

# NEW ZEALAND DATA SHEET

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## 1 PRODUCT NAME

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CARVEDILOL SANDOZ, tablets, uncoated, 6.25 mg, 12.5 mg and 25 mg

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## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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Each tablet contains carvedilol 6.25 mg, 12.5 mg or 25 mg.

Excipients with known effect: Lactose

For the full list of excipients, See section 6.1

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## 3 PHARMACEUTICAL FORM

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Carvedilol Sandoz 6.25 mg: yellow, round, convex, scored uncoated tablet, coded 'C2' on one side.

Carvedilol Sandoz 12.5 mg: red/brown, round, convex, scored uncoated tablet, coded 'C3' on one side.

Carvedilol Sandoz 25 mg: white to almost white, round, convex, scored uncoated tablet, coded 'C4' on one side.

Tablets can be divided into equal doses.

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## 4 CLINICAL PARTICULARS

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### 4.1 Therapeutic indications

#### **Hypertension:**

Carvedilol Sandoz is indicated for the management of essential hypertension. It can be used alone or in combination with other antihypertensive agents (e.g. calcium channel blockers, diuretics).

#### **Treatment of angina pectoris:**

Carvedilol Sandoz is efficacious in the treatment of chronic stable angina and unstable angina.

#### **Chronic heart failure (CHF):**

Unless a contraindication exists, Carvedilol Sandoz is indicated for the treatment of all patients with stable and symptomatic mild, moderate and severe chronic heart failure of ischaemic or non-ischaemic aetiology in combination with standard therapy (including ACE inhibitors and diuretics with or without digitalis).

#### **Left ventricular dysfunction following acute myocardial infarction:**

Long term treatment following myocardial infarction complicated by left ventricular dysfunction (LVEF < 40% or wall motion index < 1.3), including well controlled heart failure, in combination with ACE inhibitors and other treatments recommended in the management of patients after myocardial infarction.

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## 4.2 Dose and method of administration

### Method of administration

The tablets are to be swallowed with sufficient fluid. It is not necessary to take the dose in relation to meals, however for chronic heart failure patients, Carvedilol Sandoz should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects.

### Duration of treatment

Treatment with Carvedilol Sandoz 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.

### Hypertension

The recommended dose for initiation of therapy is 12.5 mg once a day for the first two days. Thereafter the recommended dosage is 25 mg once a day. If necessary, the dosage may subsequently be increased at intervals of at least two weeks to the recommended maximum daily dose of 50 mg, given once a day or in divided doses (twice daily).

### Angina pectoris

The recommended dose for initiation of therapy is 12.5 mg twice a day for the first 2 days. Thereafter the recommended dosage is 25 mg twice a day. If necessary, the dosage may subsequently be increased at intervals of at least two weeks up to the recommended maximum daily dose of 100 mg given in divided doses (twice daily).

### Chronic Heart Failure

Dosage must be tailored to suit the individual, and closely monitored by a physician during up-titration. For those patients receiving digitalis, diuretics and ACE inhibitors, dosing of these medicines should be stabilised prior to initiation of Carvedilol Sandoz treatment.

The recommended dose for initiation of therapy is 3.125 mg twice daily for two weeks. If this dose is tolerated, the dose may thereafter be increased, at intervals of not less than two weeks, to 6.25 mg, 12.5 mg and 25 mg twice daily. Doses should be increased to the highest level tolerated by the patient. The maximum recommended dose is 25 mg twice daily for all patients with severe CHF and for patients with mild to moderate CHF weighing less than 85 kg. In patients with mild to moderate CHF weighing more than 85 kg, the maximum recommended daily dose is 50 mg twice daily.

Before each dose increase, the patient should be evaluated by the physician for symptoms of worsening heart failure or vasodilation. Transient worsening of heart failure or fluid retention should be treated with increased doses of diuretics. Occasionally it may be necessary to lower the dose of Carvedilol Sandoz and, in rare cases, temporarily discontinue Carvedilol Sandoz treatment.

If Carvedilol Sandoz treatment is discontinued for more than one week, therapy should be recommenced at a lower dose level (twice daily) and up-titrated in line with the above dosing recommendation. If Carvedilol Sandoz treatment is discontinued for more than two weeks, therapy should be recommenced at 3.125 mg in line with the above dosing recommendation.

Symptoms of vasodilation may be managed initially by a reduction in the dose of diuretics. If symptoms persist, the dose of ACE inhibitor (if used) may be reduced, followed by a reduction in the dose of carvedilol if necessary. Under these circumstances, the dose of Carvedilol Sandoz

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

### **Left ventricular dysfunction following acute myocardial infarction**

Dosage must be individualised and closely monitored by a physician 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 Carvedilol Sandoz*

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. Carvedilol Sandoz can then be started between day 3 and day 21 after the myocardial infarction.

#### *First dose of Carvedilol Sandoz*

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 Special warnings and precautions for use/ General).

#### *Subsequent doses of Carvedilol Sandoz*

If the patient has tolerated the first dose (i.e. heart rate > 50 beats/minute, systolic blood pressure > 80 mm Hg, and absence of clinical signs of intolerance), the dose should be increased to 6.25 mg twice daily and maintained for 3 to 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 to 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 to 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 dosage instructions**

#### *Renal impairment*

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

#### *Hepatic impairment*

Carvedilol Sandoz is contraindicated in patients with clinical manifestations of liver dysfunction (see Section 4.3 Contraindications).

#### *Elderly*

There is no evidence to support dose adjustment.

#### *Children*

The safety and efficacy of carvedilol in children and adolescents (<18 years) has not been established (see Section 4.4 Special warnings and precautions for use/ Use in Special

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Populations: Paediatric Use and Section 5.2 Pharmacokinetic properties/ Special Populations: Children).

## 4.3 Contraindications

Carvedilol Sandoz must not be used in patients with:

- hypersensitivity to carvedilol or any component of the product.
- unstable/decompensated heart failure.
- clinically manifest liver dysfunction.

As with other  $\beta$ -blockers, Carvedilol Sandoz must not be used in patients with:

- 2nd and 3rd degree AV block (unless a permanent pace maker is in place)
- severe bradycardia (< 50 bpm)
- sick sinus syndrome (including sino-atrial block)
- severe hypotension (systolic blood pressure < 85 mmHg)
- cardiogenic shock
- history of bronchospasm or asthma
- history of other obstructive lung disorders

## 4.4 Special warnings and precautions for use

### General

There are a number of important pharmacokinetic and pharmacodynamics interactions with other drugs (e.g. digoxin, cyclosporine, rifampicin, anaesthetic drugs, anti-arrhythmic drugs) (see Section 4.5 Interactions with other medicines and other forms of interactions).

### Chronic heart failure

In chronic heart failure patients, worsening cardiac failure or fluid retention may occur during up-titration of Carvedilol Sandoz. If such symptoms occur, diuretics should be increased and the Carvedilol Sandoz dose should not be advanced until clinical stability resumes. Occasionally, it may be necessary to lower the Carvedilol Sandoz dose or, in rare cases, temporarily discontinue it. Such episodes do not preclude subsequent successful titration of Carvedilol Sandoz. Carvedilol Sandoz should be used with caution in combination with digitalis glycosides, as both medicines slow atrioventricular (AV) conduction (see Section 4.5 Interactions with other medicines and other forms of interactions).

### Renal function in congestive heart failure

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

### Left ventricular dysfunction following acute myocardial infarction

Before treatment with Carvedilol Sandoz 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 Dose and method of administration).

### Chronic obstructive pulmonary disease

Carvedilol should be used with caution, in patients with chronic obstructive pulmonary disease (COPD) with a bronchospastic component who are not receiving oral or inhaled medication, and only if the potential benefit outweighs the potential risk. In patients with a tendency to bronchospasm, respiratory distress can occur as a result of a possible increase in airway

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resistance. Patients should be closely monitored during initiation and up-titration of carvedilol and the dose of Carvedilol Sandoz should be reduced if any evidence of bronchospasm is observed during treatment.

## **Diabetes**

Care should be taken in the administration of Carvedilol Sandoz to patients with diabetes mellitus, as it may be associated with worsening control of blood glucose, or the early signs and symptoms of acute hypoglycaemia may be masked or attenuated. (See Section 4.4 Special warnings and precautions for use and Section 4.5 Interactions with other medicines and other forms of interactions).

## **Peripheral vascular disease and Raynaud's Phenomenon.**

Carvedilol Sandoz should be used with caution in patients with peripheral vascular disease (e.g. Raynaud's phenomenon) as  $\beta$ -blockers can precipitate or aggravate symptoms of arterial insufficiency.

## **Thyrotoxicosis**

Carvedilol Sandoz, like other agents with  $\beta$ -blocking properties, may obscure the symptoms of thyrotoxicosis.

## **Bradycardia**

Carvedilol Sandoz may induce bradycardia. If the patient's pulse rate decreases to less than 55 beats per minute, the dosage of Carvedilol Sandoz should be reduced.

## **Hypersensitivity**

Care should be taken in administering Carvedilol Sandoz 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 severity of hypersensitivity reactions.

## **Severe cutaneous adverse reactions (SCARs)**

Very rare cases of severe cutaneous adverse reactions such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported during treatment with carvedilol (see Section 4.8 Undesirable effects/ Post-Marketing experience). Carvedilol 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  $\beta$ -blocker therapy should take Carvedilol Sandoz only after consideration of the risk-benefit ratio.

## **Pheochromocytoma**

In patients with pheochromocytoma, an  $\alpha$ -blocking agent should be initiated prior to the use of any  $\beta$ -blocking agent. Although Carvedilol Sandoz has both  $\alpha$ - and  $\beta$ -blocking pharmacological activities, there is no experience with its use in this condition. Caution should therefore be taken in the administration of Carvedilol Sandoz to patients suspected of having pheochromocytoma.

## **Prinzmetal's variant angina**

Agents with non-selective  $\beta$ -blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There is no clinical experience with Carvedilol Sandoz in these

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patients although the  $\alpha$ -blocking activity of Carvedilol Sandoz may prevent such symptoms. Caution should, however, be taken in the administration of Carvedilol Sandoz to patients suspected of having Prinzmetal's variant angina.

## Contact lenses

Wearers of contact lenses should bear in mind the possibility of reduced lacrimation.

## Withdrawal syndrome

Carvedilol Sandoz treatment should not be discontinued abruptly, particularly in patients suffering from ischaemic heart disease. The withdrawal of Carvedilol Sandoz should be gradual (over a period of two weeks).

## Use in Special Populations

### Paediatric Use

See Section 4.2 Dose and method of administration/ Special Dosage Instructions

### Elderly Use

A study in elderly hypertensive patients showed that there was no difference in the adverse event profile as compared to younger patients. Another study, which included elderly patients with coronary heart disease, showed no difference in the adverse events reported vs. those reported by younger patients. Therefore, no dose adjustment of the starting dose is required in the elderly population (see Section 4.2 Dose and method of administration/ Special Dosage Instructions).

### Renal Impairment

The autoregulatory renal blood supply is preserved and the glomerular filtration is unchanged during chronic treatment with carvedilol. In patients with moderate to severe renal insufficiency, no changes in carvedilol dosage recommendations are warranted (see Section 4.2 Dose and method of administration/ Special Dosage Instructions).

### Hepatic Impairment

Carvedilol is contraindicated in patients with clinically manifest liver dysfunction (see Section 4.3 Contraindications). A pharmacokinetic study in cirrhotic patients has shown that exposure (AUC) to carvedilol was increased by 6.8 folds in patients with liver impairment as compared to healthy subjects.

### Diabetic Patients

Beta-blockers may increase insulin resistance and mask hypoglycaemic symptoms. However, numerous studies have established that vasodilating  $\beta$ -blockers like carvedilol are associated with more favourable effects on glucose and lipid profiles. Carvedilol has been shown to exhibit modest insulin-sensitising properties and can relieve some manifestations of the metabolic syndrome.

## 4.5 Interaction with other medicines and other forms of interaction

### Pharmacokinetic interactions

#### *Effects of carvedilol on the pharmacokinetics of other drugs.*

Carvedilol is a substrate as well as an inhibitor of P-glycoprotein. Therefore the bioavailability of drugs transported by P-glycoprotein may be increased with concomitant administration of

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carvedilol. In addition, the bioavailability of carvedilol can be modified by inducers or inhibitors of P-glycoprotein.

*Digoxin:* An increased exposure of digoxin of up to 20% has been shown in some studies in healthy subjects and patients with heart failure. A significantly larger effect has been seen in male patients compared to female patients. Therefore monitoring of digoxin levels is recommended when initiating, adjusting or discontinuing carvedilol (see Section 4.4 Special warnings and precautions for use). Carvedilol had no effect on digoxin administered intravenously.

*Cyclosporin:* Two studies in renal and cardiac transplant patients receiving oral cyclosporin have shown an increase in cyclosporin plasma concentration following the initiation of carvedilol. It appears that carvedilol increases exposure to oral cyclosporin by around 10 to 20%. In an attempt to maintain therapeutic cyclosporin levels, an average 10 - 20% reduction of the cyclosporin dose was necessary. The mechanism for the interaction is not known but inhibition of intestinal P glycoprotein by carvedilol may be involved. Therefore, due to wide inter-individual variability of cyclosporin levels, it is recommended that cyclosporin concentrations are monitored closely after initiation of carvedilol therapy and that the dose of cyclosporin be adjusted as appropriate. In case of i.v. administration of cyclosporin, no interaction with carvedilol is expected.

### **Effects of other drugs on the pharmacokinetics of carvedilol**

Inhibitors as well as inducers of CYP2D6 and CYP2C9 can modify the systemic and/or presystemic metabolism of carvedilol stereoselectively, leading to increased or decreased plasma concentrations of R and S-carvedilol (see Section 5.2 Pharmacokinetic properties/ Metabolism). Some examples observed in patients or in healthy subjects are listed below but the list is not exhaustive.

*Rifampicin:* In a study in 12 health subjects, exposure to carvedilol decreased by around 60% during concomitant administration with rifampicin and a decrease effect of carvedilol on the systolic blood pressure was observed. The mechanism for the interaction is not known but it may be due to the induction of the intestinal P glycoprotein by rifampicin. A close monitoring of the  $\beta$ -blockade activity in patients receiving concomitant administration of carvedilol and rifampicin is appropriate.

*Amiodarone:* An in vitro study with human liver microsomes has shown that amiodarone and desethylamiodarone inhibited the oxidation of R and S-carvedilol. The trough concentration of R and S-carvedilol was significantly increased by 2.2 fold in heart failure patients receiving carvedilol and amiodarone concomitantly as compared to patients receiving carvedilol monotherapy. The effect on S-carvedilol was attributed to desethylamiodarone, a metabolite of amiodarone, which is a strong inhibitor of CYP2C9. A monitoring of the  $\beta$ -blockade activity in patients treated with the combination carvedilol and amiodarone is advised.

*Fluoxetine and Paroxetine:* In a randomized, cross-over study in 10 patients with heart failure, co-administration of fluoxetine, a strong inhibitor of CYP2D6, resulted in stereoselective inhibition of carvedilol metabolism with a 77% increase in mean R(+) enantiomer AUC, and a non-statistically 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 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**

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*Insulin or oral hypoglycaemics:* Agents with ( $\beta$ -blocking properties may enhance the blood-sugar-reducing effect of insulin and oral hypoglycaemics. The signs of hypoglycaemia may be masked or attenuated (especially tachycardia). In patients taking insulin or oral hypoglycaemics, regular monitoring of blood glucose is therefore recommended (see Section 4.4 Special warnings and precautions for use/ General).

*Catecholamine-depleting agents:* Patients taking both agents with ( $\beta$ -blocking properties and a medicine that can deplete catecholamines (e.g. reserpine and monoamine oxidase inhibitors) should be observed closely for signs of hypotension and/or severe bradycardia.

*Non-dihydropyridines calcium channel blockers, amiodarone or other antiarrhythmics:* In combination with carvedilol can increase the risk of AV conduction disturbances. Isolated cases of conduction disturbance (rarely with haemodynamic compromise) have been observed when carvedilol is co-administered with diltiazem. As with other agents with  $\beta$ -blocking properties, if carvedilol is to be administered orally with non-dihydropyridines calcium channel blockers of the verapamil or diltiazem type, amiodarone or other antiarrhythmics it is recommended that ECG and blood pressure be monitored.

*Clonidine:* Concomitant administration of clonidine with agents with ( $\beta$ -blocking properties may potentiate blood-pressure and heart-rate-lowering effects. When concomitant treatment with agents with ( $\beta$ -blocking properties and clonidine is to be terminated, the ( $\beta$ -blocking agent should be discontinued first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage.

*Antihypertensives:* As with other agents with  $\beta$ -blocking activity, carvedilol may potentiate the effect of other concomitantly administered medicines that are anti-hypertensive in action (e.g.  $\alpha_1$ -receptor antagonists) or have hypotension as part of their adverse effect profile.

*Anaesthetic agents:* Careful monitoring of vital signs is recommended during anaesthesia due to the synergistic negative inotropic and hypotensive effects of Carvedilol Sandoz and anaesthetic medicines.

*Non-steroidal anti-inflammatory drugs (NSAIDs):* The concurrent use of NSAIDs and  $\beta$  -adrenergic blockers may result in an increase in blood pressure and lower blood pressure control.

*Beta-agonist bronchodilators:* Non-cardioselective  $\beta$ -blockers oppose the bronchodilator effects of  $\beta$  -agonist bronchodilators. Careful monitoring of patients is recommended.

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

### **4.6 Fertility, pregnancy and lactation**

#### **Use in pregnancy**

Studies in animals have shown reproductive toxicity (see Section 5.3 preclinical safety data). The potential risk for humans is unknown.

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 carvedilol has any teratogenic effects.

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

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

## Use in lactation

Animal studies demonstrated that carvedilol and/or its metabolites are excreted in rat breast milk. The excretion of carvedilol in human milk has not been established. However, most  $\beta$ -blockers, in particular lipophilic compounds, will pass into human breast milk although to a variable extent. Breastfeeding is therefore not recommended during administration of Carvedilol Sandoz.

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and to use machines have been performed.

Because of individually variable reactions (e.g. dizziness, tiredness), the ability to drive, operate machinery, or work without firm support may be impaired. This applies particularly at the start of treatment, after dose increases, on changing products, and in combination with alcohol.

## 4.8 Undesirable effects

Clinical trials

Adverse Event (AE) Frequency

AE's occurring  $\geq 10\%$  are described as very common.

AE's occurring  $\geq 1\%$  and  $< 10\%$  are described as common.

AE's occurring  $\geq 0.1\%$  and  $< 1\%$  are described as uncommon.

AE's occurring  $\geq 0.01\%$  and  $< 0.1\%$  are described as rare.

AE's occurring  $< 0.01\%$  are described as very rare.

Table 1 below summarises undesirable effects that have been reported in associated with the use of carvedilol in pivotal clinical trials with the following indications: chronic heart failure, left ventricular dysfunction following acute myocardial infarction, hypertension and the long term management of coronary heart disease:

Table 1: Adverse Drug Reactions in Clinical Trials

System Organ Class	Adverse Reaction	Frequency
Blood and Lymphatic System Disorders	Anaemia	Common
	Thrombocytopenia	Rare
	Leukopenia	Very rare
Cardiac Disorders	Cardiac failure	Very common
	Bradycardia	Common
	Hypovolaemia	Common
	Fluid overload	Common
	Atrioventricular block	Uncommon
	Angina pectoris	Uncommon
Eye Disorders	Visual impairment	Common

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<b>System Organ Class</b>	<b>Adverse Reaction</b>	<b>Frequency</b>
	Lacrimation decreased (dry eye)	Common
	Eye irritation	Common
Gastrointestinal Disorders	Nausea	Common
	Diarrhoea	Common
	Vomiting	Common
	Dyspepsia	Common
	Abdominal pain	Common
	Constipation	Uncommon
	Dry mouth	Rare
General Disorders and Administration Site Conditions	Asthenia (fatigue)	Very common
	Oedema	Common
	Pain	Common
Hepatobiliary Disorders	Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT) increased	Very rare
Immune System Disorders	Hypersensitivity (allergic reactions)	Very rare
Infections and Infestations	Pneumonia	Common
	Bronchitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
Metabolism and Nutrition Disorders	Weight increase	Common
	Hypercholesterolaemia	Common
	Impaired blood glucose control (hyperglycaemia, hypoglycaemia) in patients with pre-existing diabetes	Common
Musculoskeletal and Connective Tissue Disorders	Pain in extremities	Common
Nervous System Disorders	Dizziness	Very common
	Headache	Very common
	Syncope, presyncope	Common
	Paraesthesia	Uncommon
Psychiatric Disorders	Depression, depressed mood	Common

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System Organ Class	Adverse Reaction	Frequency
	Sleep disorders	Uncommon
Renal and Urinary Disorders	Renal failure and renal function abnormalities in patients with diffuse vascular disease and/or underlying renal insufficiency	Common
	Micturition disorders	Rare
Reproductive System and Breast Disorders	Erectile dysfunction	Uncommon
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	Common
	Pulmonary oedema	Common
	Asthma in predisposed patients	Common
	Nasal congestion	Rare
Skin and Subcutaneous Disorders	Skin reactions (e.g. allergic exanthema, dermatitis, urticarial, pruritus, psoriatic and lichen planus like skin lesions)	Uncommon
Vascular Disorders	Hypotension	Very common
	Orthostatic hypotension	Common
	Disturbances of peripheral circulation (cold extremities, peripheral vascular disease, exacerbation of intermittent claudication and Reynaud's phenomenon)	Common
	Hypertension	Common

### Description of selected adverse reactions

The frequency of adverse reactions is not dose-dependent, with the exception of dizziness, abnormal vision and bradycardia. 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 carvedilol dose (see Section 4.4 Special warnings and precautions for use).

Cardiac failure was a very commonly reported adverse event in both placebo (14.5%) and carvedilol-treated (15.4%) patients, in patients with left ventricular dysfunction following acute myocardial infarction.

Reversible deterioration of renal function has been observed with carvedilol therapy in chronic heart failure patients with low blood pressure, ischaemic heart disease and diffuse vascular disease and/or underlying renal insufficiency (see Section 4.4 Special warnings and precautions for use).

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## **Post-marketing experience**

The following adverse events have been identified during post-marketing use of carvedilol. Because these events are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency and/or establish a causal relationship to drug exposure.

### *Renal and urinary disorders*

Isolated cases of urinary incontinence in women, which resolved upon discontinuation of the medication, have been reported.

### *Skin and subcutaneous tissue disorders:*

#### *Alopecia.*

Severe cutaneous adverse reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome) (see Section 4.4 Special warnings and precautions for use).

### *Metabolism and nutrition disorders - Class effect*

Due to the  $\beta$ -blocking properties, it is also possible for latent diabetes mellitus to become manifest, manifest diabetes to be aggravated, and blood glucose counter-regulation to be inhibited.

## **Reporting of suspected adverse reactions**

Reporting suspected adverse reaction after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

## **4.9 Overdose**

### Signs and symptoms

In the event of overdosage, there may be severe hypotension, bradycardia, heart failure, cardiogenic shock and cardiac arrest. There may also be respiratory problems, bronchospasm, vomiting, disturbed consciousness and generalised seizures.

### Management

The patient should be monitored for the above mentioned signs and symptoms and managed according to the best judgement of the treating physicians and according to standard practice for patients with  $\beta$ -blocker overdose (e.g. atropine, transvenous pacing, glucagon, phosphodiesterase inhibitors such as amrinone or milrinone,  $\beta$ -sympathomimetics).

### Important note

In cases of severe intoxication with shock, supportive treatment must be continued for a sufficiently long period, as a prolongation of elimination half-life and redistribution of carvedilol from deeper compartments are to be expected. The duration of the supportive/antidote therapy depends on the severity of the overdosage. The supportive treatment should therefore be continued until the patient's condition has stabilised.

Contact the Poisons Information Centre on (telephone 0800 POISON or 0800 764766) for advice on management of overdose.

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## **5 PHARMACOLOGICAL PROPERTIES**

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## 5.1 Pharmacodynamic properties

### *Pharmacotherapeutic group*

Cardiovascular system; Beta blocking agents; Alpha and beta blocking agents;

ATC code: C07AG

### **Mechanism of action**

Carvedilol is a multiple action adrenergic receptor blocker with  $\alpha_1$ ,  $\beta_1$  and  $\beta_2$  adrenergic receptor blockade properties. Carvedilol has been shown to have organ-protective effects. Carvedilol is a potent antioxidant and a scavenger of reactive oxygen radicals. Carvedilol is racemic, and both R(+) and S(-) enantiomers have the same  $\alpha$ -adrenergic receptor blocking properties and antioxidant properties. Carvedilol has antiproliferative effects on human vascular smooth muscle cells.

A decrease in oxidative stress has been shown in clinical studies by measuring various markers during chronic treatment of patients with carvedilol.

Carvedilol's  $\beta$ -adrenergic receptor blocking properties are non-selective for the  $\beta_1$  and  $\beta_2$ -adrenoceptors and are associated with the laevorotatory S(-) enantiomer.

Carvedilol has no intrinsic sympathomimetic activity and (like propranolol) it has membrane stabilising properties. Carvedilol suppresses the renin-angiotensin-aldosterone system through  $\beta$ -blockade, which reduces the release of renin, thus making fluid retention rare.

Carvedilol reduces peripheral vascular resistance via selective blockade of  $\alpha_1$ -adrenoceptors. Carvedilol attenuates the increase in blood pressure induced by phenylephrine, an  $\alpha_1$ -adrenoceptor agonist, but not that induced by angiotensin II.

Carvedilol has no adverse effect on the lipid profile. A normal ratio of high-density lipoproteins to low density lipoproteins (HDL/LDL) is maintained.

### **CLINICAL TRIALS**

Clinical studies showed the following results for carvedilol:

#### ***Hypertension***

Carvedilol lowers blood pressure in hypertensive patients by a combination of  $\beta$ -blockade and  $\alpha_1$  mediated vasodilation. Some of the limitations of traditional  $\beta$ -blockers do not appear to be shared by some of the vasodilating  $\beta$ -blockers, such as carvedilol. A reduction in blood pressure is not associated with a concomitant increase in total peripheral resistance, as observed with pure  $\beta$ -blocking agents. Heart rate is slightly decreased. Renal blood flow and renal function are maintained in hypertensive patients. Carvedilol has been shown to maintain stroke volume and reduce total peripheral resistance. Blood supply to distinct organs and vascular beds including kidneys, skeletal muscles, forearms, legs, skin, brain or the carotid artery is not compromised by Carvedilol. There is a reduced incidence of cold extremities and early fatigue during physical activity. The long-term effect of Carvedilol on hypertension is documented in several double-blind controlled studies.

#### ***Renal impairment***

Several open studies have shown that carvedilol is an effective agent in patients with renal hypertension. The same is true in patients with chronic renal failure or those on haemodialysis or after renal transplantation. Carvedilol causes a gradual reduction in blood pressure both on dialysis and non-dialysis days, and the blood pressure lowering effects are comparable with those seen in patients with normal renal function.

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On the basis of results obtained in comparative trials on haemodialysed patients it was concluded that carvedilol was more effective than calcium channel blockers and was better tolerated.

## ***Coronary heart disease***

In patients with coronary heart disease, carvedilol has demonstrated anti-ischaemic (improved total exercise time, time to 1 mm ST segment depression and time to angina) and anti-anginal properties that were maintained during long-term treatment. Acute haemodynamic studies have demonstrated that carvedilol significantly decreases myocardial oxygen demand and sympathetic overactivity. It also decreases the myocardial preload (pulmonary artery pressure and pulmonary capillary wedge pressure) and afterload (total peripheral resistance).

## ***Chronic heart failure***

Carvedilol significantly reduces mortality and hospitalisations and improves symptoms and left ventricular function in patients with ischaemic or non-ischaemic chronic heart failure. The effect of carvedilol is dose dependent.

## ***Renal impairment***

Carvedilol reduces morbidity and mortality in dialysis patients with dilated cardiomyopathy. A meta-analysis of placebo-controlled clinical trials including a large number of patients (>4000) with mild to moderate chronic kidney disease supports carvedilol treatment of patients with left ventricular dysfunction with or without symptomatic heart failure to reduce rates of all cause of mortality as well as heart failure related events.

## ***Left ventricular dysfunction following acute myocardial infarction***

In a double-blind placebo-controlled study in 1959 patients with a recent myocardial infarction and left ventricular ejection fraction < 40% or wall motion index < 1.3 (with or without symptomatic heart failure), carvedilol did not show a statistically significant reduction of the co-primary endpoint; all-cause mortality or cardiovascular hospitalisation (8% reduction vs placebo,  $p = 0.297$ ), but significantly reduced all-cause mortality by 23% ( $p = 0.031$ ), all-cause mortality or non-fatal myocardial infarction by 29% ( $p = 0.002$ ), mortality due to cardiovascular causes by 25% ( $p = 0.024$ ) and hospitalisation for non-fatal myocardial infarction by 41% ( $p = 0.014$ ). Additionally a post-hoc analysis showed that carvedilol significantly reduced death or major cardiovascular hospitalisation by 17% ( $p = 0.019$ ).

## **5.2 Pharmacokinetic properties**

### Absorption

Following oral administration of a 25mg capsule to healthy subjects, carvedilol is rapidly absorbed with a peak plasma concentration  $C_{max}$  of 21mg/L reached after approximately 1.5 hours ( $t_{max}$ ). The  $C_{max}$  values are linearly related to the dose. Following oral administration, carvedilol undergoes extensive first pass metabolism that results in an absolute bioavailability of about 25% in healthy male subjects. Carvedilol is a racemate and the S(-)-enantiomer appears to be metabolised more rapidly than the R(+)-enantiomer, showing an absolute oral bioavailability of 15% compared to 31% for the R(+)-enantiomer. The maximal plasma concentration of R-carvedilol is approximately 2 fold higher than that of S-carvedilol.

In vitro studies have shown that carvedilol is a substrate of the efflux transporter P-glycoprotein. The role of P-glycoprotein in the disposition of carvedilol was also confirmed in vivo in healthy subjects.

### Distribution

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Carvedilol is a highly lipophilic compound, showing a plasma protein binding of around 95%. The distribution volume ranges between 1.5 and 2 L/kg.

## Metabolism

In humans, carvedilol is extensively metabolised in the liver via oxidation and conjugation into a variety of metabolites that are mainly eliminated in the bile. Enterohepatic circulation of the parent substance has been shown in animals.

Demethylation and hydroxylation at the phenol ring produce 3 metabolites with  $\beta$ -adrenergic receptor blocking activity. Based on pre-clinical studies, the 4'-hydroxy-phenol 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. Two of the hydroxy-carbazole metabolites of carvedilol are extremely potent antioxidants, demonstrating a 30 to 80 fold greater potency than carvedilol.

Pharmacokinetic studies in humans have shown that the oxidative metabolism of carvedilol is stereoselective. The results of an in vitro study suggested that different cytochrome P450 isoenzymes may be involved in the oxidation and hydroxylation processes including CYP2D6, CYP3A4, CYP2E1, CYP2C9 as well as CYP1A2.

Studies in healthy volunteers and in patients have shown that the R-enantiomer is predominantly metabolised by CYP2D6. The S-enantiomer is mainly metabolised by CYP2D6 and CYP2C9.

## *Genetic polymorphism*

The results of clinical pharmacokinetic studies in human subjects have shown that CYP2D6 plays a major role in the metabolism of R and S-carvedilol. As a consequence, plasma concentrations of R and S-carvedilol are increased in CYP2D6 slow metabolisers. The importance of CYP2D6 genotype in the pharmacokinetics of R and S-carvedilol was confirmed in population pharmacokinetics studies, whereas other studies did not confirm this observation. It was concluded that CYP2D6 genetic polymorphism may be of limited clinical significance.

## Elimination

Following a single oral administration of 50mg carvedilol, around 60% is secreted into the bile and eliminated with the faeces in the form of metabolites within 11 days. Following a single oral dose, only about 16% are excreted into the urine in the form of carvedilol or its metabolites. The urinary excretion of unaltered drug represents less than 2%. After intravenous infusion of 12.5mg to healthy volunteers, the plasma clearance of carvedilol reaches around 600mL/min and the elimination half-life around 2.5 hours. The elimination half-life of a 50mg capsule observed in the same individuals was 6.5 hours corresponding to the absorption half-life from the capsule. Following oral administration, the total body clearance of the S-carvedilol is approximately two times larger than that of the R-carvedilol.

## Special patient considerations

### *Renal impairment*

In patients with hypertension and renal insufficiency, the area under plasma level-time curve, elimination half-life and maximum plasma concentration does not change significantly. Renal excretion of unchanged carvedilol decreases in the patients with renal insufficiency; however changes in pharmacokinetic parameters are modest.

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Carvedilol is not eliminated during dialysis because it does not cross the dialysis membrane, probably due to its high plasma protein binding.

## *Hepatic impairment*

See Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use/ Use in Special Populations.

## *Heart failure*

In a study in 24 Japanese patients with heart failure, the clearance of R-and S-carvedilol was significantly lower than previously estimated in healthy volunteers. These results suggested that the pharmacokinetics of R-and S-carvedilol is significantly altered by heart failure.

## *Elderly use*

Age has no statistically significant effect on the pharmacokinetics of carvedilol in hypertensive patients.

## *Children*

Investigation in paediatrics has shown that the weight-adjusted clearance is significantly larger in paediatrics as compared to adults.

## **5.3 Preclinical safety data**

### *Carcinogenicity*

In carcinogenicity studies conducted in rats and mice, employing dosages up to 75 mg/kg/day and 200 mg/kg/day respectively (38 to 100 times the maximum recommended human dose [MRHD]), carvedilol had no carcinogenic effect.

### *Mutagenicity*

Carvedilol was not mutagenic in in vitro or in vivo mammalian tests and non-mammalian tests.

### *Impairment of fertility*

Administration of carvedilol to adult female rats at maternally toxic doses ( $\geq 200$  mg/kg,  $\geq 100$  times MRHD) resulted in impairment of fertility (poor mating, fewer corpora lutea, and fewer implants).

### *Teratogenicity*

There is no evidence from animal studies that carvedilol has any teratogenic effects. Doses  $> 60$  mg/kg ( $> 30$  times MRHD) caused delays in physical growth/development of offspring. There was embryotoxicity (increased post-implantation deaths) but no malformations in rats and rabbits at doses of 200 mg/kg and 75 mg/kg, respectively (38 to 100 times MRHD).

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## **6 PHARMACEUTICAL PARTICULARS**

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### **6.1 List of excipients**

Lactose

Microcrystalline cellulose

Crospovidone

Povidone

Colloidal anhydrous silica

Magnesium stearate

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Iron oxide yellow (6.25 mg and 12.5mg)

Iron oxide red (12.5mg)

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

3 years

## 6.4 Special precautions for storage

Store in a dry place below 25 °C and protect from light.

## 6.5 Nature and contents of container

PVC/Al blister packs of 30\* and 60 tablets.

Not all pack sizes may be marketed

## 6.6 Special precautions for handling, reconstitution and disposal

No special requirements

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## 7 MEDICINE SCHEDULE

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Prescription Medicine.

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## 8 SPONSOR

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Sandoz New Zealand Limited

12 Madden Street

Auckland 1010

New Zealand

Telephone: 0800 726 369

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## 9 DATE OF FIRST APPROVAL

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05 Mar 2015

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## 10 DATE OF REVISION OF THE TEXT

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20 March 2023

### SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Change in sponsor details