Data Sheet

Dilatrend®

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

Alpha (α) and beta (β) adrenergic receptor blocking agent

Description

Active ingredient

carvedilol
1 tablet contains 3.125 mg, 6.25 mg, 12.5 mg or 25 mg carvedilol.
(Note: The 3.125mg tablets are not currently marketed.)
Tablets for oral administration.

Excipients

Lactose, sucrose, povidone, crospovidone, colloidal silicon dioxide, magnesium stearate, yellow iron oxide (6.25 mg and 12.5 mg tablets only), red iron oxide (3.125 mg and 12.5 mg tablets only).

Appearance

Dilatrend 6.25 mg tablet: yellow, round biconvex tablet, with a bilateral scoreline engraved with 'BM' on one side and 'F1' on the other side.

Dilatrend 12.5 mg tablet: light brown, round biconvex tablet, with a bilateral scoreline engraved with 'BM' on one side and 'H3' on the other side.

Dilatrend 25 mg tablet: white to pale yellowish beige, round biconvex tablet, with a bilateral scoreline engraved with 'BM' on one side and 'D5' on the other side.

Clinical Particulars

Therapeutic Indications

Hypertension

Dilatrend 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

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

Chronic heart failure (CHF)

Unless a contraindication exists, Dilatrend 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 $\leq$ 40% or wall motion index $\leq$ 1.3), including well controlled heart failure, in combination with ACE inhibitors and other treatments recommended in the management of patients after myocardial infarction.

Dosage and 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, Dilatrend should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects.

Duration of treatment

Treatment with Dilatrend 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 Dilatrend 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 Dilatrend and, in rare cases, temporarily discontinue Dilatrend treatment.

If Dilatrend 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 Dilatrend 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 Dilatrend 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 Dilatrend

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

First dose of Dilatrend

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 Warnings and Precautions; General).

Subsequent doses of Dilatrend

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 Dilatrend dosing recommendations are warranted in patients with moderate to severe renal insufficiency.

Hepatic impairment
Dilatrend is contraindicated in patients with clinical manifestations of liver dysfunction (see Contraindications).

Elderly
There is no evidence to support dose adjustment.

Contraindications

Dilatrend 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 β–blockers, Dilatrend 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

Warnings and Precautions

General

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

Renal function in congestive heart failure
Reversible deterioration of renal function has been observed with Dilatrend 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 Dilatrend 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 Dosage and 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 resistance. Patients should be closely monitored during initiation and up-titration of carvedilol and the dose of Dilatrend should be reduced if any evidence of bronchospasm is observed during treatment (see Interactions with other Medicinal Products and other Forms of Interaction).

Diabetes

Care should be taken in the administration of Dilatrend 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 Dilatrend may be associated with worsening control of blood glucose (see Interactions with other Medicinal Products and other Forms of Interaction).

Peripheral vascular disease

Dilatrend should be used with caution in patients with peripheral vascular disease as β-blockers can precipitate or aggravate symptoms of arterial insufficiency.

Raynaud's phenomenon

Dilatrend should be used with caution in patients suffering from peripheral circulatory disorders (e.g. Raynaud's phenomenon) as there may be exacerbation of symptoms.

Thyrotoxicosis

Dilatrend, like other agents with β-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 Dilatrend and anaesthetics (see Interactions with other Medicinal Products and other Forms of Interaction).

Bradycardia

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

Hypersensitivity

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

Psoriasis

Patients with a history of psoriasis associated with β-blocker therapy should take Dilatrend 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 (see Interactions with other Medicinal Products and other Forms of Interaction).

Pheochromocytoma

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

Prinzmetal's variant angina

Agents with non-selective β-blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There is no clinical experience with Dilatrend in these patients although the α-blocking activity of Dilatrend may prevent such symptoms. Caution should, however, be taken in the administration of Dilatrend 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

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

Ability to drive and use machines

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

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.

Interactions with other Medicinal Products and other Forms of Interaction

Pharmacokinetic interactions

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

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 Pharmacokinetic Properties; Metabolism). Some examples observed in patients or in healthy subjects are listed below but the list is not exhaustive.

Digoxin: Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Increased monitoring of digoxin levels is recommended when initiating, adjusting or discontinuing carvedilol (see Warnings and Precautions; General).

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 the absorption of oral (po) cyclosporin through inhibition of P-glycoprotein activity in the intestine. In an attempt to maintain therapeutic cyclosporin levels, an average 10 - 20% reduction of the cyclosporin dose was necessary. Therefore, due to wide interindividual 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.

Rifampicin: In a study in 12 health subjects, rifampicin administration decreased the carvedilol plasma levels most likely by induction of P-glycoprotein leading to a decrease of the intestinal absorption of carvedilol and a decrease of the antihypertensive effect.

Amiodarone: In patients with heart failure, amiodarone decreased the clearance of S-carvedilol likely by inhibition of CYP2C9. The mean R-carvedilol plasma concentration was not altered. Consequently, there is a potential risk of increased β-blockade caused by a raised plasma S-carvedilol concentration.

Fluoxetine: 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. However, no differences in adverse events, blood pressure or heart rate were noted between treatment groups.

Pharmacodynamic interactions

Insulin or oral hypoglycaemics: Agents with β-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 Warnings and Precautions; General).

Catecholamine-depleting agents: Patients taking both agents with β-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.

Verapamil, diltiazem, amiodarone or other antiarrhythmics: In combination with Dilatrend can increase the risk of AV conduction disturbances (see Warnings and Precautions; General).

Clonidine: Concomitant administration of clonidine with agents with β-blocking properties may potentiate blood-pressure- and heart-rate-lowering effects. When concomitant treatment with agents with β-blocking properties and clonidine is to be terminated, the β-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 and Precautions; General): Isolated cases of conduction disturbance (rarely with haemodynamic compromise) have been observed when Dilatrend is co-administered with diltiazem. As with other agents with β-blocking properties, if Dilatrend 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.

Antihypertensives: As with other agents with β-blocking activity, carvedilol may potentiate the effect of other concomitantly administered medicines that are anti-hypertensive in action (e.g. α_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 Dilatrend and anaesthetic medicines (see Warnings and Precautions; General).

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 (see Warnings and Precautions; General).

Digoxin: The combined use of beta-blockers and digoxin may result in additive prolongation of atrioventricular (AV) conduction time (see Warnings and Precautions; General).

Use in Special Populations

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.

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

Nursing mothers

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 Dilatrend.

Undesirable Effects

Clinical trials

Adverse Event (AE) Frequency

AE's occurring at ≥ 10% are described as very common.
AE's occurring at ≥ 1% and < 10% are described as common.
AE's occurring at ≥ 0.1% and < 1% are described as uncommon.
AE's occurring at ≥ 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 Dilatrend 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.

Gastrointestinal 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 and Precautions; General).

Others
Common: vision abnormalities.
Rare: renal failure and renal function abnormalities in patients with diffuse vascular disease and/or impaired renal function (see Warnings and Precautions; General).

Undesirable effects in left ventricular dysfunction following acute myocardial infarction
In a phase III, randomised, double-blind, parallel group study the effects of Dilatrend on mortality and morbidity in patients with left ventricular dysfunction following acute myocardial infarction, with or without clinical evidence of heart failure, was investigated. Adverse events observed with $\geq$ 2% incidence in the Dilatrend arm or that had a higher incidence than the placebo arm are listed below:

Table 1: Adverse events observed with ≥ 2% incidence in the Dilatrend arm or that had a higher incidence than the placebo arm

Body System/Adverse Event	Placebo *n* = 980 No. (%)	Carvedilol *n* = 969 No. (%)
Blood and lymphatic system disorders		
Anaemia	20 (2.0)	35 (3.6)
Cardiac disorders		
Cardiac Failure	142 (14.5)	149(15.4)
Bradycardia	37 (3.8)	63 (6.5)
Gastrointestinal disorders		
Diarrhoea	31 (3.2)	35 (3.6)
Dyspepsia	21 (2.1)	23 (2.4)
General disorders and administration site conditions		
Oedema Peripheral	28 (2.9)	43 (4.4)
Pain	18 (1.8)	21 (2.2)
Asthenia	56 (5.7)	66 (6.8)
Infections and infestations		
Bronchitis	22 (2.2)	29 (3.0)
Pneumonia	40 (4.1)	41 (4.2)
Upper Respiratory Infection	66 (6.7)	66 (6.8)
Urinary Tract Infection	13 (1.3)	19 (2.0)
Metabolism and nutrition disorders		
Hyperglycaemia	30 (3.1)	30 (3.1)
Nervous system disorders		
Dizziness	105 (10.7)	144 (14.9)
Syncope	19 (1.9)	38 (3.9)
Psychiatric disorders		
Depression	15 (1.5)	25 (2.6)
Renal and urinary disorders		
Renal Failure	9 (0.9)	25 (2.6)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	88 (9.0)	94 (9.7)
Pulmonary Oedema	31 (3.2)	42 (4.3)
Vascular disorders		
Hypotension	114 (11.6)	176 (18.2)
Hypertension	77 (7.9)	79 (8.2)
Peripheral Vascular Disorder	16 (1.6)	30 (3.1)
Orthostatic Hypotension	9 (0.9)	20 (2.1)

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

The profile of adverse events associated with the use of Dilatrend 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.

Gastrointestinal system

Common: gastro-intestinal upset (with symptoms such as nausea, abdominal pain, diarrhoea).
Uncommon: constipation and vomiting.

Skin and appendages

Uncommon: skin reactions (e.g. allergic exanthema, dermatitis, urticaria and pruritus).

Blood chemistry and haematology

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

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.

Post-marketing experience

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.

Metabolism and nutrition disorders - Class effect
Due to the β-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.

Overdose

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) e.g. milrinone, should be considered.

If peripheral vasodilation dominates the intoxication profile then norfenephrine 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, β-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 overdosage. The supportive treatment should therefore be continued until the patient's condition has stabilised.

Pharmacological Properties and Effects

Pharmacodynamic Properties

Mechanism of action

Carvedilol is a multiple action adrenergic receptor blocker with α_1, β_1 and β_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 α-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 β-adrenergic receptor blocking properties are non-selective for the β_1 and β_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 β-blockade, which reduces the release of renin, thus making fluid retention rare.

Carvedilol reduces peripheral vascular resistance via selective blockade of α_1-adrenoceptors. Carvedilol attenuates the increase in blood pressure induced by phenylephrine, an α_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/efficacy studies

Clinical studies showed the following results for Dilatrend:

Hypertension

Dilatrend lowers blood pressure in hypertensive patients by a combination of β-blockade and α_1 mediated vasodilation. A reduction in blood pressure is not associated with a concomitant increase in total peripheral resistance, as observed with pure β-blocking agents. Heart rate is slightly decreased. Renal blood flow and renal function are maintained in hypertensive patients. Dilatrend 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 Dilatrend. There is a reduced incidence of cold extremities and early fatigue during physical activity. The long-term effect of Dilatrend on hypertension is documented in several double-blind controlled studies.

Coronary heart disease

In patients with coronary heart disease, Dilatrend 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 Dilatrend 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

Dilatrend 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 Dilatrend is dose dependent.

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), Dilatrend 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 Dilatrend significantly reduced death or major cardiovascular hospitalisation by 17% ($p = 0.019$).

Pharmacokinetic Properties

Absorption

Following oral administration, carvedilol is rapidly absorbed. Carvedilol is a substrate of the intestinal efflux transporter P-glycoprotein which plays a major role in the bioavailability of certain drugs. 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 in the liver via oxidation and conjugation 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.

The oxidative metabolism of carvedilol is stereoselective. The R-enantiomer is predominantly metabolised by CYP2D6 and CYP1A2, while the S-enantiomer is mainly metabolised by CYP2C9 and to a lesser extend by CYP2D6. Other CYP450 isoenzymes involved in the metabolism of carvedilol include CYP3A4, CYP2E1 and CYP2C19. The maximal plasma concentrations of R-carvedilol are approximately 2 fold higher than that S-carvedilol.

The R-enantiomer is predominantly metabolised through hydroxylation.

In slow metabolisers of CYP2D6 an increase of the plasma concentration of carvedilol, mainly the R-enantiomer may occur, leading to an increase in the α-blocking activity.

Demethylation and hydroxylation at the phenol ring produce 3 metabolites with β-adrenergic receptor blocking activity. Based on pre-clinical studies, the 4'-hydroxy-phenol metabolite is approximately 13 times more potent than carvedilol for β-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).

Patients with heart failure

In a study in 24 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.

Geriatric use

Age has no statistically significant effect on the pharmacokinetics of carvedilol in hypertensive patients. A study in elderly hypertensive patients showed that there was no difference in the adverse event profile compared to younger patients. Another study which included elderly patients with coronary heart disease showed no difference in the adverse events reported versus those reported by younger patients.

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_1 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.

Preclinical Safety

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).

Pharmaceutical Particulars

Storage

Dilatrend tablets should be stored in a dry place below 30 ºC and protected from light.

Dilatrend tablets should not be used after the expiry date printed on the pack.

Disposal of medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

Medicine Classification

Prescription medicine

Packs

Tablets 6.25 mg 30’s
Tablets 12.5 mg 30’s
Tablets 25 mg 30’s
(Note: Dilatrend 3.125 mg tablets are not currently available.)

Name and Address

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