bradycardia can also occur.

Calcium channel blockers: Synergism occurs if CARVETREND and diltiazem are used concomitantly. The risk of atrioventricular (AV) conduction disturbances can be increased in combination with CARVETREND. Cases of conduction disturbance (some with
haemodynamic compromise) have been observed when CARVETREND and verapamil, diltiazem and/or

amiodarone are co-administered. When CARVETREND is used simultaneously with calcium antagonists, caution should be exercised, particularly in the

case of verapamil. This combination is contraindicated in patients with disturbed heart function. It is recommended that ECG and blood pressure be monitored.

Anaesthetic agents: It is recommended that CARVETREND therapy be discontinued at least 48 hours before anaesthesia. Careful monitoring of vital signs is recommended during anaesthesia due to the synergistic negative inotropic and hypotensive effects of CARVETREND and anaesthetic medicines (see section 4.4).

NonSteroidal anti-inflammatory drugs (NSAIDS): The concurrent use of CARVETREND with NSAIDs may result in an increased blood pressure and an impaired control of blood pressure.

Beta agonist bronchodilators: CARVETREND opposes the bronchodilator effects of beta agonists, and careful monitoring of patients is advised.

Alcohol and hydralazine: Increased plasma levels of carvedilol have been observed when CARVETREND was administered with hydralazine and alcohol, as these agents are metabolised by the liver.

Dihydropyridines: Since heart failure and severe hypotension have been reported, the administration of CARVETREND with dihydropyridines should be done under close supervision.

Nitrates: Increased hypotensive effects.

Oestrogens and corticosteroids: The antihypertensive effect of CARVETREND is decreased due to retention of sodium and water.

Sympathomimetics with alpha-mimetic and beta-mimetic effects: There is a risk of hypertension and excessive bradycardia.

Ergotamine: Vasoconstriction is increased.

Neuromuscular blocking agents: An increase in neuromuscular block.

Other antihypertensive medicines: CARVETREND may potentiate the effects of other concomitantly administered antihypertensives (e.g. alpha-1-receptor antagonists) and medicines with antihypertensive adverse reactions such as barbiturates, phenothiazines, tricyclic antidepressants, vasodilating agents and alcohol.

Other: Myocardial depressant agents including antiarrhythmic like quinidine, disopyramide, lignocaine,

procainamide and phenytoin due to the probability of increased AV conduction time and a negative inotropic effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety has not been established and CARVETREND should not be used in pregnant women. Beta blockers reduce placental perfusion, which may result in intrauterine foetal death, and immature and premature deliveries. In addition, adverse effects (especially
hypoglycaemia and bradycardia) may occur in the foetus and neonate. There may be an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. There is no evidence from animal studies that CARVETREND has any teratogenic
effects. CARVETREND should not be used during pregnancy unless the potential benefit for the mother outweighs the potential risk for the foetus/neonate. Treatment should be discontinued 2 - 3 days before expected birth. If not possible, the newborn should be monitored for the first 2 - 3 days of life.
Administration to pregnant mothers shortly before giving birth or during labour may result in the newborn infants being born hypotonic, collapsed and hypoglycaemic.

Breastfeeding

As carvedilol is excreted into breast milk, it should not be administered when breastfeeding.

Fertility

There is no data on fertility with CARVETREND.

4.7 Effects on ability to drive and use machines

CARVETREND has minor influence on the ability to drive and use machines.
Vision abnormalities, dizziness, headaches, fatigue and reduced alertness, especially at initiation and dose adjustment of therapy are some of the common side effects caused by the use of carvedilol.
Caution should be used when driving a motor vehicle, operating machinery or performing potentially dangerous tasks, where loss of concentration may lead to an accident.

4.8 Undesirable effects

a. Summary of the safety profile

With the exception of bradycardia, abnormal vision and dizziness, the adverse event frequency is not dose dependent. These effects are usually mild, short-term and usually occur at the beginning of treatment.

b. Tabulated list of adverse effects

System Organ Class	**Frequency**	**Side effects**
Infections and infestations	Frequent	Pneumonia, bronchitis, upper respiratory tract infection, urinary tract infection
Blood and lymphatic system disorders	Frequent Less frequent	Anaemia Thrombocytopaenia and hypercholesterolaemia, reduced peripheral circulation, Raynaud's phenomenon or symptom exacerbation of intermittent claudication leukopenia, changes in serum transaminases
Immune system disorders	Less frequent	Hypersensitivity
Endocrine disorders	Frequent	Hyperglycaemia (patients with pre-existing diabetes mellitus). It is possible for latent diabetes mellitus to become evident and existing diabetes to be exacerbated due to the beta blocking properties of CARVETREND
Metabolism and nutrition disorders	Frequent	Weight increase, hypercholesterolaemia, impaired blood glucose control in patients with pre-existing diabetes

Psychiatric disorders	Frequent Less frequent	Depression, depressed mood Sleep disturbances, confusion
Nervous system disorders	Frequent Less frequent	Headache and dizziness, syncope, pre-syncope Paraesthesia
Eye disorders	Frequent	Visual impairment, reduced lacrimation, eye irritation
Cardiac disorders	Frequent Less frequent	Hypotension, bradycardia, postural hypotension, cardiac failure, hypervolaemia, generalised fluid overload, hypertension, oedema AV block, cardiac failure during dosage increase, angina pectoris or progression of heart failure
Vascular disorders	Frequent	Oedema of the legs, dependent and genital oedema, disturbances of peripheral circulation (cold extremities, peripheral vascular disease, exacerbation of intermittent claudication and Raynaud's phenomenon), orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Asthma and dyspnoea in predisposed patients, pulmonary oedema, wheezing in patients with asthma and COPD Flu-like symptoms, stuffy nose
Gastrointestinal disorders	Frequent Less frequent	Vomiting, nausea, diarrhoea, abdominal pain, dyspepsia Constipation, dryness of the mouth

Hepatobiliary disorders	Frequent	Increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT)
Skin and subcutaneous tissue disorders	Less frequent	Existing lesions can be aggravated, psoriatic skin lesions may occur, isolated or less frequently skin reactions, e.g. pruritus, urticaria, lichen planus-like reactions and allergic exanthema, dermatitis, increased sweating, alopecia, severe cutaneous adverse reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)
Musculoskeletal, connective tissue and bone disorders	Frequent	Pain in extremities
Renal and urinary disorders	Frequent Less frequent	Renal abnormalities in patients with diffuse vascular disease and/or impaired function, micturition disturbances and acute renal failure Micturition disorders, urinary incontinence in women
Reproductive system and breast disorders	Less frequent	Sexual impotence, erectile dysfunction
General disorders and administrative site conditions	Frequent	Asthenia (fatigue), pain

c. Description of selected adverse reactions

Dizziness, syncope, headache and asthenia are usually mild and are more likely to occur at the beginning of

treatment.

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

Cardiac failure is a commonly reported adverse event in both placebo and carvedilol-treated patients (14,5 % and 15,4 % respectively, in patients with left ventricular dysfunction following acute myocardial infarction).

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

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

CARVETREND may cause urinary incontinence in women which resolves upon discontinuation of the medicine.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms

Symptoms may include bradycardia, severe hypotension, heart failure, cardiogenic shock and cardiac arrest. Vomiting, bronchospasm, respiratory problems, disturbed consciousness and generalized seizures have also been observed.

Management of overdose

The patient must be kept under observation preferably under intensive care conditions where necessary. The patient should be made to lie down, to improve brain blood supply.

Intravenous injection of atropine up to 3 mg should be used to treat the bradycardia immediately.

Sympathomimetics such as dobutamine, isoprenaline, adrenaline or orciprenaline, based on body mass and effect, may be used. When further measures are deemed necessary, it is recommended that noradrenaline be preferred to isoprenaline in order to restore

circulation.

The recommended initial dose of noradrenaline is intravenous 5 micrograms (µg) - 10 micrograms (µg) and repeated accordingly to the patient's response; alternatively use an Intravenous (IV) infusion at 5 micrograms (µg)/minute till a satisfactory clinical response is achieved. Glucagon may be preferred in severe overdosage. The recommended starting dose is 1 mg - 10 mg intravenously followed by a 2 mg - 2,5 mg per hour as a long-term infusion to sustain heart function. Norfenefrine or noradrenaline may be administered while continuously evaluating the circulatory conditions in cases where intoxication is dominated by peripheral vasodilation.

When bradycardia is resistant to therapy, therapy with a pacemaker should be considered.

Beta-sympathomimetics (IV and/or aerosol) should be used for bronchospasm.

IV injection of clonazepam or diazepam is recommended for seizures. In cases where there are symptoms of shock during severe intoxication, antidote treatment should be continued for a relatively long period due to the elimination of carvedilol from its binding sites.

Important note:

In the event of severe intoxication where there are symptoms of shock, treatment with antidotes must be continued for a sufficiently long period of time since a prolonged elimination half-life of CARVETREND from deeper compartments can be expected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha and beta blocking agents

ATC code: C07AG02

Pharmacological classification: A: 7.1.3 Other hypotensives.

Mechanism of action

In the same dosage range, carvedilol exhibits both nonselective beta blocking properties which are associated with the laevorotary S(-) enantiomer and acts as an antihypertensive agent having vasodilating properties. Carvedilol is racemic, and both R(+) and S(-) enantiomers have the same alpha adrenergic receptor blocking properties and antioxidant properties.

Carvedilol is a competitive, nonselective antagonist of beta 1- and beta 2- adrenoreceptors; as demonstrated in both *in vivo* and *in vitro* animal studies. Its beta blockade activity leads to a reduction of peripheral vascular resistance via suppression of the renin-angiotensin-

aldosterone system and vasodilation. Selective blockade of alpha 1- adrenoreceptors is responsible mainly for vasodilation. Carvedilol attenuates the increase in blood pressure induced by phenylephrine, an alpha 1-adrenoceptor agonist, but not that induced by angiotensin II. Carvedilol has intrinsic sympathomimetic activity. The pharmacological

action of carvedilol in congestive heart failure has not been established (see section 4.1).

5.2 Pharmacokinetic properties

Absorption:

Carvedilol undergoes extensive first-pass hepatic metabolism resulting in a low and variable absolute bioavailability of 25 %. Maximum serum levels are reached approximately one (1) hour after a single oral dose. Metabolism is primarily hepatic. Linear correlation between dose and serum concentration has been observed.

Distribution:

Carvedilol is extensively (approximately 98 %) bound to plasma protein (primarily alpha-acid glycoproteins

and also albumin). The average elimination half-life is 6 - 10 hours.

The distribution volume is approximately 2 L/kg. The rate of absorption (time to reach maximum serum concentration), but not the extent of absorption (bioavailability) is decreased by food.

Biotransformation:

In humans, carvedilol is extensively metabolised into a variety of metabolites that are eliminated mainly in the bile. The first-pass effect after oral administration amounts to about 60-75 %. Carvedilol is metabolised extensively by the liver and glucuronidation is one of the major reactions. Demethylation and hydroxylation at the phenol ring produce 3 metabolites with beta-adrenergic receptor blocking activity. Based on pre-clinical studies, the *4'-hydroxyphenol* metabolite is approximately 13 times more potent than carvedilol for beta blockade. Compared to carvedilol, the three active metabolites exhibit weak vasodilating activity. In humans, the concentrations of the three active metabolites are about 10 times lower than that of the parent substance.

Elimination:

Elimination is primarily biliary. The average elimination half-life is 6 - 10 hours. Plasma clearance is approximately 500-700 mL/min. The primary route of excretion is via the faeces. The metabolites are mainly excreted in the bile, whereas a small part (approximately 15 %) is excreted by the kidneys.

Pharmacokinetics in special patient groups

Patients with renal impairment:

Dosage adjustment in renally impaired patients is not required. In patients with hypertension and renal insufficiency, the area under the plasma level-time curve, elimination half-life and maximum plasma concentration does not change significantly. Renal excretion of the unchanged medicine decreases in the patients with renal insufficiency; however pharmacokinetic parameters are modest. Carvedilol is not eliminated during dialysis because it does not cross the dialysis membrane, probably due to its high plasma protein binding.

Patients with hepatic impairment:

In patients with cirrhosis of the liver, the systemic availability of the medicine is increased by up to 80 % because of reduction in the first-pass effect. Therefore, carvedilol is contraindicated in patients which clinically

manifest liver dysfunction (see section 4.3).

Geriatric use:

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

Diabetic patients:

In hypertensive patients with non-insulin dependent diabetes no influence of carvedilol on fasting or post-prandial blood glucose concentration, glycosylated haemoglobin A1 or need for change of the dose of antidiabetic agents was found. In patients with non-insulin

dependent diabetes, carvedilol had no statistically significant influence on the glucose tolerance test. In hypertensive non-diabetic patients with impaired insulin sensitivity (syndrome X) carvedilol improved the insulin sensitivity. The same results were found in hypertensive patients with non- insulin dependent diabetes.

Hypertension:

Carvedilol is an antihypertensive agent with vasodilating and nonselective beta blocking properties in the same dose range. *In vitro* and *in vivo* animal studies have indicated that carvedilol is a competitive, nonselective antagonist of both beta 1- and beta 2- adrenoreceptors. Clinical studies have shown that the balance of vasodilation and beta

receptor blockade provided by carvedilol results in the following desirable haemodynamic and metabolic effects:

- myocardial function is maintained. A smaller reduction in the resting heart rate is observed with carvedilol compared to the effect seen with beta receptor blocking medicines which lack additional vasodilating properties. Peripheral blood flow is maintained.
- cholesterol, triglycerides, high-density lipoproteins and low-density lipoproteins are not affected. Serum electrolytes are not affected. The activity of plasma renin is reduced, leaving the renal function unaffected.

Paediatric population

There is no data available on pharmacokinetics in people younger than 18 years of age.

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 foetal 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

Silica colloidal anhydrous

Crospovidone

Lactose monohydrate

Magnesium stearate

Povidone K25

Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store at or below 30 °C in a cool dry place.

6.5 Nature and contents of container

CARVETREND is available in OPA/Al/PVC and aluminium foil blister packs of 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

Tel: +27 21 707 7000

Cell: 0860-PHARMA (742 762)

8. REGISTRATION NUMBER(S)

CARVETREND 6,25 mg: A37/7.1.3/0276

CARVETREND 12,5 mg: A37/7.1.3/0277

CARVETREND 25 mg: A37/7.1.3/0278

9. DATE OF FIRST AUTHORISATION

Date of registration: 03 June 2005

10. DATE OF REVISION OF THE TEXT

04 July 2024

NAMIBIA:

CARVETREND 6,25 mg: NS2 08/7.1.3/0105

CARVETREND 12.5 mg: NS2 08/7.1.3/0104

CARVETREND 25 mg: NS2 08/7.1.3/0103

BOTSWANA:

CARVETREND 6,25 mg: S2 BOT1101790

CARVETREND 12.5 mg: S2 BOT1101791

CARVETREND 25 mg: S2 BOT1101792

MOZAMBIQUE

CARVETREND 6,25 mg: 2851

CARVETREND 12.5 mg: 2853

ZAMBIA:

CARVETREND 6,25 mg: POM 051/014

CARVETREND 12.5 mg: POM 051/015