Dilatrend®

Carvedilol

COMPOSITION

Active substance: carvedilol

PHARMACEUTICAL FORM AND AMOUNT OF ACTIVE INGREDIENT PER UNIT

Dilatrend scored tablets: yellow tablets containing 6.25 mg carvedilol

Dilatrend scored tablets: pale brown tablets containing 12.5 mg carvedilol

Dilatrend scored tablets: white to pale yellow/beige tablets containing 25 mg carvedilol

INDICATIONS AND POTENTIAL USES

Essential (mild to moderate) hypertension and chronic angina pectoris for prevention of attacks.

Treatment of mild to severe cases of stable heart failure (NYHA class II–IV) due to ischemia or cardiomyopathy as an adjunct to standard therapy (diuretics, digoxin, ACE inhibitor).

DOSAGE AND ADMINISTRATION

Essential hypertension

Adults

The initial dosage is 12.5 mg once daily for the first two days. Thereafter a dose of 25 mg once daily is recommended. If the effect is inadequate, the daily dose may be increased after a minimum of two weeks to 50 mg taken as one or two individual doses. The maximum daily dose in hypertension is 50 mg.

Elderly patients

Initially 12.5 mg once daily. In some patients this dose is sufficient for adequate control of blood pressure. If the effect is inadequate, the daily dose may be increased stepwise at intervals of at least two weeks up to a maximum of 50 mg taken as one or two individual doses.

Angina pectoris

The initial dosage is 12.5 mg twice daily for the first two days. Thereafter a dose of 25 mg twice daily is recommended. If the effect is inadequate, the dose may be increased

stepwise at intervals of at least two weeks up to a maximum daily dose of 100 mg taken as two individual doses.

Elderly patients

In general a dose of 25 mg twice daily should not be exceeded.

Treatment of mild to severe heart failure (NYHA class II–IV)

The dosage must be individually determined and the patient must be closely monitored during the titration phase.

The dose of digitalis, diuretics and ACE inhibitor should have been stabilised before the start of Dilatrend therapy.

The recommended dosage for initiation of therapy is 3.125 mg twice daily (½ a tablet of Dilatrend 6.25 mg twice daily) for two weeks. If this dose is tolerated, the dose can be increased progressively at intervals of at least two weeks to 6.25 mg twice daily (1 tablet of Dilatrend 6.25 mg twice daily), then to 12.5 mg twice daily (1 tablet of Dilatrend 12.5 mg twice daily), and then to 25 mg twice daily (1 tablet of Dilatrend 25 mg twice daily). The dose should be increased to the highest level that the patient tolerates.

The maximum recommended dose is 25 mg twice daily in patients weighing up to 85 kg and 50 mg twice daily in patients weighing more than 85 kg.

Before each dose increment, the physician should examine the patient for signs and symptoms of deteriorating heart failure, vasodilation (fall in blood pressure, dizziness) or bradycardia. Transient deterioration of heart failure or fluid retention should be treated with increased doses of diuretics, although it will occasionally be necessary to reduce the dose of Dilatrend or to interrupt treatment temporarily.

If treatment with Dilatrend is interrupted for more than two weeks, it should be reinitiated with a dose of 3.125 mg; this dose should then be increased at intervals of two weeks, as indicated above.

Signs and symptoms of vasodilation should be treated initially with a reduction in the dose of diuretic. If they persist, the dose of the ACE inhibitor should be reduced, after which the dose of Dilatrend should be reduced. Under these circumstances the dose of Dilatrend should not be increased until the signs and symptoms of deterioration of heart failure or vasodilatation have improved.

The safety and efficacy of Dilatrend in patients under 18 years of age have not been investigated.

Patients with renal impairment

No reduction in the initial dose is required in patients with renal impairment (see *Pharmacokinetics: Pharmacokinetics in special patient populations*).

Patients with hepatic impairment

Dilatrend is contraindicated in patients with clinically manifest liver failure (see *Pharmacokinetics* and *Contraindications,* 'clinically manifest liver failure').

Correct method of administration

The tablets should be taken with an adequate amount of liquid.

It is not necessary to take the tablets with meals, however patients with heart failure should take the tablets with food in order to slow the rate of absorption and reduce the incidence of orthostatic effects.

Treatment with Dilatrend is generally long-term therapy. It should not be stopped abruptly, but must be tapered off over a number of days (e.g. by halving the dose every three days). This is particularly important in patients who also have coronary artery disease.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or any of the constituent excipients
- Decompensated chronic heart failure of NYHA class II–IV in patients who require support with intravenous inotropic agents
- Chronic obstructive pulmonary disease
- Bronchial asthma (there have been two reports of death after status asthmaticus; these occurred after a single dose)
- Allergic rhinitis
- Glottal edema
- Cor pulmonale
- Sick sinus syndrome (including sinoatrial block)
- Severe hypotension (systolic blood pressure <85 mmHg)
- Second- and third-degree AV block
- Severe bradycardia (less than 45–50 beats per minute at rest)
- Cardiogenic shock
- Myocardial infarction with complications
- Clinically manifest liver failure
- Metabolic acidosis
- Concomitant administration of MAO inhibitors (with the exception of MAO-B inhibitors)
- Poor metabolisers of debrisoquine and mephenytoin

WARNINGS AND PRECAUTIONS

Patients with pheochromocytoma may be treated with Dilatrend only in conjunction with effective alpha-receptor blockade.

Dilatrend should be used with caution in patients with decompensated heart failure treated with digitalis (e.g. digoxin), diuretics and/or ACE inhibitors, since digitalis and

Dilatrend may prolong AV conduction and Dilatrend may increase digitalis levels (see *Interactions*).

Because therapeutic experience is inadequate, Dilatrend should not be used in:

- Children
- Labile or secondary hypertension
- Unstable angina pectoris
- Complete bundle branch block
- End-stage peripheral arterial occlusive disease, since beta-blockers may cause or exacerbate signs and symptoms of arterial insufficiency in these patients
- Fresh myocardial infarction
- Tendency to orthostatic hypotension
- Concomitant treatment with certain antihypertensive agents ($alpha_1$-receptor antagonists).

Beta-blocker therapy may increase sensitivity to allergens and susceptibility to severe anaphylactic reactions in patients with a history of serious hypersensitivity reactions and in those undergoing desensitisation therapy. Caution is therefore required in these patients.

Patients with psoriasis or a family history of psoriasis should be given drugs with beta-blocking properties, including Dilatrend, only after a careful risk-benefit analysis.

Where Dilatrend has to be discontinued in hypertensive patients who also have coronary heart disease, it is recommended that the dose be reduced stepwise, as in the case of other drugs with beta-blocking properties.

Bradycardia occurred in 2% of hypertensive patients and 9% of heart failure patients in clinical studies. If the heart rate falls below 55 beats per minute, the dose should be reduced. Hypotension occurred in 9.7% and syncope in 3.4% of heart failure patients treated with Dilatrend as compared to 3.6% and 2.5% of the placebo-treated patients. The risk of occurrence of these effects was greatest during the first 30 days of treatment, i.e. during the dose titration phase (see *Dosage and administration*).

Careful monitoring of blood pressure and ECG parameters is required during concomitant treatment with calcium channel blockers of the verapamil or diltiazem type or with other antiarrhythmics.

In elderly patients the first dose of Dilatrend may be followed by an exaggerated fall in blood pressure.

It can be assumed that by causing beta-blockade, Dilatrend may mask the signs and symptoms of hyperthyroidism such as tachycardia. Abrupt cessation of beta-blockade may be followed by exacerbation of the signs and symptoms of hyperthyroidism.

If – where warranted in exceptional cases – agents with beta-blocking properties (such as carvedilol) and clonidine are used concomitantly, clonidine may be gradually withdrawn only after treatment with Dilatrend has been discontinued several days previously (see *Interactions*).

Because of the synergistic negative inotropic effects of carvedilol and anesthetics, careful monitoring of vital signs is recommended in patients undergoing surgery under general anesthesia (see *Interactions*).

Renal and cardiac transplant patients receiving oral ciclosporin showed increased ciclosporin plasma concentrations after starting treatment with carvedilol. Because of the wide interindividual variability of ciclosporin levels, it is therefore recommended that ciclosporin concentrations be closely monitored after initiation of carvedilol therapy and that the dose of ciclosporin be adjusted as appropriate (see *Interactions*).
Particularly careful medical supervision is required in patients with diabetes mellitus. Diabetics should be informed that Dilatrend may mask or attenuate the signs and symptoms of hypoglycemia, especially tachycardia. Non-selective beta-blockers may intensify insulin-induced hypoglycemia and delay normalisation of serum glucose levels. Regular monitoring of blood glucose is required and the dose of insulin or oral antidiabetic agents may need to be adjusted.

Symptoms may be exacerbated in patients with intermittent claudication or Raynaud's phenomenon.

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

Patients with heart failure may suffer an exacerbation of heart failure or fluid retention during the dose titration phase of Dilatrend therapy. If such effects occur, the dose of diuretic should be increased and the dose of Dilatrend not increased until the patient's condition stabilises. Occasionally it will be necessary to reduce the dose of Dilatrend or discontinue treatment (see *Dosage and administration*).

Reversible deterioration of renal function has been observed in association with Dilatrend in patients with decompensated heart failure and low blood pressure (systolic pressure < 100 mmHg), coronary heart disease or other vascular diseases and/or with renal impairment. Renal function returned to baseline when the medication was discontinued. In heart failure patients with these risk factors, renal function should be monitored during the dose titration phase and the dose reduced or treatment discontinued if deterioration occurs.

In patients with pheochromocytoma, an alpha-blocker should be initiated prior to the use of any beta-blocker. Although Dilatrend combines both these pharmacological properties, no experience is as yet available. Therefore caution is required when Dilatrend is administered to patients with pheochromocytoma.

Substances with non-selective activity can provoke chest pain in patients with Prinzmetal's angina. No clinical experience is available on the use of Dilatrend in these patients, though the alpha-blocking activity of Dilatrend could prevent these symptoms. Due caution should be exercised when Dilatrend is administered to these patients.

Patients with bronchospastic disease should generally not receive beta-blockers, since the increased airway resistance may lead to dyspnea. Nevertheless Dilatrend may be used with caution in patients who fail to respond to or do not tolerate treatment with other antihypertensives. If Dilatrend is administered, the smallest effective dose should be used with caution in order to minimise inhibition of endogenous or exogenous beta-agonists. Increased airway resistance may lead to dyspnea.

Patients with bronchospastic disease were included in the clinical trials if they required no oral or inhalational medication for the treatment of their bronchospastic disease. The dosage recommendations are to be strictly observed and the dose should be reduced at the first suspicion of bronchospasm during the dose titration phase.

Dilatrend can be administered to patients with left ventricular failure whose heart failure is already being treated with digitalis, diuretics and/or an ACE inhibitor. However, as these patients require a certain amount of sympathomimetic stimulation for circulatory support, the dosage recommendations for patients with heart failure should be followed (see *Interactions*).

In heart failure patients with diabetes, Dilatrend therapy can lead to worsening of hyperglycemia and thus necessitate intensification of the hypoglycemic therapy. It is recommended that blood glucose levels be closely monitored when Dilatrend is used, when the dosage is adjusted or when Dilatrend is discontinued.

Liver damage

Mild hepatocellular damage confirmed by rechallenge has been observed occasionally in patients treated with Dilatrend. In controlled studies in patients with hypertension, the incidence of hepatic impairment reported as adverse events was 1.1% (13 out of 1142) in patients treated with Dilatrend compared to 0.9% (4 out of 462) in patients who received placebo. One patient treated with carvedilol in a placebo-controlled study withdrew because of hepatic impairment.

In controlled studies in chronic heart failure, the incidence of hepatic impairment reported as adverse events was 5.0% (38 out of 765) in patients treated with Dilatrend compared to 4.6% (20 out of 437) in patients who received placebo. Three patients treated in placebo-controlled studies with carvedilol (0.4%) and two patients treated with placebo (0.5%) withdrew because of hepatic impairment.

The liver damage, which occurred after short- and/or long-term therapy, proved to be reversible and resulted in only mild clinical manifestations. There were no reports of death due to hepatic impairment.

Laboratory tests should be performed at the first symptoms or signs of hepatic impairment (e.g. pruritus, dark urine, sustained loss of appetite, jaundice, tenderness in the right upper quadrant, or unexplained flu-like symptoms). If the patient's laboratory test results confirm the presence of liver damage or jaundice, carvedilol should be discontinued and not restarted.

Patients should be given the following advice

- They should not interrupt or discontinue treatment with Dilatrend without first consulting their doctor.
- Heart failure patients should visit their doctor at the first sign or symptom of worsening of their heart failure (weight increase or shortness of breath).
- Their blood pressure may fall when they stand up. Such falls in blood pressure could result in dizziness and, rarely, fainting. Patients should sit or lie down if they experience these symptoms.
- Patients who experience dizziness or tiredness should not drive vehicles or perform dangerous tasks. This applies also to all patients at the start of treatment and during the dose titration phase.
- They should contact their doctor if they experience dizziness or fainting during the dose titration phase.
- They should take Dilatrend with food.
- Diabetic patients should inform their doctor of any change in their blood glucose levels.
- Tear flow may be reduced in contact lens wearers.

INTERACTIONS

The following interactions should be borne in mind when Dilatrend is used concomitantly with other medicinal products:

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, CYP1A2 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 *Pharmacokinetics* and *Metabolism*). Some examples observed in patients or healthy subjects are listed below, but the list is not exhaustive.

Digoxin: Concomitant administration of Dilatrend and digoxin can lead to an increase in digoxin levels. Dilatrend can cause a clinically relevant increase (60%) in the maximum plasma concentration of digoxin. The AUC of digitoxin is slightly increased (+13%). It is recommended that digoxin and digitoxin plasma levels be determined when initiating, adjusting or discontinuing Dilatrend (see *Warnings and precautions).*

Ciclosporin: Two studies in renal and cardiac transplant patients receiving oral ciclosporin have shown an increase in ciclosporin plasma concentration following the initiation of carvedilol. It appears that carvedilol increases the absorption of oral ciclosporin through inhibition of P-glycoprotein activity in the intestine. In an attempt to

maintain therapeutic ciclosporin levels, an average 10–20% reduction of the ciclosporin dose was necessary. Because of the wide interindividual variability of ciclosporin levels, it is therefore recommended that ciclosporin concentrations be closely monitored after initiation of carvedilol therapy and that the dose of ciclosporin be adjusted as appropriate (see *Warnings and precautions*).

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

Amiodarone: In patients with heart failure, amiodarone decreased the clearance of S-carvedilol, probably by inhibiting CYP2C9. The mean R-carvedilol plasma concentration was not altered. Consequently, there is a potential risk of increased beta-blockade due to a rise in plasma S-carvedilol concentration.

Fluoxetine: In a randomised, cross-over study in 10 patients with heart failure, coadministration of fluoxetine, a potent CYP2D6 inhibitor, resulted in stereoselective inhibition of carvedilol metabolism, with a 77% increase in mean R(+)-enantiomer $AUC_{0\text{-}12}$. However, no differences in adverse events, blood pressure or heart rate were noted between the two treatment groups.

Pharmacodynamic interactions

Insulin or oral hypoglycemics: The effect of insulin or oral hypoglycemic agents may be enhanced. The signs and symptoms of hypoglycemia, especially tachycardia, may be masked or attenuated. Regular blood glucose determinations are therefore required in diabetics (see *Warnings and precautions*).

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

Verapamil, diltiazem, amiodarone and other antiarrhythmics: As with other beta-blockers, caution is required during concomitant treatment with oral calcium channel blockers of the verapamil or diltiazem type, amiodarone or other antiarrhythmics, as combined use may increase the risk of AV conduction disturbances. Calcium channel blockers and antiarrhythmics should not be administered intravenously during treatment with Dilatrend.

Catecholamine-depleting agents: Patients taking both agents with beta-blocking properties and agents that deplete catecholamine stores (e.g. reserpine and monoamine oxidase [MAO] inhibitors) should be observed closely for signs of hypotension and/or severe bradycardia.

Like other beta-blockers, Dilatrend may enhance the blood pressure reduction brought about by other drugs whose therapeutic or side effect profile includes the lowering of blood pressure.

Nifedipine: Concomitant use of nifedipine and Dilatrend can result in an exaggerated fall in blood pressure.

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

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 may be gradually withdrawn only after treatment with Dilatrend has been discontinued several days previously (see *Warnings and precautions*).

Concomitant administration of Dilatrend and cardiac glycosides can prolong atrioventricular conduction.

Inhibitors of oxidative metabolism (e.g. cimetidine) increase plasma levels of Dilatrend (carvedilol AUC increased by 30%).

Anesthetic agents: Careful monitoring of vital signs is recommended during anesthesia because of the synergistic negative inotropic and hypotensive effects of Dilatrend and anesthetic agents (see *Warnings and precautions*).

NSAIDs: Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) and beta-adrenergic blockers may increase blood pressure and result in impaired 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*).

Anesthesia and major operations

If treatment with Dilatrend has to be continued perioperatively, particular caution is required with the use of anesthetic agents that impair myocardial function, such as ether, cyclopropane and trichloroethylene. See *Overdosage* for information on the treatment of bradycardia and hypotension.

PREGNANCY AND LACTATION

Animal studies have shown adverse effects on the fetus (see *Preclinical data*) and no data are available in humans. Dilatrend has been found in the milk of animals. Therefore Dilatrend must not be used during pregnancy or lactation.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Owing to the possible side effects of Dilatrend (e.g. dizziness, tiredness), caution is required when driving a motor vehicle and operating machinery. Particular caution is required at the start of treatment, after dose increases, on changing products or in conjunction with alcohol.

UNDESIRABLE EFFECTS

Hypertension

Dilatrend has been evaluated for safety in hypertensive patients in more than 2193 patients in US trials and in 2976 patients in international trials. Approximately 36% of the total treated population received Dilatrend for at least 6 months. In general, Dilatrend was well tolerated up to daily doses of 50 mg. Most adverse events reported during Dilatrend therapy were of mild to moderate intensity. In the US controlled trials comparing carvedilol monotherapy at doses up to 50 mg (n=1142) with placebo (n=462), 4.9% of Dilatrend patients discontinued treatment vs 5.2% of placebo patients. The commonest reason for discontinuing the study medication was hypotension (1% on Dilatrend vs 0% on placebo). The overall incidence of undesirable effects in the US placebo-controlled trials increased with the Dilatrend dose. This was confirmed for the individual adverse event 'dizziness', the incidence of which increased from 2% to 5% on increasing the daily Dilatrend dose from 6.25 mg to 50 mg.

Table 1 lists the adverse events in US placebo-controlled clinical trials of hypertension that occurred with an incidence of over 1% regardless of causality and were more frequent in drug-treated patients than placebo-treated patients.

Table 1: Adverse events in US placebo-controlled studies on hypertension; incidence ≥1%, regardless of cause – withdrawal rates due to adverse events

	Adverse events		Withdrawal rate	
	Dilatrend **(n=1142) Incidence (%)**	**Placebo (n=462) Incidence (%)**	***Dilatrend*** **(n=1142) Withdrawals (%)**	**Placebo (n=462) Withdrawals (%)**
Infections				
Viral infection	1.8	1.3	-	-
Blood and lymphatic system				
Thrombocytopenia	1.1	0.2	-	-
Metabolism, nutritional disorders				
Hypertriglyceridemia	1.2	0.2	-	-
Nervous system				
Dizziness	6.2	5.4	0.4	1.3
Sleep disturbance	1.6	0.6	-	0.2
Drowsiness	1.8	1.5	-	-
Fatigue	4.3	3.9	0.3	0.2
Cardiovascular system				
Bradycardia	2.1	0.2	0.4	-
Orthostatic hypotension	1.8	-	1.0	-
Limb edema	1.7	1.5	0.1	0.4
Peripheral edema	1.4	0.4	0.2	-
Respiratory tract, thoracic and/or mediastinal disorders				

	Adverse events		Withdrawal rate	
	Dilatrend **(n=1142) Incidence (%)**	**Placebo (n=462) Incidence (%)**	***Dilatrend*** **(n=1142) Withdrawals (%)**	**Placebo (n=462) Withdrawals (%)**
Rhinitis	2.1	1.9	-	-
Pharyngitis	1.5	0.6	-	-
Dyspnea	1.4	0.9	0.4	0.2
Gastrointestinal tract				
Abdominal pain	1.4	1.3	0.1	-
Diarrhea	2.2	1.3	0.1	-
Skin and subcutaneous tissue				
Injury	2.9	2.6	0.1	-
Skeletal muscle, connective tissue, bone				
Back pain	2.3	1.5	0.1	-
Kidneys and urinary tract				
Urinary tract infection	1.8	0.6	-	-

Heart failure

Dilatrend has been evaluated for safety in heart failure in more than 1900 patients worldwide, of whom 1300 participated in the US trial programme. Fifty-four percent of the total treated population received Dilatrend for at least 6 months and 20% received Dilatrend for at least 12 months. The adverse event profile of Dilatrend in heart failure patients was consistent with the pharmacology of the substance and the health status of the patients. In the US trial programme comparing daily Dilatrend doses of up to 100 mg (n=765) with placebo (n=437), 5.4 % of Dilatrend patients discontinued treatment with Dilatrend because of adverse events vs 8.0 % of placebo patients.

Table 2 lists the adverse events in US placebo-controlled trials of chronic heart failure patients that occurred with an incidence of over 2% regardless of causality and were more frequent in drug-treated patients than placebo-treated patients. The study medication (active drug or placebo) was administered to the patients in both the Dilatrend (carvedilol) and placebo groups for a median 6.33 months.

Table 2: Adverse events in US placebo-controlled trials in chronic heart failure (NYHA class II–III); incidence >2%, regardless of causality – withdrawal rates due to adverse events

	Adverse events		Withdrawal rate	
	Dilatrend **(n=765) Incidence (%)**	**Placebo (n=437) Incidence (%)**	***Dilatrend*** **(n=765) Withdrawals (%)**	**Placebo (n=437) Withdrawals (%)**
Infections				
Upper airway infection	18.3	17.6	-	-
Fever	3.1	2.3	-	-

	Adverse events		Withdrawal rate	
	Dilatrend **(n=765) Incidence (%)**	**Placebo (n=437) Incidence (%)**	***Dilatrend*** **(n=765) Withdrawals (%)**	**Placebo (n=437) Withdrawals (%)**
Blood and lymphatic system				
Thrombocytopenia	2.0	0.5	0.1	-
Drug level increased	5.1	3.7	-	0.2
Metabolism, nutritional disorders				
Hyperglycemia	12.2	7.8	0.1	-
Weight gain	9.7	6.9	0.1	0.5
Gout	6.3	6.2	-	-
Blood urea nitrogen (BUN) increased	6.0	4.6	0.3	0.2
Non-protein nitrogen (NPN) increased	5.8	4.6	0.3	0.2
Hypercholesterolemia	4.1	2.5	-	-
Dehydration	2.1	1.6	-	-
Hypervolemia	2.0	0.9	-	-
Nervous system				
Dizziness	32.4	19.2	0.4	-
Headache	8.1	7.1	0.3	-
Pain	8.6	7.6	-	0.2
Fatigue	23.9	22.4	0.7	0.7
Sweating increased	2.9	2.1	-	-
Paresthesia	2.0	1.8	0.1	-
Eyes / visual disturbances				
Visual disturbances	5.0	1.8	0.1	-
Cardiovascular system				
Bradycardia	8.8	0.9	0.8	-
Hypotension	8.5	3.4	0.4	0.2
Syncope	3.4	2.5	0.3	0.2
Hypertension	2.9	2.5	0.1	-
AV block	2.9	0.5	-	-
Generalised edema	5.1	2.5	-	-
Limb edema	3.7	1.8	-	-
Leg edema	2.2	0.2	0.1	0.2
Angina pectoris aggravated	2.0	1.1	-	-
Respiratory tract, thoracic and/or mediastinal disorders				
Sinusitis	5.4	4.3	-	-
Bronchitis	5.4	3.4	-	0.2
Chest pain	14.4	14.2	0.1	-
Pharyngitis	3.1	2.7	-	-
Gastrointestinal tract				
Diarrhea	11.8	5.9	0.3	-
Nausea	8.5	4.8	-	-
Abdominal pain	7.2	7.1	0.3	-
Vomiting	6.3	4.3	0.1	-

	Adverse events		Withdrawal rate	
	Dilatrend **(n=765) Incidence (%)**	**Placebo (n=437) Incidence (%)**	***Dilatrend*** **(n=765) Withdrawals (%)**	**Placebo (n=437) Withdrawals (%)**
Skin and subcutaneous tissue				
Injury	5.9	5.5	-	-
Various infections	2.2	0.9	-	-
Skeletal muscle, connective tissue, bone				
Back pain	6.9	6.6	-	-
Joint pain	6.4	4.8	0.1	0.2
Myalgia	3.4	2.7	-	-
Kidneys and urinary tract				
Urinary tract infection	3.1	2.7	-	-
Hematuria	2.9	2.1	-	-

Table 3: Adverse events in the COPERNICUS multicentre placebo-controlled trial of treatment in severe heart failure (NYHA class IV); incidence >2%, regardless of causality

	Dilatrend **(n=1156) Withdrawals (%)**	**Placebo (n=1133) Withdrawals (%)**
Proportion of patients with at least one adverse event	75.7	75.4
Infections		
Infection	2.5	2.4
Blood and lymphatic system	6.0	4.6
Anemia	2.4	2.0
Endocrine system	2.8	2.2
Diabetes mellitus	2.0	1.7
Metabolism, nutritional disorders	32.1	29.4
Weight gain	11.7	10.7
Peripheral edema	7.0	6.4
Generalised edema	6.0	4.9
Hyperglycemia	4.5	3.3
Gout	3.5	2.7
Hypokalemia	2.5	3.4
Hyperkalemia	3.3	1.9
Creatinine increased	2.9	1.4
Visual disturbances	5.9	4.4
Ocular accommodation disturbances	2.8	2.2
Nervous system	29.9	24.1
Dizziness	24.1	16.8
Headache	4.8	3.0
Asthenia	10.9	9.4

	Dilatrend (n=1156) Withdrawals (%)	Placebo (n=1133) Withdrawals (%)
Cardiovascular system	54.5	53.3
Heart failure	26.0	31.5
Hypotension	13.9	8.2
Chest pain	6.8	7.6
Bradycardia	10.3	2.7
Syncope	7.6	5.0
Angina pectoris	5.5	4.1
Atrial fibrillation	2.2	4.3
Ventricular tachycardia	1.6	3.9
Hypertension	2.6	2.2
Unstable angina pectoris	2.0	2.7
First-degree AV block	2.3	1.6
Peripheral vascular disorder	1.6	2.4
Myocardial infarction	1.6	2.2
Ventricular fibrillation	1.0	2.1
Sudden death	3.9	6.1
Respiratory tract, thoracic and/or mediastinal disorders	34.1	33.7
Upper respiratory infection	13.6	12.6
Dyspnea	11.2	11.0
Bronchitis	5.2	4.5
Cough increased	4.5	4.2
Pulmonary edema	3.5	4.1
Lung disorder	4.0	3.2
Pneumonia	3.2	3.9
Gastrointestinal tract	17.6	17.2
Diarrhea	4.8	3.1
Nausea	3.8	3.3
Abdominal pain	2.2	3.0
Kidneys and urinary tract	8.6	10.0
Kidney function abnormal	2.1	2.3
Urinary tract infection	1.6	2.4
Skin and subcutaneous tissue	7.1	6.9
Accidental injury	1.7	2.0
Skeletal muscle, connective tissue, bone	5.5	5.3
Muscle cramps	2.0	1.2
Limb pain	2.1	2.5
Back pain	2.9	1.4

Table 4: Adverse events from hypertension and angina studies (n=3014 patients) and postmarketing experience

	Frequency [%]
Infections	

	Frequency [%]
Flu-like symptoms and limb pain	1.7
Nervous system	
Headache	7.7
Dizziness	7.4
Asthenia (including fatigue)	5.9
Depressed mood	0.5
Sleep disturbance	0.5
Paresthesia	0.8
Eyes / visual disturbances	
Impaired vision	0.6
Eye irritation	0.3
Reduced lacrimation	0.3
Cardiovascular system	
Orthostatic symptoms	2.6
Hypotension	1.3
Bradycardia	1.1
Angina pectoris	0.8
Syncope (particularly at the start of treatment)	0.6
Peripheral circulatory disturbances (cold extremities and, rarely, peripheral edema)	0.5
AV block	0.1
Respiratory tract, thoracic and/or mediastinal disorders	
Wheeze	1.5
Nasal congestion	0.9
Dry mouth	0.6
Gastrointestinal tract	
Nausea	1.9
Diarrhea	1.1
Abdominal pain	0.9
Constipation	0.4
Vomiting	0.4
Skin and subcutaneous tissue	
Allergic exanthema	0.2
Urticaria	0.1
Pruritus	0.1
Kidneys and urinary tract	
Disturbances of micturition	0.4
Reproductive system and breast	
Impotence	0.2

Laboratory tests

- Liver and biliary tract: isolated cases of increased serum transaminases.
- Blood and lymphatic system: isolated cases of thrombocytopenia and leukopenia.

The following have also been observed

- Exacerbation of symptoms in patients with intermittent claudication or Raynaud's phenomenon.
- Exacerbation of existing heart failure in isolated cases.
- Mild liver damage in rare cases (see *Warnings and Precautions*).
- Lichen planus-like reactions.
- Induction or exacerbation of psoriasis.
- A single case of Stevens-Johnson syndrome.

In patients with a tendency to bronchospastic reactions, respiratory distress and/or asthmatic attacks can occur as a result of a possible increase in airway resistance (see *Warnings and precautions*).

Postmarketing experience

Metabolism, nutritional disorders

Because of the beta-blocking properties the possibility cannot be excluded that latent diabetes mellitus could become manifest or that manifest diabetes could be aggravated or blood glucose counter-regulation inhibited (see *Warnings and precautions*). Hypoglycemia has occasionally been observed.

Skin and subcutaneous tissue disorders

Alopecia

Renal and urinary disorders

There have been isolated reports of urinary incontinence in women that resolved on discontinuing the product.

OVERDOSAGE

Signs and symptoms

Overdose can lead to severe hypotension, bradycardia, heart failure, cardiogenic shock and cardiac arrest. Respiratory symptoms, bronchospasm, vomiting, disturbances of consciousness and generalised convulsions can also occur.

Treatment

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

Patients should be placed in the supine position.

- Atropine: 0.5–2 mg i.v. (for bradycardia)
- Glucagon: initially 1–10 mg i.v., then 2–5 mg/h by slow infusion (to support cardiovascular function)

- Sympathomimetics, depending on body weight and effect: dobutamine, isoprenaline, orciprenaline or adrenaline. If a positive inotropic effect is required, phosphodiesterase (PDE) inhibitors (e.g. milrinone) should be considered. If the clinical picture of intoxication is dominated by peripheral vasodilation, administration of norfenefrine or norepinephrine with continuous monitoring of cardiovascular function is required. Pacemaker therapy should be given for refractory bradycardia. If bronchospasm is present, beta-sympathomimetics (as aerosols or, if the effect is inadequate, i.v.) or aminophylline i.v. should be given. For convulsions, slow i.v. administration of diazepam or clonazepam is recommended.

Warning

In cases of severe intoxication with shock, countermeasures should be continued for a sufficiently long period, as prolongation of elimination half-life and redistribution of Dilatrend from deeper compartments are to be expected.

PROPERTIES AND EFFECTS

ATC code: C07AG02

Mechanism of action and pharmacodynamics

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 beta-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 lipid profile. A normal ratio of high-density lipoproteins to low-density lipoproteins (HDL/LDL) is maintained.

Clinical efficacy

Hypertension

Carvedilol lowers blood pressure in hypertensive patients by a combination of beta-blockade and alpha$_1$-mediated vasodilation. The 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 carotid arteries is not compromised by carvedilol. Cold extremities and early fatigue during physical activity occur rarely. 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-ischemic (improved total exercise time, exercise time to 1 mm ST segment depression and time to angina) and anti-anginal properties that were maintained during long-term treatment. Acute hemodynamic studies have demonstrated that carvedilol significantly decreases myocardial oxygen demand and sympathetic activity. It also decreases ventricular preload (pulmonary artery pressure and pulmonary capillary wedge pressure) and afterload (total peripheral resistance).

Pharmacodynamics and clinical studies in the indication 'Treatment of mild to severe heart failure'

Studies on mild to moderate heart failure

The cause of the beneficial effects of Dilatrend in heart failure has not been elucidated. Two placebo-controlled studies compared the acute hemodynamic effects of Dilatrend with baseline measurements in 59 and 49 patients with NYHA class II–IV heart failure who were receiving diuretics, ACE inhibitors and digitalis. Significant reductions in blood pressure, pulmonary arterial pressure, pulmonary capillary pressure and heart rate were found. Initial effects on cardiac output, stroke volume index and peripheral vascular resistance were slight and variable. The studies reassessed the hemodynamic effects after 12–14 weeks. Dilatrend significantly reduced blood pressure, pulmonary arterial pressure, right atrial pressure, peripheral vascular resistance and heart rate, whereas stroke volume index increased. In 839 patients with NYHA class II–III heart failure treated for 26–52 weeks in the four American placebo-controlled studies, left ventricular ejection fraction as measured by radionuclide ventriculography increased by an average of 8 ejection fraction units in the Dilatrend-treated patients compared to 2 ejection fraction units in the placebo-controlled patients. This effect of the treatment was significant in each of the studies.

An American double-blind placebo-controlled stratified study programme included 1094 patients with NYHA class II–III heart failure and an ejection fraction of ≤0.35 (696 patients randomised to the carvedilol group). Most of the patients had been treated with digitalis, diuretics and ACE inhibitors before the start of the study. The patients were assigned to the individual treatment plans on the basis of their exercise tolerance. A double-blind placebo-controlled study performed in Australia and New Zealand included 415 patients with less severe heart failure (half of the patients randomised to the

carvedilol group). All the protocols excluded patients expected to need a heart transplant during the 6–12-month period of double-blind treatment. All the randomised patients had shown good tolerance of carvedilol during a 2-week period of treatment with 6.25 mg twice daily.

In each study a primary endpoint was either progression of heart failure or exercise tolerance or quality of life (Minnesota Living with Heart Failure Questionnaire). In these studies numerous secondary endpoints were defined, e.g. NYHA class, general well-being as assessed by physician and patient, and cardiovascular-related hospitalisations. Mortality was not a predefined endpoint in any of the studies, but was analysed in all the studies. Other analyses that were not planned in advance were overall death rate and total and cardiovascular-related hospitalisations. Where the primary endpoint of a study showed no significant benefit of treatment, the attribution of significance with respect to the other results is complex and the values concerned must be interpreted with caution.

The results of the American and Australian-New Zealand studies were as follows:

Reduction of progression of heart failure

An American multicentre study with 366 patients had as its primary endpoint total cardiovascular-related mortality, cardiovascular-related hospitalisations and increase in medication for heart failure. Progression of heart failure was reduced by 47% (p=0.008) during a mean follow-up period of 7 months.

In the Australian-New Zealand study, mortality and total hospitalisations fell by 25% over 18–24 months. In the three largest American studies, mortality and total hospitalisations fell by 19%, 39% and 49%, these figures being nominally statistically significant in the latter two studies. The results of the Australian-New Zealand study were borderline in terms of statistical significance.

Functional measures

NYHA class was not a primary endpoint in any, but was a secondary endpoint in all, of the multicentre studies. All the studies identified at least a trend towards an improvement in NYHA class. Exercise tolerance was the primary endpoint in three studies, and in none of these was a significant effect identified.

Subjective measures

Quality of life as assessed by a standardised questionnaire (primary endpoint of one study) was not influenced by carvedilol. Nevertheless, it was shown that general well-being as assessed both by the physician and by the patient improved significantly.

Studies on severe heart failure

In a large multicentre, placebo-controlled, double-blind mortality study (COPERNICUS), 2289 patients with stable severe chronic heart failure of ischemic or non-ischemic origin who received standard therapy were randomly assigned to treatment with either carvedilol (1133 patients) or placebo (1156 patients).

The patients suffered from impaired left ventricular systolic function and had a mean ejection fraction of 19.8% in the placebo group and 19.9% in the carvedilol group.

Mortality regardless of cause was reduced by 35% from 19.7% per patient year in the placebo group to 12.8% per patient year in the carvedilol group (Cox proportional hazards model, p=0.00013). The occurrence of sudden cardiac death was reduced by 41% in the carvedilol group (5.3% vs 8.9%).

Results of the COPERNICUS study:

The combined secondary endpoints 'mortality or hospitalisation due to heart failure', 'mortality or hospitalisation due to cardiovascular disease' and 'mortality or hospitalisation regardless of cause' were all significantly lower in the carvedilol group than in the placebo group (reduction by 31%, 27% and 24% respectively per patient year, p<0.00004 in all cases).

The incidence of severe adverse events during the study was lower in the carvedilol group (39.0% vs 45.4%). During the first 90 days the incidence of deterioration of heart failure was similar in the carvedilol and placebo groups (15.4% vs 14.8%). The incidence of serious deterioration of heart failure during the study was lower in the carvedilol group (14.6% vs 21.6%).

PHARMACOKINETICS

Absorption

Dilatrend is rapidly absorbed following oral administration. Carvedilol is a substrate of the intestinal efflux transporter P-glycoprotein, which plays a major role in the bioavailability of certain drugs.
The maximum plasma concentration is reached after approximately 1–2 hours. There is pronounced first-pass metabolism, and absolute bioavailability is approximately 25% (12–49%). The first-pass extraction is stereospecific, the bioavailability of the R-enantiomer ($alpha_1$-blocking activity) being approximately 2.5 times higher than that of the S-enantiomer (beta- and $alpha_1$-blocking activity).

Simultaneous food intake does not influence bioavailability, however the t_{max} is delayed.

Dilatrend is highly lipophilic.

When used as directed, Dilatrend is unlikely to accumulate during long-term treatment.

Distribution

Steady-state volume of distribution (VD_{ss}) is approximately 2 l/kg. Dilatrend is 98% bound to plasma proteins.

Metabolism

In all animal species studied and also in humans, Dilatrend is almost completely broken down in the liver by oxidation and conjugation to a variety of metabolites.

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 extent by CYP2D6. Other CYP450 isoenzymes involved in the metabolism of carvedilol include CYP3A4, CYP2E1 and CYP2C19.

The peak plasma concentration of R-carvedilol is approximately twice that of S-carvedilol.

The R-enantiomer is predominantly metabolised by hydroxylation.

In poor metabolisers of CYP2D6 (sparteine/debrisoquine-type) there may be an increase in the plasma concentration of carvedilol, mainly the R-enantiomer, leading to an increase in alpha-blocking activity.

Demethylation and hydroxylation at the phenol ring result in the formation of three active metabolites with beta-blocking activity. In animals, the 4'-hydroxyphenol metabolite is approximately 13 times more potent than Dilatrend in terms of beta-blockade. Compared to Dilatrend, the three principal metabolites exhibit weak vasodilating activity. Plasma levels (C_{max}) of the active metabolites after 1 hour were as follows: M_2 3.9 ng/ml, M_4 4.1 ng/ml, M_5 3.3 ng/ml (approximately 20% those of carvedilol: C_{max} 49 ng/ml).

In addition, two hydroxycarbazole metabolites are very potent antioxidants, having a 30–80 times greater activity in this respect than Dilatrend.

Elimination

The half-life of Dilatrend after oral administration is approximately 6–10 hours. Plasma clearance is 590 ml/min. Elimination is predominantly biliary and via the feces. Less than 2% of unaltered substance is eliminated via the urine, approximately 15% in the form of metabolites.

Pharmacokinetics in special patient populations

Patients with renal impairment

Glomerular filtration and autoregulation of renal perfusion are unaffected during chronic treatment with carvedilol.

No significant changes in elimination half-life or maximum plasma concentration are observed in hypertensive patients with renal insufficiency. However, the AUC is increased by 40–50% in patients with renal impairment. Renal excretion of the parent substance is decreased in patients with renal insufficiency; however, change in pharmacokinetic parameters is 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 dialysis or after renal transplantation. After oral administration of 10 mg Dilatrend, plasma concentration reached a maximum after 1–5 hours both on dialysis days and on ‘dialysis-free’ days. After 24 hours the substance could no longer be detected in plasma.

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, possibly due to its high plasma protein binding.

Data from comparative studies in hemodialysis patients show that carvedilol is more effective than diltiazem in silent ischemia.

Patients with hepatic impairment

In patients with cirrhosis of the liver, the systemic availability of the drug 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 failure (see *Contraindications*).

Heart failure patients

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 suggest that the pharmacokinetics of R- and S-carvedilol are significantly altered by heart failure.

Elderly patients

The pharmacokinetics of Dilatrend are affected by patient age. Plasma levels of Dilatrend are approximately 50% higher in older than in younger patients. The C_{max} and AUC may be elevated in elderly patients. In such cases the dose should be adjusted.

Children and adolescents

Only limited data are available on pharmacokinetics in patients under 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, glycosylated hemoglobin 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 induced a modest improvement in insulin sensitivity. The same results were found in hypertensive patients with non-insulin dependent diabetes.

PRECLINICAL DATA

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.

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 (≥200

mg/kg, ≥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 the growth/development of offspring. Embryotoxicity (increased post-implantation deaths) was observed, but no malformations, in rabbits and rats at doses of 75 mg/kg and 200 mg/kg, respectively (38 to 100 times MRHD).

ADDITIONAL INFORMATION

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the pack.

Special precautions for storage

Do not store above 30°C. Store in the original pack to protect the contents from light.

Any medicinal product remaining unused after the end of treatment or by the expiry date should be properly disposed of.

PACKS

Scored tablets 6.25 mg	30
Scored tablets 12.5 mg	30
Scored tablets 25 mg	30

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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