

# Datasheet

## DP-Carvedilol

**Carvedilol tablets 3.125 mg, 6.25 mg, 12.5 mg and 25 mg**

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### Composition

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#### **Active ingredient**

carvedilol

1 tablet contains 3.125 mg, 6.25 mg, 12.5 mg or 25 mg carvedilol.

Tablets for oral administration.

#### **Excipients**

The tablet cores contain: microcrystalline cellulose, lactose monohydrate, crospovidone, povidone, colloidal silicon dioxide anhydrous, and magnesium stearate. The tablets are coated with Opadry II White YS-22-18096 which is comprised of: hydroxypropyl methylcellulose, titanium dioxide, polydextrose, triethyl citrate and polyethylene glycol).

#### **Appearance**

DP-Carvedilol 3.125mg tablet: White, oval shaped, film-coated tablets with "P" embossed on one side and plain on the other.

DP-Carvedilol 6.25mg tablet: White, oval shaped, film-coated tablets with "P" embossed on one side and "6.25" on the other.

DP-Carvedilol 12.5mg tablet: White, oval shaped, film-coated tablets with "P" embossed on one side and "12.5" on the other.

DP-Carvedilol 25mg tablet: White, oval shaped, film-coated tablets with "P" embossed on one side and "25" on the other.

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### Properties and Effects

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#### **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 the 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.

## ***Efficacy***

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. 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.

### **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 all cause mortality and the need for cardiovascular hospitalization. Carvedilol also increases ejection fraction and improves symptoms in patients with ischaemic or non-ischaemic chronic heart failure. The effect of carvedilol is dose dependent.

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## **Pre-clinical Safety Data**

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

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

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

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### ***Absorption***

Following oral administration, carvedilol is rapidly absorbed. In healthy volunteers the maximum serum concentration is reached after approximately one hour. The absolute bioavailability of carvedilol in humans is approximately 25%.

### ***Distribution***

Carvedilol is a highly lipophilic compound, approximately 98% to 99% bound to plasma proteins. The distribution volume is approximately 2 L/kg.

### ***Metabolism***

In humans, carvedilol is extensively metabolised into a variety of metabolites that are mainly eliminated in the bile. The first-pass effect after oral administration amounts to about 60-75%. Enterohepatic circulation of the parent substance has been shown in animals.

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. Two of the hydroxy-carbazole metabolites of carvedilol are extremely potent antioxidants, demonstrating a 30 to 80 fold greater potency than carvedilol.

### ***Elimination***

The average elimination half-life of carvedilol is approximately 6 hours. Plasma clearance is approximately 500-700 mL/min. The primary route of excretion is via the faeces. Elimination is mainly biliary. A minor part is eliminated via the kidneys in the form of various metabolites.

### ***Pharmacokinetics in special populations***

#### **Patients with renal impairment**

The autoregulatory blood supply is preserved and the glomerular filtration is unchanged during chronic treatment with carvedilol.

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.

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

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.

#### **Patients with hepatic impairment**

In patients with cirrhosis of the liver, the systemic availability of carvedilol is increased by up to 80% because of a reduction in the first-pass effect. Therefore, carvedilol is contraindicated in patients with clinically manifest liver dysfunction (see Contraindications).

#### **Geriatric use**

The pharmacokinetics of carvedilol in hypertensive patients were not affected by age. A study in elderly hypertensive patients showed that there was no difference in the adverse event profile. Another study, which included elderly patients with coronary heart disease, showed no difference in the adverse events reported.

#### **Paediatric use**

There is limited data available on pharmacokinetics in people younger than 18 years of age.

#### **Diabetic patients**

In hypertensive patients with non-insulin-dependent diabetes no influence of carvedilol on fasting or post-prandial blood glucose concentration, glycolated haemoglobin A<sub>1</sub> 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.

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## **Indications and Usage**

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### ***Hypertension***

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

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

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

### ***Chronic heart failure***

DP-Carvedilol is indicated for the treatment of symptomatic patients with stable, mild, moderate and severe chronic heart failure of ischaemic or non-ischaemic etiology. In combination with ACE inhibitors, diuretics, and optional digitalis (standard therapy), DP-Carvedilol reduces morbidity (cardiovascular hospitalisation and patient well being) and mortality as well as delaying progression of the disease.

DP-Carvedilol can be used as an adjunct to standard therapy, and may be used in patients who are not receiving digitalis, hydralazine or nitrate therapy.

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## **Dosage and Administration**

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### ***Duration of treatment***

Treatment with DP-Carvedilol 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.

### ***Essential 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).

### ***Symptomatic stable 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 DP-Carvedilol 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 DP-Carvedilol and, in rare cases, temporarily discontinue DP-Carvedilol treatment.

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

### ***Special dosage instructions***

#### **Renal impairment**

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

#### **Hepatic impairment**

DP-Carvedilol is contraindicated in patients with clinical manifestations of liver dysfunction (see Contraindications).

#### **Elderly**

There is no evidence to support dose adjustment.

#### **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, DP-Carvedilol should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects.

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## **Contraindications**

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DP-Carvedilol 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, DP-Carvedilol 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

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## **Warnings / Precautions**

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### ***Chronic Heart Failure***

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

### ***Renal function in Congestive Heart Failure***

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

### ***Diabetes***

Care should be taken in the administration of DP-Carvedilol to patients with diabetes mellitus, as the early signs and symptoms of acute hypoglycaemia may be masked or attenuated. In chronic heart failure patients with diabetes, the use of DP-Carvedilol may be associated with worsening control of blood glucose.

### ***Peripheral vascular disease***

DP-Carvedilol should be used with caution in patients with peripheral vascular disease as  $\beta$ -blockers can precipitate or aggravate symptoms of arterial insufficiency.

### ***Raynaud's phenomenon***

DP-Carvedilol should be used with caution in patients suffering from peripheral circulatory disorders (eg Raynaud's phenomenon) as there may be exacerbation of symptoms.

### ***Thyrotoxicosis***

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

### ***Anaesthesia and major surgery***

Caution should be exercised in patients undergoing general surgery, because of the synergistic negative inotropic effects of DP-Carvedilol and anaesthetics.

### ***Bradycardia***

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

### ***Hypersensitivity***

Care should be taken in administering DP-Carvedilol to patients with a history of serious hypersensitivity reactions, and in those undergoing desensitisation therapy, as  $\beta$ -blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions.

### ***Psoriasis***

Patients with a history of psoriasis associated with  $\beta$ -blocker therapy should take DP-Carvedilol only after consideration of the risk-benefit ratio.

### ***Concomitant use of calcium channel blockers***

Careful monitoring of ECG and blood pressure is necessary in patients receiving concomitant therapy with calcium channel blockers of the verapamil or diltiazem type or other antiarrhythmic medicines.

### ***Pheochromocytoma***

In patients with pheochromocytoma, an  $\beta$ -blocking agent should be initiated prior to the use of any  $\beta$ -blocking agent. Although DP-Carvedilol 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 DP-Carvedilol 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 DP-Carvedilol in these patients although the  $\alpha$ -blocking activity of DP-Carvedilol may prevent such symptoms. Caution should, however, be taken in the administration of DP-Carvedilol 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***

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

### ***Fitness to drive***

No studies have been performed on the effects of DP-Carvedilol on patients' fitness to drive or to operate machinery.

Because of individually variable reactions (eg 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.

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## **Pregnancy, nursing mothers**

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Pregnancy category C

### ***Pregnancy***

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.

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

### ***Lactation***

Animal studies demonstrated that carvedilol or its metabolites are excreted in breast milk. It is not known whether carvedilol is excreted in human milk. Breastfeeding is therefore not recommended during administration of DP-Carvedilol.

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## **Undesirable Effects**

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### **Adverse Event (AE) Frequency**

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

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

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

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

AE's occurring at  $< 0.01\%$  are described as very rare including isolated cases

The frequency of adverse experiences is not dose-dependent, with the exception of dizziness, abnormal vision and bradycardia.

### ***Undesirable effects in chronic heart failure***

Adverse experiences most frequently observed in the DP-Carvedilol group in clinical trials in chronic heart failure patients and not seen at an equivalent incidence among placebo treated patients are described below.

#### ***Central nervous system***

*Very common:* dizziness, headache are usually mild and occur particularly at the start of treatment. Asthenia (including fatigue) also occurs very commonly.

#### **Cardiovascular system**

*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 cardiac failure during up-titration.

#### **Gastro-intestinal system**

*Common:* nausea, diarrhoea and vomiting.

#### **Haematology**

*Rare:* thrombocytopenia.

Leucopenia has been reported in isolated cases.

#### **Metabolic**

*Common:* weight increase and hypercholesterolaemia. Hyperglycaemia, hypoglycaemia and worsening control of blood glucose are also common in patients with pre-existing diabetes mellitus (see Warnings / Precautions).

#### **Others**

*Common:* vision abnormalities.

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

### **Undesirable effects in hypertension and the long term management of coronary heart disease**

The profile of adverse events associated with the use of DP-Carvedilol in the treatment of hypertension and the long-term management of coronary heart disease is consistent with that observed in chronic heart failure. The incidence of adverse events in these patient populations is lower, however.

Adverse experiences reported in clinical trials in patients with hypertension and coronary heart disease are:

#### **Central nervous system**

*Common:* dizziness, headaches and fatigue, which are usually mild and occur particularly at the beginning of treatment.

*Uncommon:* depressed mood, sleep disturbance, paraesthesia.

#### **Cardiovascular system**

*Common:* bradycardia, postural hypotension and uncommonly syncope, especially at the beginning of treatment.

*Uncommon:* 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.

### **Respiratory system**

*Common:* asthma and dyspnoea in predisposed patients.

*Rare:* stuffy nose.

### **Gastro-intestinal system**

*Common:* gastro-intestinal upset (with symptoms such as nausea, abdominal pain, diarrhoea).

*Uncommon:* constipation and vomiting.

### **Skin and appendages**

*Uncommon:* skin reactions (eg allergic exanthema, dermatitis, urticaria and pruritus).

### **Blood chemistry and haematology**

Isolated cases of increases in ALAT, ASAT and gamma GT, thrombocytopenia and leucopenia.

### **Others**

*Common:* pain in the extremities, reduced lacrimation and eye irritation.

*Uncommon:* cases of sexual impotence and disturbed vision.

*Rare:* dryness of the mouth and disturbances of micturition.

Isolated cases of allergic reactions have been reported.

### **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.

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## **Interactions**

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(Also see Warnings/Precautions)

### **Pharmacokinetic interactions**

*Digoxin:* Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Both digoxin and carvedilol slow AV conduction. Increased monitoring of digoxin levels is recommended when initiating, adjusting or discontinuing carvedilol.

*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.

*Inducers and inhibitors of hepatic metabolism:* Rifampicin reduced plasma concentrations of carvedilol by about 70%. Cimetidine increased AUC by about 30% but caused no change in  $C_{max}$ . Care may be required in those patients receiving inducers of mixed function oxidases eg rifampicin, as serum levels of carvedilol may be reduced, or inhibitors of mixed function oxidases eg cimetidine, as serum levels of carvedilol may be increased.

However, based on the relatively small effect of cimetidine on carvedilol levels, the likelihood of any clinically important interaction is minimal.

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

*Cyclosporin:* Modest increases in mean trough cyclosporin concentrations were observed following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30% of patients, the dose of cyclosporin had to be reduced in order to maintain cyclosporin concentrations within the therapeutic range, while in the remainder no adjustment was needed. On average, the dose of cyclosporin was reduced about 20% in these patients. Due to wide interindividual variability in the dose adjustment required, it is recommended that cyclosporin concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporin be adjusted as appropriate.

*Verapamil, diltiazem, or other antiarrhythmics:* In combination with carvedilol can increase the risk of AV conduction disturbances (see Warnings).

### **Pharmacodynamic interactions**

*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.

*Calcium channel blockers (see Warnings/Precautions):* Isolated cases of conduction disturbance (rarely with haemodynamic compromise) have been observed when carvedilol is co-administered with diltiazem. As with other agents with  $\beta$ -blocking properties, if carvedilol is to be administered orally with calcium channel blockers of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored.

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

Careful attention must be paid during anaesthesia to the synergistic negative inotropic and hypotensive effects of carvedilol and anaesthetic medicines.

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## **Overdosage**

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### **Symptoms and signs of intoxication**

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.

### ***Treatment of intoxication***

In addition to general procedures, the vital parameters must be monitored and corrected, if necessary, under intensive care conditions. The following supportive therapies can be used:

Patients should be placed in the supine position.

Atropine: 0.5 to 2 mg i.v. (for excessive bradycardia).

Glucagon: initially 1 to 10 mg i.v. then 2 to 5 mg/h as a long-term infusion (to support cardiovascular function).

Sympathomimetics according to body-weight and effect: dobutamine, isoprenaline, orciprenaline or adrenaline. If positive inotropic effect is required, phosphodiesterase inhibitors (PDE) eg milrinone should be considered.

If peripheral vasodilation dominates the intoxication profile then norfenefrine or noradrenaline should be administered with continuous monitoring of the circulatory conditions.

In the case of bradycardia resistant to medication, pacemaker therapy should be initiated.

### ***Treatment of bronchospasm***

For bronchospasm,  $\beta$ -sympathomimetics (as aerosol or i.v.) or aminophylline i.v. should be given.

### ***Treatment of seizures***

In the event of seizures, slow i.v. injection of diazepam or clonazepam is recommended.

### ***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 overdose. The supportive treatment should therefore be continued until the patient's condition has stabilised.

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## **Stability**

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DP-Carvedilol tablets should be stored in a dry place below 25°C and protected from light.

DP-Carvedilol tablets should not be used after the expiry date printed on the pack.

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## **Medicine Classification**

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Prescription medicine

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## **Packs**

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Tablets 3.125 mg 30, 60, 100, 250 and 500 in blisters or plastic bottles

Tablets 6.25 mg 30, 60, 100, 250 and 500 in blisters or plastic bottles

Tablets 12.5mg 30, 60, 100, 250 and 500 in blisters or plastic bottles

Tablets 25 mg 30, 60, 100, 250 and 500 in blisters or plastic bottles

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**Name and Address**

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**Date of Preparation**

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6<sup>th</sup> January 2005