SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DILATREND 25 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Carvedilol 25 mg

Excipients:

Lactose (produced from cow's milk) 10 mg

Sucrose 25 mg

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Tablets

White to pale yellowish-beige round tablet with notches on 2 sides.

4. CLINICAL PROPERTIES

4.1. Therapeutic indications

Hypertension

Carvedilol is indicated for the treatment of essential hypertension. It can be used alone or in combination with other antihypertensive agents (calcium channel blockers and diuretics; especially thiazide diuretics).

Coronary heart disease

Used for the prophylactic treatment of stable angina.

Chronic heart failure

Carvedilol is indicated for the treatment of stable, mild, moderate and severe chronic heart failure. It is usually used in combination with Angiotensin Converting Enzyme (ACE) inhibitors, diuretics and optionally with digitalis (standard therapy).

4.2. Posology and method of administration

Posology/frequency and duration of administration:

Carvedilol treatment is a long-term therapy.

Treatment should not be discontinued abruptly and when it is discontinued, it should be gradually tapered over a period of weeks. This is particularly important for patients who also have coronary artery disease.

Unless otherwise recommended by a doctor;

Essential hypertension:

The recommended dose for the first 2 days at the beginning of treatment is 12.5 mg once daily. Thereafter, the recommended dose is 25 mg once daily. If necessary, the dose may be increased at intervals of at least 2 weeks to a maximum daily dose of 50 mg once daily or divided in half.

Coronary heart disease:

At the beginning of treatment, the recommended dose is 12.5 mg twice daily for the first 2 days. Thereafter, the recommended dose is 25 mg twice daily. If necessary, the dose may be increased at intervals of at least 2 weeks to a maximum daily dose of 100 mg (twice daily).

Symptomatic, stable, chronic heart failure:

Dosage should be adjusted individually and closely monitored by a physician during dose escalation. In patients taking digitalis, diuretics and Angiotensin Converting Enzyme (ACE) inhibitors, the doses of these medicines should be stabilized before starting carvedilol treatment.

The recommended dose at the start of treatment is 3.125 mg twice daily for 2 weeks. If this dose is tolerated, the dose may be increased at intervals of at least two weeks, first to 6.25 mg twice daily, then to 12.5 mg twice daily and then to 25 mg twice daily. The dose should be increased to the maximum tolerated by the patient.

The maximum recommended dose in patients under 85 kilograms with mild, moderate or severe chronic heart failure is 25 mg twice daily. In patients over 85 kilograms with mild or moderate heart failure, the maximum recommended dose is 50 mg twice daily.

Before each dose increase, the patient should be evaluated by a physician for symptoms of worsening heart failure or vasodilation. Transient worsening of heart failure or fluid retention should be treated by increasing the diuretic dose; rarely it may be necessary to reduce the dose of carvedilol or temporarily stop carvedilol treatment. If carvedilol treatment has been interrupted for more than one week, it is recommended to start treatment with a lower dose twice daily and increase the dose as described above. If carvedilol treatment has been interrupted for more than two weeks, it is recommended to start treatment with 3.125 mg twice daily and increase the dose as described above.

Initially, the dose of diuretics should be reduced in the treatment of vasodilatation symptoms.

If symptoms persist, the dose of ACE inhibitor (if used) may be reduced, followed by a reduction in the dose of carvedilol if necessary. Under these circumstances, the dose of carvedilol should not be increased until the symptoms of worsening heart failure or vasodilatation have stabilized.

Method of administration:

The tablet should be taken with water. In patients with chronic heart failure, DILATREND should be given with food.

Additional information on special populations:

Renal impairment:

According to available pharmacokinetic data on patients with varying degrees of renal dysfunction (including renal impairment), no change in the carvedilol dosing schedule is recommended in patients with moderate to severe renal impairment.

Hepatic impairment:

Carvedilol is contraindicated in patients with clinically evident liver dysfunction.

Pediatric population:

Safety and efficacy in children (<18 years) have not been evaluated.

Geriatric population:

Symptomatic chronic heart failure: no special use required.

Hypertension: An initial dose of 12.5mg daily is recommended. This provides satisfactory control in some cases. If response is inadequate, the dose may be increased to a maximum of 50 mg once daily or daily in divided doses.

Angina: The maximum recommended daily dose is 50 mg given in divided doses.

4.3. Contraindications

Carvedilol should not be used in the following patients:

- Hypersensitivity to carvedilol or other excipients contained in the medicine
- Unstable/decompensated heart failure
- Clinically significant liver dysfunction,
- Patients with significant fluid retention

As with other β- blockers, carvedilol should not be used in patients with:

- 2nd and 3rd degree AV block (unless a permanent pacemaker is implanted)
- Severe bradycardia (<50 beats/minute),
- Sick sinus syndrome (including sino-atrial block)
- Severe hypotension (systolic blood pressure <85 mmHg),
- Cardiogenic shock,
- Patients with a history of bronchospasm or asthma
- Metabolic acidosis

4.4. Special warnings and precautions for use

DILATREND contains lactose. Patients with rare hereditary galactose intolerance, Lapp lactose insufficiency or glucose-galactose malabsorption problems should not use this medicine.

It contains sucrose. Patients with rare inherited fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency should not use this medicine.

Chronic congestive heart failure: In patients with congestive heart failure, worsening of heart failure or fluid retention may occur during dose escalation of carvedilol. In this case, diuretics should be increased and the dose of carvedilol should not be increased until clinical equilibrium is achieved. It may sometimes be necessary to reduce the dose of carvedilol or, rarely, to temporarily stop the use of the medicine. Such periods do not preclude the subsequent successful administration of carvedilol. Care should be taken when carvedilol is used in combination with digitalis glycosides, as both medicines slow down AV conduction.

Renal function in congestive heart failure: Reversible worsening of renal function has been found with carvedilol treatment in patients with congestive heart failure with low blood pressure (systolic BP <100 mm Hg), ischemic heart disease and extensive vascular disease and/or underlying renal impairment. In congestive heart failure patients with these risk factors, renal function should be monitored during dose escalation and the dose should be reduced or discontinued if renal impairment worsens.

Chronic obstructive pulmonary disease: In patients with chronic obstructive pulmonary disease (COPD) with bronchospasm and not receiving oral or inhaled medication, carvedilol should be used only if the potential benefit outweighs the potential risk. In patients with a tendency to bronchospasm, respiratory distress may be observed due to a possible increase in resistance in the airway. Patients should be closely monitored during carvedilol initiation and dose escalation and the dose of carvedilol should be reduced if bronchospasm occurs during treatment.

Diabetes: Caution should be exercised when using carvedilol in patients with diabetes mellitus as early signs and symptoms of acute hypoglycemia may be masked or reduced. In diabetic patients with chronic heart failure, the use of carvedilol may complicate the control of blood glucose. Due to the β- blocker properties of the medicine, latent diabetes mellitus may become apparent, overt diabetes may worsen and blood glucose regulation may be impaired.

Peripheral vascular disease: β- blockers may accelerate or exacerbate symptoms of arterial insufficiency, carvedilol should be used with caution in patients with peripheral vascular disease.

Raynaud's phenomenon: Carvedilol should be used with caution in patients with peripheral circulatory disorders as symptoms may be exacerbated.

Thyrotoxicosis: As with other agents with β- blocking properties, carvedilol may mask symptoms of thyrotoxicosis.

Anesthesia and general surgery: Caution should be exercised in patients undergoing general surgery because of the synergistic negative inotropic effects of carvedilol and anesthetic medicines.

Bradycardia: Carvedilol may cause bradycardia. If the pulse rate falls below 55 beats per minute, the dose of carvedilol should be reduced.

Hypersensitivity: Because β- blockers may increase sensitivity to allergens and the degree of anaphylactic reactions, carvedilol should be used with caution in patients with a history of severe hypersensitivity reactions and in patients undergoing desensitization therapy.

Psoriasis: In patients with a history of β- blocker induced psoriasis, carvedilol should be used only after taking into account the risk-benefit ratio.

Concomitant use with calcium channel blockers: In patients treated with carvedilol concomitantly with calcium channel blockers such as verapamil or diltiazem or other antiarrhythmic medicines, ECG and blood pressure should be carefully monitored.

Pheochromocytoma: In patients with pheochromocytoma, a β- blocker should be initiated before using a α- blocker. Although carvedilol shows both α- blocker and β- blocker pharmacologic activity, there is no experience with its use in these conditions. Therefore, caution should be exercised in the administration of carvedilol in patients with suspected pheochromocytoma.

Prinzmetal variant angina: In patients with Prinzmetal variant angina, non-selective β- blocker activity may cause chest pain. Although the α- blocker activity of carvedilol may prevent such symptoms, there is no clinical experience with the use of carvedilol in such patients. Nevertheless, carvedilol should be used with caution in patients with suspected Prinzmetal variant angina.

Contact lenses: Contact lens wearers should consider the risk of reduced tear production.

Discontinuation syndrome: Carvedilol treatment should not be stopped abruptly, especially in patients with ischemic heart disease. In these patients, discontinuation of carvedilol should be gradual (over a 2-week period).

Serious skin reactions (SCARs): Serious skin reactions such as Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported very rarely due to carvedilol use (see section 4.8 Undesirable effects). Carvedilol should be discontinued immediately in patients with serious skin reactions thought to be related to carvedilol treatment.

Symptomatic hypotension and syncope may occur.

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

Pharmacokinetic interactions:

Carvedilol is not only a substrate but also an inhibitor of P-glycoprotein. Therefore, the bioavailability of medicines transported by P-glycoprotein may be increased by carvedilol taken concomitantly. In addition, the bioavailability of carvedilol may be modified by inducers or inhibitors of P-glycoprotein.

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

Digoxin: Co-administration of digoxin and carvedilol increases digoxin concentrations by up to 15%. Both carvedilol and cardiac glycosides slow AV conduction. More careful monitoring of digoxin levels is recommended when carvedilol is started, dose adjusted or discontinued.

Insulin and oral hypoglycemic medicines: β- blocking medicines may increase the blood glucose lowering effect of insulin and oral hypoglycemics. Symptoms of hypoglycemia may be masked or reduced (especially tachycardia). Regular monitoring of blood glucose is therefore recommended in patients taking insulin or oral hypoglycemics.

Inducers and inhibitors of liver metabolism (CYP2D6 and CYP2C9): Rifampicin decreases carvedilol plasma concentrations by approximately 70%. Cimetidine increases the AUC by approximately 30% but does not change the maximum concentration (Cmax).

Since serum levels of carvedilol may decrease in patients receiving mixed-function oxidase inducers such as rifampicin and serum levels may increase in patients receiving mixed-function inhibitors such as cimetidine, these patients should be carefully monitored.

Since the effect of cimetidine on carvedilol levels is low, the possibility of any clinical interaction is minimal.

Medicines that cause catecholamine-depletion: Patients taking a catecholamine-depleting medicine (e.g. reserpine and/or monoamine oxidase inhibitors) in combination with medicines with β- blocker properties should be closely monitored for signs of hypotension and/or severe bradycardia.

Cyclosporine: Slight increases in mean cyclosporine concentrations were observed after carvedilol treatment in 21 renal transplant patients with chronic vascular rejection. In approximately 30% of patients, cyclosporine dose reduction was required to maintain cyclosporine concentrations within the therapeutic range, while no adjustment was required in other patients. On average, the dose of cyclosporine was reduced by approximately 20% in these patients. Because of the wide individual variability in the dose adjustment required, it is recommended that cyclosporine concentrations are closely monitored after initiation of carvedilol treatment and the cyclosporine dose adjusted accordingly.

Verapamil, diltiazem and other antiarrhythmics: In combination with carvedilol, they may increase the risk of AV conduction disorders (see Special Warnings and Special Precautions for Use).

Fluoxetine: In a randomized, crossover study in 10 patients with heart failure, co-administration of fluoxetine, a potent CYP2D6 inhibitor, resulted in stereoselective inhibition of carvedilol metabolism with a 77% increase in mean R(+) enantiomer AUC. However, no differences in adverse effects, blood pressure or heart rate were observed between the treated groups.

Pharmacodynamic interactions:

Clonidine: Co-administration of clonidine with β- blocking agents may potentiate its blood pressure and heart rate lowering effects. When treatment with clonidine co-administered with β- blocking medicines is to be discontinued, the β- blocking agent should be discontinued first. Clonidine treatment can be discontinued after a few days by gradually reducing the dose.

Calcium channel blockers: (See Special Warnings and Special Precautions for Use) In isolated cases, conduction disturbance (rarely with hemodynamic imbalance) has been observed when carvedilol and diltiazem were administered orally together. As with other medicines with β- blocker activity, ECG and blood pressure should be carefully monitored when calcium channel blockers such as verapamil or diltiazem are administered orally with carvedilol.

As with other agents with β- blocker activity, carvedilol may potentiate the effect of concomitantly administered medicines with antihypertensive effects (e.g. α1 receptor antagonists) or medicines with hypotension as part of their adverse effect profile.

During anesthesia, special attention should be paid to the synergistic negative inotropic and hypotensive effects of carvedilol and anesthetic medicines.

NSAIDs: Concomitant use with non-steroidal anti-inflammatory drugs may cause an increase in blood pressure and reduce blood pressure control.

Additional information for special populations

Pediatric population

Safety and efficacy in children (<18 years) have not been evaluated.

4.6. Pregnancy and lactation

General advice

Pregnancy category is C. D in 2nd and 3rd trimester.

Women of childbearing potential / Contraception

There are insufficient data on the use of carvedilol in women of childbearing potential.

Pregnancy

There are insufficient data on the use of carvedilol in pregnant women.

Animal studies are insufficient in terms of its effect on pregnancy, embryonal/fetal development, parturition and postnatal development (see section 5.3). The potential risk in humans is unknown.

Beta blockers reduce placental perfusion, which may lead to intrauterine fetal death and immature and premature births. In addition, adverse effects (especially hypoglycemia and bradycardia) may occur in the fetus and newborn. In the postnatal period, there may be an increased risk of cardiac and pulmonary complications. Animal studies have not provided substantiated evidence of teratogenicity with carvedilol.

DILATREND should not be used in pregnancy unless absolutely necessary (if the expected benefits outweigh the potential risks).

Lactation

It is not known whether carvedilol is excreted in human milk. Animal studies have shown that carvedilol and its metabolites are excreted in milk. The decision whether to discontinue breastfeeding or DILATREND treatment should be made taking into account the benefit of breastfeeding for the child and the benefit of DILATREND treatment for the woman.

Fertility

No data available.

4.7. Effects on ability to drive and use machines

No studies have been conducted on the effect of carvedilol on the ability of patients to drive or use machines. The ability to drive, operate machinery or work unassisted may be impaired due to reactions (dizziness, fatigue) that vary from person to person. This is especially true at the beginning of treatment, after dose escalation, when changing medication and when alcohol is used concomitantly.

4.8. Undesirable effects

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

Infections and infestations

Common: Bronchitis, pneumonia, upper respiratory tract infection, urinary tract infection

Diseases of the blood and lymphatic system

Common: Anemia

Rare: Thrombocytopenia

Very rare: Leukopenia

Immune system diseases

Very rare: Hypersensitivity (allergic reaction)

Metabolic and nutritional disorders

Common: Weight gain, hypercholesterolemia, impaired blood glucose control in patients with pre-existing diabetes (hyperglycemia, hypoglycemia)

Psychiatric disorders

Common: Depression, depressed mood

Uncommon: Sleep disorders

Nervous system disorders

Very common: Dizziness, headache

Uncommon: Presyncope, syncope, paresthesia

Eye diseases

Common: Visual disturbances, decreased eye secretion (dry eye), eye irritation

Cardiac diseases

Very common: Cardiac failure

Common: Bradycardia, edema (including generalized, peripheral, dependent and genital edema, edema of the legs), hypervolemia, fluid overload

Uncommon: Atrio-ventricular block (AV block), angina pectoris

Vascular diseases

Very common: Hypotension

Common: Orthostatic hypotension, peripheral circulatory disorders (cold extremities, peripheral vascular disease, intermittent claudication exacerbation and Reynaud's phenomenon)

Respiratory, chest disorders and mediastinal diseases

Common: Dyspnea, pulmonary edema, asthma in predisposed patients

Rare: Nasal congestion, wheezing and flu-like symptoms

Gastrointestinal diseases

Common: Nausea, diarrhea, vomiting, dyspepsia, abdominal pain

Uncommon: Constipation

Rare: Dry mouth

Hepato-biliary diseases

Very rare: Increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyltransferase (GGT) values

Skin and subcutaneous tissue diseases

Uncommon: Skin reactions (allergic exanthema, dermatitis, increased sweating, urticaria, pruritus, psoriatic and lichen-planus-like skin lesions) alopecia

Very rare: Serious skin reactions such as Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) (see Section 4.4. Important warnings and precautions for use)

Musculoskeletal disorders, connective tissue and bone diseases

Common: Pain in the extremities

Kidney and urinary tract diseases

Common: In patients with renal impairment and diffuse vascular disease and/or underlying renal impairment, renal dysfunction, voiding disorders

Very rare: Urinary incontinence in women

Reproductive system and breast diseases

Uncommon: Erectile dysfunction

General disorders and diseases related to the application area

Very common: Asthenia (fatigue)

Common: Pain

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is essential. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals should report any suspected adverse reaction via the national reporting system.

4.9. Overdose

Intoxication symptoms

In case of overdose, severe hypotension, bradycardia, heart failure, cardiogenic shock and cardiac arrest may occur. Respiratory problems, bronchospasm, vomiting, impaired consciousness and generalized seizures may also occur.

Treatment of intoxication: In addition to general procedures, vital parameters should be monitored and corrected, if necessary under intensive care conditions. The following supportive therapies may also be applied:

The patient should be in a supine position.

Atropine: 0,5-2 mg i.v. (for extreme bradycardia)

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

Sympathomimetics that may be used depending on body weight and effects: dobutamine, isoprenaline, orsiprenaline or adrenaline. If a positive inotropic effect is required, phosphodiesterase inhibitors such as milrinone should be considered.

If peripheral vasodilatation is prominent in the intoxication profile, norphenephrine or noradrenaline may be given with continuous monitoring of circulatory conditions.

In case of medicine-resistant bradycardia, a “pacemaker” should be applied.

Treatment of bronchospasm: In case of bronchospasm, β- sympathomimetics (aerosol or i.v.) or aminophylline i.v. should be given.

Treatment of seizures: For seizures, slow i.v. injection of diazepam or clonazepam is recommended.

Important Note:

In severe intoxication with symptoms of shock, supportive therapy should be continued for a sufficiently long period of time, as the elimination half-life of carvedilol may be prolonged and redistribution from deeper compartments can be expected. The duration of supportive/antidote therapy depends on the severity of the overdose. Supportive therapy should be continued until the patient's condition stabilizes.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: α and β adrenergic receptor blockers

ATC code: C07AG02

Carvedilol, α1, β1 and β2 is an adrenergic receptor blocker. Carvedilol has been shown to have organ-protective effects. Carvedilol is an effective antioxidant and eliminates reactive oxygen radicals. Carvedilol is racemic and both the R(+) and S(-) isomers α1 have adrenergic receptor blocking and antioxidant properties. Carvedilol has antiproliferative effects on human vascular smooth muscle cells.

In clinical studies, a decrease in oxidative stress during chronic carvedilol treatment has been shown by measuring various parameters.

The β-adrenergic receptor blocking property is non-selective for, β1 and β2 adrenoceptors and is associated with the S(-) enantiomer of carvedilol. Carvedilol has no intrinsic sympathomimetic activity and, like propranolol, has membrane-stabilizing properties. Carvedilol suppresses the renin-angiotensin-aldosterone system with a β-blocking effect that reduces the release of renin; therefore fluid retention is rare.

Carvedilol reduces peripheral vascular resistance due to its selective α1 blocking effect.

Carvedilol reduces the increase in blood pressure caused by phenylephrine, an α1 adrenoreceptor agonist, but not the increase caused by angiotensin II.

Carvedilol has no adverse effect on lipid profile. The ratio between high density lipoproteins and low density lipoproteins (HDL/LDL) is maintained.

Efficacy

According to the results obtained in clinical trials:

Hypertension

In hypertensive patients, carvedilol lowers blood pressure through its vasodilator effect mediated through β- blocker effect and α1. As observed with β- blocking agents, the decrease in blood pressure is not accompanied by a concomitant increase in total peripheral resistance. Heart rate decreases slightly. Renal blood flow and renal function are preserved in hypertensive patients. Carvedilol has been shown to preserve stroke volume and reduce total peripheral resistance. Blood supply to specific organs and vascular beds, including kidney, skeletal muscle, forearm, leg, skin, brain or carotid arteries is not adversely affected by carvedilol. The incidence of coldness in the extremities and early fatigue during physical activity is reduced. The long-term effect of carvedilol on hypertension has been demonstrated in double-blind controlled studies.

Coronary Heart Disease

In patients with coronary heart disease, carvedilol has shown persistent anti-ischemic (improvement in total exercise time, time to 1 mm ST segment depression and time to angina) and anti-anginal effects during long-term treatment. Acute hemodynamic studies showed that carvedilol significantly reduced myocardial oxygen demand and sympathetic overactivity. Carvedilol also reduces myocardial preload (pulmonary artery pressure and pulmonary capillary wedge pressure) and afterload (total peripheral resistance).

Chronic Heart Failure

Carvedilol significantly reduces all-cause mortality and the need for hospitalization for cardiovascular causes. Carvedilol also increases ejection fraction. It improves symptoms in patients with chronic heart failure of ischemic or non-ischemic origin. This effect of carvedilol is dose dependent.

5.2. Pharmacokinetic properties

General properties

Absorption:

After oral administration, carvedilol is rapidly absorbed. In healthy volunteers, the maximum plasma concentration is reached after approximately 1 hour. The absolute bioavailability of carvedilol in humans is approximately 25%.

Distribution:

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

Biotransformation:

The majority of carvedilol is converted to various metabolites, which are eliminated mainly in bile. The first-pass effect after oral administration is approximately 60-75%. Carvedilol is largely metabolized in the liver and one of the main reactions is glucuronidation. Demethylation and hydroxylation of the phenol ring results in 3 metabolites with β-receptor blocker activity. According to preclinical studies, the 4'-hydroxyphenol metabolite has 13 times stronger β-blocker effect than carvedilol. Compared to carvedilol, its three active metabolites show weak vasodilator activity. In humans, the concentrations of the three active metabolites are 10 times lower than the parent substance. Two of the hydroxy-carbazole metabolites of carvedilol are extremely potent antioxidants, 30-80 times more potent than carvedilol.

Elimination:

The mean elimination half-life of carvedilol is approximately 6 hours. Plasma clearance is approximately 500-700 ml/min. The main route of excretion is feces. Elimination is mostly through bile. A small proportion is eliminated through the kidneys in the form of various metabolites.

Characteristic features in patients

Patients with renal impairment:

During chronic treatment with carvedilol, autoregulatory blood flow is maintained and glomerular filtration is not altered.

In patients with hypertension and renal impairment, the area under the plasma level-time curve, elimination half-life and maximum plasma concentration do not change significantly. Renal excretion of the medicine in unchanged form is reduced in patients with renal insufficiency; however, changes in pharmacokinetic parameters are not significant.

Studies have shown that carvedilol is an effective agent in patients with renal hypertension. The same efficacy applies to patients with chronic renal impairment or under hemodialysis or after renal transplantation. Carvedilol causes a gradual decrease in blood pressure both on dialysis days and non-dialysis days and its blood pressure lowering effect is comparable to that observed in patients with normal renal function. Carvedilol is not eliminated during dialysis as it does not cross the dialysis membrane, probably due to its high binding to plasma proteins.

Based on results from comparative studies in patients undergoing hemodialysis, carvedilol is more effective and better tolerated than calcium channel blockers.

Patients with hepatic impairment:

In patients with liver cirrhosis, the systemic utilization of the medicine was increased by up to 80% due to a reduction in the first-pass effect. Therefore, carvedilol is contraindicated in patients with clinically significant hepatic impairment (see Contraindications).

Geriatric use:

The pharmacokinetics of carvedilol in hypertensive patients are not affected by age. A study in elderly hypertensive patients showed no difference in the adverse event profile. Another study of elderly patients with coronary heart disease showed no difference in reported adverse events.

Pediatric use:

Data on pharmacokinetics in patients under 18 years of age are limited.

Diabetic patients:

In hypertensive patients with non-insulin-dependent diabetes mellitus, carvedilol had no effect on fasting or post-prandial blood glucose concentration, glycosylated hemoglobin A1 or the need for dose modification of antidiabetic agents.

In non-insulin-dependent diabetic patients, carvedilol had no statistically significant effect on glucose tolerance test. In hypertensive non-diabetic patients with reduced insulin sensitivity (Syndrome X), carvedilol improved insulin sensitivity. The same results were found in hypertensive patients with non-insulin-dependent diabetes.

5.3. Preclinical safety data

In carcinogenicity studies in rats and mice, doses up to 75 mg/kg/day and 200 mg/kg/day (38 to 100 times the maximum recommended dose [MRHD] for humans) were administered, respectively, and no carcinogenic effect of carvedilol was observed.

Carvedilol is not mutagenic in in vivo and in vitro tests in mammals and non-mammals.

Administration of carvedilol at doses toxic in pregnancy (MHRD ≥200 mg/kg, ≥100 times) caused fertility disorders (poor mating, decreased corpora lutea, fertilization and embryonic response). Doses >60 mg/kg (>30 times the MHRD) caused delayed physical growth/development of offspring. Embryotoxicity (increased post-fertilization mortality) was observed, but at doses of 200 mg/kg and 75 mg/kg (38 to 100 times the maximum recommended dose for humans [MHRD]), respectively, no malformations were observed in treated rats and rabbits. A summary of all preclinical safety information can be found in the expert reports from October 1999 to March 2000.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Lactose (produced from cow's milk)

Sucrose

Povidone K25

Crospovidone

Colloidal anhydride silica

Magnesium stearate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

60 months

6.4. Special measures for storage

Store at room temperature below 30°C, protected from light and moisture.

6.5. Characteristics and contents of container

DILATREND 25 mg tablets, 30 pieces, in blister.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.

Halkalı Merkez Mah. Basın Ekspres Cad.

No: 1 34303 Küçükçekmece - İstanbul/TÜRKİYE

Phone: 0 212 692 92 92

Fax: 0 212 697 00 24

8. MARKETING AUTHORIZATION NUMBER

2018/184

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 05.04.2018

Date of last renewal: 05.04.2018

10. DATE OF REVISION OF THE TEXT

05.04.2018