

SUMMARY OF PRODUCT CHARACTERISTIC

1. NAME OF THE MEDICINAL PRODUCT

CALBICOR® 6.25 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Each tablet contains 6.25 mg carvedilol

Excipients:

Lactose monohydrate (bovine) (62.58 mg)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Light yellow, round and slightly dished tablets with score on one side, “C2” logo on the other side tablets.

4. CLINICAL PARTICULARS

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 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 drugs 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. The maximum recommended dose in patients over 85 kilograms with mild or moderate heart failure 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 is interrupted for more than one week, it is recommended to start treatment with a lower dose twice daily and to 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 indicated above.

In the treatment of vasodilation symptoms, the dose of diuretics should be reduced initially. If symptoms persist, the dose of ACE inhibitor (if used) may be reduced, followed by a further 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, CALBICOR® should be given with food.

Additional information for special populations:**Renal impairment:**

Based on available pharmacokinetic data in 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 significant hepatic 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 12.5 mg 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 beta-blockers, carvedilol should not be used in patients with

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

4.4 Special warnings and precautions for use**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 drug.

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 drugs 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 who are 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 mellitus

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 beta-blocker properties of the drug, latent diabetes mellitus may become apparent, overt diabetes may worsen and blood glucose regulation may be impaired.

Peripheral vascular disease

Carvedilol should be used with caution in patients with peripheral vascular disease, as beta-blockers may accelerate or exacerbate symptoms of arterial insufficiency.

Raynaud's phenomenon

Carvedilol should be used with caution in patients with impaired peripheral circulation as symptoms may be exacerbated.

Thyrotoxicosis

As with other agents with beta-blocker properties, carvedilol may mask symptoms of thyrotoxicosis.

Anaesthesia and major surgery

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

Bradycardia

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

Hypersensitivity

Since beta-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 psoriasis due to beta-blocker therapy, carvedilol should be used only after taking into account the risk-benefit ratio.

Phaeochromocytoma

In patients with pheochromocytoma, administration of an alpha-blocker should be initiated before the use of a beta-blocker. Although carvedilol shows both alpha-blocker and beta-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's variant angina

In patients with Prinzmetal variant angina, non-selective beta-blocker activity may cause chest pain. Although the alpha-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 be aware of the risk of reduced tears.

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.

CALBICOR[®] contains lactose of bovine origin. Patients with rare hereditary galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption problems should not use this medicine.

4.5 Interaction 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 drugs transported by P-glycoprotein may be increased by carvedilol taken

together. 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 drugs: Beta-blocker drugs may increase the blood glucose-lowering effect of insulin and oral hypoglycemics. Symptoms of hypoglycemia may be masked or reduced (especially tachycardia). Therefore, regular monitoring of blood glucose is 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 (C_{max}).

Since serum levels of carvedilol may decrease in patients receiving mixed-function oxidase inducers such as rifampicin and may increase in those 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.

Drugs that cause catecholamine depletion: Patients receiving a drug that causes catecholamine depletion (e.g. reserpine and/or monoamine oxidase inhibitors) in combination with drugs with beta-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 beta-blockers may potentiate its blood pressure and heart rate lowering effects. When treatment with clonidine co-administered with beta-blockers is to be discontinued, the beta-blocker 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 instability) has been observed when carvedilol and diltiazem were administered orally together. As with other drugs with beta-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 beta-blocker activity, carvedilol may potentiate the effect of concomitantly administered drugs with antihypertensive effects (e.g. 1 receptor antagonists) or drugs with hypotension as part of their adverse effect profile.

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

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

Additional information on special populations

Pediatric population

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

4.6 Fertility, pregnancy and lactation

General advice

Pregnancy category 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 period

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

Animal studies are insufficient for the 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 can 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.

CALBICOR[®] should not be used in pregnancy unless necessary.

Lactation period

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 stop breastfeeding or CALBICOR[®] treatment should be made taking into account the benefit of breastfeeding for the child and the benefit of CALBICOR[®] treatment for the woman.

Reproductive ability (Fertility)

No data available.

4.7 Effects on ability to drive and use machines

There have been no studies on the effect of carvedilol on patients' ability to drive or use machines. The ability to drive, operate machinery or work unassisted may be impaired due to individual reactions (dizziness, fatigue). 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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)

Metabolism and nutritional diseases

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

Psychiatric illnesses

Common: Depression, depressed mood

Uncommon: Sleep disorders

Nervous system diseases

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

Generalized: 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 exacerbation of claudication and Reynaud's phenomenon)

Respiratory, chest and mediastinal disorders

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) levels

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. Special 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 site

Very common Asthenia (fatigue)

Common: Pain

Reporting of side effects

Talk to your doctor, pharmacist or nurse if you experience any side effects listed or not listed in this leaflet. Also reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions 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, norphenephine or noradrenaline may be given with continuous monitoring of circulatory conditions.

In case of drug-resistant bradycardia, a "pacemaker" should be applied.

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

Seizure treatment: 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: beta- and alpha-1-receptor blocking agents

ATC code: C07AG02

Carvedilol is an adrenergic receptor blocker with alpha-1, beta-1 and beta-2 adrenergic receptor blocking properties. Carvedilol has been shown to have organ protective effects. Carvedilol is an effective antioxidant and eliminates reactive oxygen radicals. Carvedilol is racemic and both R(+) and S(-) isomers have 1 adrenergic receptor blocking and antioxidant properties. Carvedilol has antiproliferative effect on human vascular smooth muscle cells.

Clinical studies have shown a decrease in oxidative stress during chronic carvedilol treatment by measuring various parameters.

Beta-adrenergic receptor blockade is non-selective for beta-1 and beta-2 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 through its beta-blocker effect, which reduces renin release; thus fluid retention is rare.

Carvedilol reduces peripheral vascular resistance due to its selective alpha-1 blockade effect.

Carvedilol reduces the increase in blood pressure caused by phenylephrine, an alpha-1 adrenoceptor 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.

Effectiveness

According to the results obtained in clinical trials:

Hypertension

Carvedilol lowers blood pressure in hypertensive patients with its beta-blocker effect and alpha-1 mediated vasodilator effect. As observed with beta-blocker agents, the decrease in blood pressure is not accompanied by an 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 features

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% binds to plasma proteins. The volume of distribution is approximately 2 L/kg.

Biotransformation:

Most of carvedilol is converted to various metabolites, which are eliminated mainly in bile. The first-pass effect after oral administration averages 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 beta-receptor blocker activity. According to preclinical studies, the 4'-hydroxyphenol metabolite has 13 times more potent beta-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 to 700 ml/min. The main route of excretion is faeces. Elimination is mostly through bile. A small portion is eliminated through the kidneys in the form of different metabolites.

Characteristic features in patients

Patients with kidney disorders:

During chronic treatment with carvedilol, autoregulatory blood flow is maintained and glomerular filtration is unchanged.

In patients with hypertension and renal insufficiency, the area under the plasma level-time curve, elimination half-life and maximum plasma concentration do not change significantly. Renal excretion of the drug 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, it was concluded that carvedilol was more effective and better tolerated than calcium channel blockers.

Patients with liver failure:

In patients with liver cirrhosis, the systemic utilization of the drug is 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:

In patients under 18 years of age, data on pharmacokinetics 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 MHRD) has 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 PARTICULARS

6.1 List of excipients

Lactose monohydrate, spray dried (bovine origin)
Corn Starch
Sodium lauryl sulfate
Magnesium Stearate
Croscarmellose sodium
Colloidal silicon dioxide
Yellow iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store in the package at room temperature below 25°C, protected from light and moisture.

6.5 Nature and contents of container

30 tablets in white opaque PVC/PE/PVDC/Al foil blister packs.

6.6. Disposal of medicinal product residues and other special precautions

Unused products or waste materials should be disposed of in accordance with the "Regulation on Control of Medical Waste" and "Regulation on Control of Packaging and Packaging Waste".

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first approval: {DD month YYYY}

Date of renewal of the approval: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{DD month YYYY}

[To be completed nationally]