PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

DILATREND® 6,25 mg tablet

DILATREND® 12,5 mg tablet

DILATREND® tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Each DILATREND tablet contains 25 mg carvedilol.

DILATREND tablets contain sugar (sucrose and lactose) – (see section 4.4).

Excipients with known effect

This medicinal product contains sugar (sucrose and lactose) – (see section 4.4).

Each DILATREND 6,25 mg tablet contains 51,8 mg lactose monohydrate and 21,25 mg sucrose.

Each DILATREND 12,5 mg tablet contains 59,1 mg lactose monohydrate and 12,5 mg sucrose.

Each DILATREND tablet contains 10 mg lactose monohydrate and 25 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

DILATREND 6,25 mg tablets are yellow, round tablet with a bilateral score line and coded BM on one side and F1 on the other side.

DILATREND 12,5 mg tablets are light brown, round tablet with a bilateral score line and coded BM on one side and H3 on the other side.

DILATREND Tablets are off-white to yellowish pale-beige, round biconvex tablet, with a bilateral score line and coded BM on one side and D5 on the other side.

The tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Essential hypertension

DILATREND is indicated for treatment of mild to moderate essential hypertension.

Symptomatic congestive heart failure (CHF)

DILATREND is indicated for the treatment of mild, moderate, and severe stable, symptomatic heart failure of ischaemic or cardiomyopathic origin. DILATREND may be used

as adjunct to standard therapy. DILATREND has been used in patients unable to tolerate an ACE-inhibitor and patients who are, or are not, taking digoxin.

Left ventricular dysfunction following uncomplicated acute myocardial infarction

DILATREND is indicated for long term treatment following otherwise uncomplicated myocardial infarction, but with left ventricular dysfunction (left ventricular ejection fraction (LVEF) ≤ 40 % or wall motion index ≤ 1,3), in combination with ACE-inhibitors and other treatments recommended in the management of patients after myocardial infarction.

4.2. Posology and method of administration

Posology

Essential hypertension

Adults

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. Combination with a diuretic may also give the desired response.

Elderly

The recommended dose for initiation of therapy is 12,5 mg once daily, which has provided satisfactory control in some patients. If the response is inadequate, the dose may be titrated at intervals of at least two weeks up to the recommended daily dose of 25 mg once a day or in divided doses.

At doses higher than 25 mg the incidence of side effects increases significantly with only a marginal increase in efficacy.

Symptomatic congestive heart failure

Dosage must be individualised and closely monitored by a medical practitioner experienced in the management of heart failure, during up-titration. For those patients receiving digoxin, 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 (half a 6,25 mg tablet) twice daily for at least 2 weeks. If this dose is tolerated, the dosage may subsequently be increased, at intervals of not less than two weeks, to 6,25 mg twice daily, followed by 12,5 mg twice daily and thereafter 25 mg twice daily. Dosing should be increased to the highest level tolerated by the patient.

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

Before each dose increase, the patient should be evaluated by the medical practitioner for symptoms of worsening heart failure or vasodilation. Transient worsening of heart failure or fluid retention should be treated with increased doses of diuretics, although occasionally it may be necessary to lower the dose of DILATREND or temporarily discontinue DILATREND treatment.

If DILATREND treatment is discontinued for more than two weeks, therapy should be recommenced at 3,125 mg (half a 6,25 mg tablet) twice daily and up-titrated in line with the above dosing recommendation.

Symptoms of vasodilation such as postural hypotension, headache and dizziness 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 DILATREND 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 otherwise uncomplicated acute myocardial infarction

Dosage must be individualised and closely monitored by a medical practitioner 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 section 4.4).

Subsequent doses of DILATREND: If the patient has tolerated the first dose (i.e. heart rate > 50 beats/minute, systolic blood pressure > 80 mmHg, measured with the patient seated, 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 (half a 6,25 mg tablet) twice daily if the patient develops signs of intolerance during this period, in particular bradycardia < 50 beats/minute, systolic blood pressure < 80 mmHg, measured with the patient seated, 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 Populations

Renal impairment

Available pharmacokinetic data (see section 5.2) 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 section 4.3).

Diabetic Patients

DILATREND may increase insulin resistance and mask hypoglycaemic symptoms and decrease the body's response to hypoglycaemia.

Elderly

There is no evidence to support dose adjustment (see section 4.4).

Paediatric population

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

Method of Administration

The tablets are to be swallowed with sufficient fluid.

In hypertensive patients it is not necessary to time the dose in relation to meals.

Duration of Treatment

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

4.3. Contraindications

DILATREND must not be used in patients with:

- Hypersensitivity to carvedilol or any component of the product.
- Severe heart disease.
- 2nd and 3rd degree atrioventricular (AV) block.
- Sick sinus syndrome (including sino-atrial block).
- Cardiogenic shock.
- Severe bradycardia (< 50 bpm).
- Asthma.
- Chronic obstructive pulmonary disease (COPD) with a bronchospastic component.
- Clinically manifest liver dysfunction.
- Safety in children has not been established.

- Severe hypotension (systolic blood pressure < 85 mmHg).

4.4. Special warnings and precautions for use

General

DILATREND should not be given to patients with bronchospasm or obstructive airways disease, allergic conditions involving the airways (e.g. allergic rhinitis, glottis oedema), metabolic acidosis, sinus bradycardia, or partial heart block. It should be given to patients with congestive heart failure only after having achieved adequate clinical control, and then only with great caution.

Patients with phaeochromocytoma should first be adequately controlled by α-blockade before initiating therapy with DILATREND. It should be used with caution in patients with renal impairment.

Chronic congestive heart failure

In congestive heart failure patients, worsening cardiac effects or fluid retention may occur during up-titration of DILATREND. If such symptoms occur, the dose of diuretics should be increased and the DILATREND dose should not be further increased until clinical stability resumes, or it may be necessary to lower the DILATREND dose or temporarily discontinue it. Such episodes do not preclude subsequent successful up-titration of DILATREND. In patients who have congestive heart failure controlled with digoxin, diuretics and/or an ACE-inhibitor, DILATREND should be used with caution as both digoxin and DILATREND slow AV conduction (see section 4.3).

Left ventricular dysfunction following uncomplicated 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 section 4.2).

Renal function in congestive heart failure (CHF)

Patients with renal insufficiency require no dosage adjustment since DILATREND is cleared mainly by the liver. Reversible deterioration of renal function has been observed with DILATREND therapy in CHF patients with low blood pressure (systolic < 100 mmHg), ischaemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency. In CHF patients with these risk factors, renal function should be monitored during up-titration of DILATREND and the medicine discontinued or dosage reduced if worsening of renal function occurs.

Bradycardia

DILATREND may induce bradycardia. If the pulse rate drops to less than 55 beats/min, the dosage must be reduced.

Prinzmetal's variant angina

DILATREND may provoke chest pain in patients with Prinzmetal's variant angina. However, there is no clinical experience with DILATREND in these patients, and caution should be exercised in the administration of DILATREND to patients suspected of having Prinzmetal's variant angina.

Chronic obstructive pulmonary disease (COPD)

DILATREND should not be used in patients with COPD with a bronchospastic component (see section 4.3). Patients with COPD should be closely monitored during initiation and up-titration of DILATREND and DILATREND should be discontinued if any evidence of bronchospasm is observed during treatment.

Diabetes

Care should be taken in the administration of carvedilol to patients with diabetes mellitus, as it may be associated with worsening control of blood glucose. Furthermore, the early signs and symptoms of acute hypoglycaemia may be masked or attenuated. In general, β-blockers may increase insulin resistance and mask hypoglycaemic symptoms.

Peripheral vascular disease and Raynaud's phenomenon

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

Thyrotoxicosis

It is to be expected that DILATREND may mask the symptoms of thyrotoxicosis.

Phaeochromocytoma

In patients with phaeochromocytoma, an α-blocking agent should be initiated prior to the use of DILATREND.

Hypersensitivity

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

Risk of Anaphylactic Reaction

While taking β-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of adrenaline used to treat allergic reaction.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported during treatment with DILATREND (see section 4.8). DILATREND should be permanently discontinued in patients who experience severe cutaneous adverse reactions possibly attributable to DILATREND.

Psoriasis

Patients with a history of psoriasis associated with β-blocker therapy should take DILATREND only after consideration of the risk-benefit ratio.

Interactions with other medicinal products

There are a number of important pharmacokinetic and pharmacodynamic interactions with other medicines (e.g. digoxin, ciclosporin, rifampicin, anaesthetic medicines, antiarrhythmic medicines) (see section 4.5).

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 in these patients should be over the course of one to two weeks.

Anaesthesia and major surgery

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

Vagal influences

The patient can be protected against vagal influences by the intravenous administration of 1 - 2 mg atropine. In case of severe postural hypotension DILATREND should be discontinued in these patients.

Excipients with known effect

DILATREND contains lactose, therefore patients with rare hereditary problems of galactose intolerance, e.g. galactosaemia, lactase deficiency, or glucose-galactose malabsorption should not take DILATREND.

DILATREND contains sucrose, therefore patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take DILATREND.

Elderly population

Studies in the elderly patients showed that there was no difference in the adverse event profile as compared to younger patients. Therefore, no starting dose adjustment is required in elderly patients (see section 4.2).

Renal impairment

The autoregulatory renal blood supply is preserved and the glomerular filtration is unchanged during chronic treatment with carvedilol. In patients with moderate to severe renal insufficiency, no changes in carvedilol dosage recommendations are warranted (see section 4.2).

Hepatic impairment

Carvedilol is contraindicated in patients with clinically manifest liver dysfunction (see section 4.3). A pharmacokinetic study in cirrhotic patients has shown that exposure (AUC) to DILATREND was increased by 6,8-fold in patients with liver impairment as compared to healthy subjects.

4.5. Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

DILATREND may potentiate the effect of other concomitantly administered medicines that are antihypertensive in action or have hypotension as part of their adverse effect profile.

Effects of DILATREND on the pharmacokinetics of other medicines

DILATREND is a substrate as well as an inhibitor of P-glycoprotein. Therefore, the bioavailability of medicines transported by P-glycoprotein may be increased with concomitant administration of DILATREND. In addition, the bioavailability of DILATREND can be modified by inducers or inhibitors of P-glycoprotein.

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

Cimetidine: Concomitant therapy with cimetidine may result in increased systemic bioavailability (about 30 %) but causes no change in C_{max} of carvedilol.

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

this isoenzyme. Both DILATREND and phenothiazines can cause hypotension, and these effects could be additive.

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

Furthermore, there is evidence that CYP3A4 is involved in the metabolism of carvedilol. As tacrolimus is a substrate of P-glycoprotein and CYP3A4, its pharmacokinetics may also be affected by carvedilol through these interaction mechanisms.

Effects of other medicines on the pharmacokinetics of DILATREND

Inhibitors as well as inducers of CYP2D6 and CYP2C9 can modify the systemic and/or pre-systemic metabolism of DILATREND stereo-selectively, leading to increased or decreased plasma concentrations of *R*- and *S*-carvedilol (see section 5.2). Some examples observed in patients or in healthy subjects are listed below but the list is not exhaustive.

Rifampicin: In a study in 12 healthy subjects, exposure to DILATREND decreased by around 60 % during concomitant administration with rifampicin and a decreased effect of

DILATREND on the systolic blood pressure was observed. The mechanism for the interaction is not known but it may be due to the induction of the intestinal P-glycoprotein by rifampicin. A close monitoring of the β-blockade activity in patients receiving concomitant administration of DILATREND and rifampicin is appropriate.

Amiodarone: An in vitro study with human liver microsomes has shown that amiodarone and desethylamiodarone inhibited the oxidation of *R*- and *S*-carvedilol. The trough concentration of *R*- and *S*-carvedilol was significantly increased by 2,2-fold in heart failure patients receiving DILATREND and amiodarone concomitantly as compared to patients receiving DILATREND monotherapy. The effect on *S*-carvedilol was attributed to desethylamiodarone, a metabolite of amiodarone, which is a strong inhibitor of CYP2C9. A monitoring of β-blockade activity in patients treated with the combination DILATREND and amiodarone is advised.

Fluoxetine and Paroxetine: In a randomised cross-over study in 10 patients with heart failure, co-administration of fluoxetine, a strong inhibitor of CYP2D6, resulted in stereo-selective inhibition of DILATREND metabolism with a 77 % increase in mean *R*-enantiomer AUC, and a non-statistically significant 35 % increase of the *S*-enantiomer's AUC as compared to the placebo group. However, no differences in adverse events, blood pressure or heart rate were noted between treatment groups. The effect of a single dose paroxetine, a strong CYP2D6 inhibitor, on DILATREND pharmacokinetics was investigated in 12 healthy subjects following single oral administration. Despite significant increase in *R*- and *S*-carvedilol exposure, no clinical effects were observed in these healthy subjects.

Alcohol: Alcohol intake is shown to have acute hypotensive effects which may augment the blood pressure reduction caused by carvedilol. As carvedilol is soluble in ethanol, the

presence of alcohol could affect the rate and/or extent of intestinal absorption of carvedilol. Also, carvedilol is partly metabolized by CYP2E1, an enzyme known to be induced and inhibited by alcohol.

Grapefruit juice: Consumption of a single dose of 300 ml grapefruit juice was shown to result in a 1.2-fold increase of the AUC of carvedilol in comparison to water. While the clinical relevance of this observation is unclear, it is advisable that patients should avoid concomitant intake of grapefruit juice at least until a stable dose-response relationship is established.

Hydralazine may increase the plasma concentration of DILATREND because it is metabolised in the liver.

Pharmacodynamic interactions

Insulin or oral hypoglycaemics: The effects of insulin or oral hypoglycaemics may be enhanced. The signs of hypoglycaemia may be masked or attenuated (especially tachycardia). In patients taking insulin or oral hypoglycaemics, regular monitoring of blood glucose is therefore recommended (see section 4.4).

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.

Digoxin: The combined use of β-blockers and digoxin may result in additive prolongation of atrioventricular (AV) conduction time (see section 4.4).

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

Non-dihydropyridine calcium channel blockers, amiodarone or other antiarrhythmics: In combination with DILATREND can increase the risk of AV conduction disturbances. Cases of conduction disturbance (some with haemodynamic compromise) have been observed when DILATREND is co-administered with diltiazem. If DILATREND is to be administered orally with non-dihydropyridine calcium channel blockers of the verapamil or diltiazem type, amiodarone or other antiarrhythmics, it is recommended that ECG and blood pressure be monitored.

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

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 section 4.4). DILATREND should be discontinued 48 hours prior to anaesthesia.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): The concurrent use of NSAIDs and DILATREND may result in an increase in blood pressure and impairment of blood pressure control.

β-agonist bronchodilators: DILATREND opposes the bronchodilator effects of β-agonist bronchodilators. Careful monitoring of patients is recommended.

4.6. Fertility, pregnancy and lactation

Pregnancy

There is no adequate clinical experience with DILATREND in pregnant women. DILATREND should not be used in pregnant women.

β-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 DILATREND has any teratogenic effects.

Breastfeeding

DILATREND and/or its metabolites are excreted in breast milk; breastfeeding is therefore not recommended during administration of DILATREND.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and to use machines have been performed. DILATREND might have minor influence on these abilities. Patients taking DILATREND should be warned not to drive or operate machinery if they experience dizziness or related symptoms. This applies particularly when starting or changing treatment and in conjunction with alcohol.

4.8. Undesirable effects

a. Summary of the safety profile: No text

b. Tabulated summary of adverse reactions

Adverse Drug Reactions (ADRs) are listed according to MedDRA system organ class and CIOMS frequency category:

Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000); unknown (frequency cannot be established from the available data).

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

Table 1 Adverse Drug Reactions in Clinical Trials		
System Organ Class	**Adverse Reaction**	**Frequency**

Blood and lymphatic system disorders	Anaemia	Common
	Thrombocytopenia	Rare
	Leukopenia	Very rare
Cardiac disorders	Cardiac failure	Very common
	Bradycardia	Common
	Hypervolaemia (fluid overload)	Common
	Atrioventricular block	Uncommon
	Angina pectoris	Uncommon
Eye disorders	Visual impairment	Common
	Decreased lacrimation (dry eye)	Common
	Eye irritation	Common
Gastrointestinal disorders	Nausea	Common
	Diarrhoea	Common
	Vomiting	Common
	Dyspepsia	Common
	Abdominal pain	Common
	Constipation	Uncommon
	Dry mouth	Rare
General disorders and administration site conditions	Asthenia (fatigue)	Very common
	Oedema	Common
	Pain	Common
Hepatobiliary disorders	Increased alanine aminotransferase (ALT), aspartate aminotransferase	Very rare

	(AST) and gamma-glutamyltransferase (GGT)	
Immune system disorders	Hypersensitivity (allergic reactions)	Very rare
Infections and Infestations	Pneumonia	Common
	Bronchitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
Metabolism and nutrition disorders	Increased weight	Common
	Hypercholesterolaemia	Common
	Impaired blood glucose control (hyperglycaemia, hypoglycaemia) in patients with pre-existing diabetes	Common
Musculoskeletal and connective tissue disorders	Pain in extremities	Common
Nervous system disorders	Dizziness	Very common
	Headache	Very common
	Syncope, presyncope	Common
	Paraesthesia	Uncommon
Psychiatric disorders	Depression, depressed mood	Common
	Sleep disorders	Uncommon
Renal and urinary disorders	Renal failure and renal function abnormalities in patients with diffuse vascular	Common

	disease and/or underlying renal insufficiency	
	Micturition disorders	Rare
Reproductive system and breast disorders	Erectile dysfunction	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Common
	Pulmonary oedema	Common
	Asthma in predisposed patients	Common
	Wheezing in patients with asthma and COPD	Common
	Nasal congestion	Rare
Skin and subcutaneous disorders	Skin reactions (e.g. allergic exanthema, dermatitis, urticaria, pruritus, psoriatic and lichen planus like skin lesions)	Uncommon
Vascular disorders	Hypotension	Very common
	Orthostatic hypotension	Common
	Disturbances of peripheral circulation (cold extremities, peripheral vascular disease, exacerbation of intermittent claudication and Raynaud's phenomenon)	Common
	Hypertension	Common

c. Description of selected adverse reactions

The frequency of adverse reactions is not dose-dependent, with the exception of dizziness, abnormal vision and bradycardia. Dizziness, syncope, headache and asthenia are usually mild and are more likely to occur at the beginning of treatment.

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

Cardiac failure was a very commonly reported adverse event in patients with left ventricular dysfunction following acute myocardial infarction.

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

Post-Marketing

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

Cardiac disorders: Sinus arrest in predisposed patients (e.g. elderly patients or patients with pre-existing bradycardia, sinus node dysfunction or atrioventricular block).

Metabolism and nutrition disorders: 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.

Psychiatric disorders: Hallucination.

Renal and urinary disorders: Cases of urinary incontinence in women, which may resolve upon discontinuation of the medication, have been reported.

Skin and subcutaneous tissue disorders: Alopecia.

Severe cutaneous adverse reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome) (see section 4.4).

Hyperhidrosis.

Reporting of suspected adverse reactions

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

4.9. Overdose

Symptoms and signs of overdose

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

Treatment of overdose

Patients should be monitored for the above-mentioned signs and symptoms and managed according to the best judgment of the treating medical practitioners and according to standard practice for patients with β-blocker overdose (e.g. atropine, transvenous pacing, glucagon, phosphodiesterase inhibitor such as amrinone or milrinone, β-sympathomimetics).

Important Note

In the event of severe intoxication where there are symptoms of shock, treatment with antidotes must be continued for a sufficiently long period of time since a prolonged elimination half-life of DILATREND from deeper compartments can be expected. The duration of the supportive therapy depends on the severity of the overdose. The supportive treatment should therefore be continued until the patient's condition has stabilised.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological classification: A 7.1.3 Other – hypotensives

Pharmacotherapeutic group: Alpha (α) and Beta (β) adrenergic receptor blocking agents, ATC code: C07AG02

Mechanism of action

Carvedilol, a racemic mixture of two enantiomers (*R*- and *S*-carvedilol), is a multiple action α- and β-adrenergic receptor blocker. The β-adrenergic receptor blockade is associated with

the *S*-enantiomer and non-selective for β1- and β2-adrenoceptors, while both enantiomers have the same blocking properties specific for α1-adrenergic receptors. At higher concentrations, carvedilol also has a weak to moderate calcium-channel blocking activity. It has no intrinsic sympathomimetic activity and it has membrane-stabilising properties.

Pharmacodynamic effects

Carvedilol reduces peripheral vascular resistance via its selective blockade of α1-adrenorceptors. Furthermore, its calcium-channel blocking activity may increase blood flow in specific vascular beds such as the cutaneous circulation. Through its β-blocking action, carvedilol suppresses the renin-angiotensin-aldosterone system, thereby reducing the release of renin and making fluid retention rare. It attenuates the increase in blood pressure induced by phenylephrine, an α1-adrenoceptor agonist, but not that induced by angiotensin II. It has potent antioxidant properties associated with both enantiomers, and is a scavenger of reactive oxygen radicals. Carvedilol has no adverse effect on the lipid profile.

5.2. Pharmacokinetic properties

Absorption

Following oral administration of a 25 mg capsule to healthy subjects, carvedilol is rapidly absorbed with a peak plasma concentration C_{max} of 21 µg/L reached after approximately 1,5 hours (t_{max}). The C_{max} values are linearly related to the dose. Following oral administration, carvedilol undergoes extensive first pass metabolism that results in an absolute availability of about 25 % in healthy male subjects. Carvedilol is a racemate and the *S*-enantiomer appears to be metabolised more rapidly than the *R*-enantiomer, showing an absolute oral availability of 15 % compared to 31 % for the *R*-enantiomer. The maximal plasma concentration of *R*-carvedilol is approximately 2-fold higher than that of *S*-carvedilol.

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

Eating a meal does not influence carvedilol bioavailability. The time to reach maximum serum concentration is delayed by eating a meal.

Carvedilol is an antihypertensive agent with vasodilating and non-selective β-blocking properties in the same dose range. In vitro and in vivo animal studies have indicated that carvedilol is a competitive, non-selective antagonist of both β1- and β2-adrenoreceptors.

Distribution

Carvedilol is a highly lipophilic compound, showing a plasma protein binding of around 95 %. The distribution volume ranges between 1,5 and 2 L/kg.

Metabolism

In humans, carvedilol is extensively metabolised in the liver via oxidation and conjugation into a variety of metabolites that are eliminated mainly in the bile.

Demethylation and hydroxylation at the phenol ring produce 3 metabolites with β-adrenergic receptor blocking activity. Based on pre-clinical studies, the 4'-hydroxyphenol 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.

Pharmacokinetic studies in humans have shown that the oxidative metabolism of carvedilol is stereo-selective. The results of an in vitro study suggested that different cytochrome P450 isoenzymes may be involved in the oxidation and hydroxylation processes including CYP2D6, CYP3A4, CYP2E1, CYP2C9 as well as CYP1A2. Studies in healthy volunteers and in patients have shown that the R-enantiomer is predominantly metabolised by CYP2D6. The S-enantiomer is mainly metabolised by CYP2D6 and CYP2C9.

Genetic polymorphism

The results of clinical pharmacokinetic studies in human subjects have shown that CYP2D6 plays a major role in the metabolism of *R*- and of *S*-carvedilol. As a consequence, plasma concentrations of *R*- and *S*-carvedilol are increased in CYP2D6 slow metabolisers. However, CYP2D6 genetic polymorphism may be of limited clinical significance.

Elimination

Following a single oral administration of 50 mg carvedilol, around 60 % is secreted into the bile and eliminated with the faeces in the form of metabolites within 11 days. Following a single oral dose, only about 16 % is excreted into the urine in form of carvedilol or its metabolites. The urinary excretion of unaltered carvedilol represents less than 2 %. After intravenous infusion of 12,5 mg to healthy volunteers, the plasma clearance of carvedilol reaches around 600 mL/min and the elimination half-life around 2,5 hours. The elimination half-life of a 50 mg capsule observed in the same individuals was 6,5 hours corresponding to the absorption half-life from the capsule. Following oral administration, the total body clearance of the *S*-carvedilol is approximately two times larger than that of the *R*-carvedilol.

Pharmacokinetics in special populations

Renal impairment

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

Hepatic impairment

In patients with cirrhosis of the liver, the systemic availability of the medicine is increased by up to 80 % because of reduction in the first-pass effect (see section 4.3).

Heart failure

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

Elderly

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

Paediatric population

The weight-adjusted clearance in children and adolescents was shown to be significantly larger than in adults.

5.3. Preclinical safety data

Carcinogenicity

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

Mutagenicity

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

Impairment of fertility

Administration of carvedilol to adult female rats at toxic doses (≥ 200 mg/kg, ≥ 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 75 mg/kg and 200 mg/kg, respectively (38 to 100 times MRHD).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

DILATREND 6,25 mg tablet: Lactose monohydrate (51,8 mg), sucrose (21,25 mg), povidone, crospovidone, colloidal anhydrous silica, magnesium stearate, yellow iron oxide (E172).

DILATREND 12,5 mg tablet: Lactose monohydrate (59,1 mg), sucrose (12,5 mg), povidone, crospovidone, colloidal anhydrous silica, magnesium stearate, yellow iron oxide (E172), red iron oxide (E172).

DILATREND 25 mg tablet: Lactose monohydrate (10 mg), sucrose (25 mg), povidone, colloidal anhydrous silica, crospovidone, magnesium stearate.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

DILATREND 6,25 mg tablets: 36 months

DILATREND 12,5 mg tablets: 48 months

DILATREND tablets: 60 months

6.4. Special precautions for storage

Store at or below 30 °C in the original package to protect from light.

Keep out of reach of children.

6.5. Nature and contents of container

The tablets are packaged in blister packs.

Available in packs containing 10, 30 or 100 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharmaco Distribution (Pty) Ltd.

3 Sandown Valley Crescent

South Tower, First Floor

Sandton 2196, Gauteng

South Africa

Ethical assistance Line: +27 (0)11 784 0077

8. REGISTRATION NUMBER(S)

DILATREND 6,25 mg: 31/7.1.3/0198

DILATREND 12,5 mg: 31/7.1.3/0199

DILATREND tablet: X/7.1.3/246

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6,25 mg – Sep 1997; 12,5 mg – Jan 1998; 25 mg – Oct 1991

10. DATE OF REVISION OF THE TEXT

30 June 2026