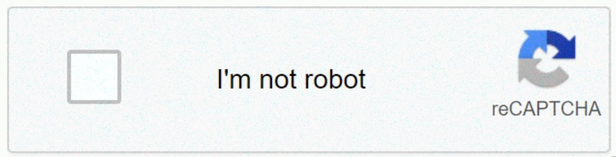

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Carvedilol full prescribing information

Essential hypertension: Carvedilol can be used to treat hypertension alone or in combination with other antihypertensivees, especially tiazid diuretics. Once daily dosing is recommended, however, the recommended maximum individual dose is 25 mg, and the recommended maximum daily dose is 50 mg. Adults: The recommended starting dose is 12.5 mg once a day for the first two days. After that, treatment continues at a dose of 25 mg/day. If necessary, the dose may be gradually increased at intervals of two weeks or less often. Chronic stable angina exitoris. The regimen is recommended twice a day. Adults: The starting dose is 12.5 mg twice a day for the first two days. After that, treatment continues at a dose of 25 mg twice a day. If necessary, the dose may be gradually increased at intervals of two weeks or less frequently to the recommended maximum dose of 100 mg per day divided into two doses (twice a day). Elderly: The recommended starting dose is 12.5 mg twice a day for two days. After that, treatment continues at a dose of 25 mg twice a day, which is the recommended maximum daily dose. Heart failure: Carvedilol is given in moderate to severe heart failure with conventional baseline therapy with diuretics, ACE inhibitors, digitalis and/or vasodilatators. The patient should be clinically stable (no change in NYHA class, no hospitalisation for heart failure) and basic therapy must be stabilised at least 4 weeks before treatment. In addition, the patient should have a reduced fraction of the left ventricle ejection, and the heart rate should be >50 bpm and the sistal blood pressure should be >85 mmHg (see contraindications). The initial dose is 3,125 mg twice a day for two weeks. If this dose is tolerated, the dose can be slowly increased with intervals of no less than two weeks to 6.25 mg twice a day, then up to 12.5 mg twice a day and eventually up to 25 mg twice a day. The dose should be increased to the highest tolerable level. The recommended maximum dose is 25 mg twice a day for patients with a body weight of less than 85 kg, 50 mg twice a day for patients with a body weight above 85 kg, provided that heart failure is not severe. Increasing the dose to 50 mg twice a day should be carefully performed under careful medical supervision of the patient. Transient worsening of heart failure symptoms may occur at the beginning of treatment or due to dose increases, especially in patients with severe heart failure and/or high doses of diuretics. This usually does not require discontinuation of treatment, but the dose should not be increased. The patient should be monitored by a doctor/cardiologist two hours after starting treatment or increasing the dose. Before increasing each dose, you should check for potential symptoms of worsening heart failure due to symptoms of excessive vasodilation (e.g. renal function, body weight, blood pressure, heart rate and rhythm). Worsening heart failure or retention is treated by increasing the dose of diuretics and the dose of Carvedilon should not be increased until the patient is stabilised. If bradycardia appears or in the case of prolongation of AV conduction, the level of digoxin should first be monitored. Occasionally, it may be necessary to reduce the dosage of Carvedilol or temporarily discontinue treatment altogether. Even in these cases, the Carvedilol dose of titration can often continue successfully. Renal function, glucose ad platelets (in the case of NIDDM and/or IDMM) should be monitored regularly during dose titration. However, after dose titration, the frequency of follow-up may decrease. If Carvedilol has been withdrawn for more than two weeks, the therapy should be reinstalled with 3,125 mg twice a day and gradually increased according to the above recommendations. Renal insufiction: The dose must be determined for each patient individually, but according to pharmacokinetic parameters, there is no evidence that the dose of Carvedilol needs to be adjusted. Patients with heart failure (see Precautions). Moderate Liver Dysfunction: Dose adjustment may be required. Children and adolescents (<18 years): Insufficient data on the efficacy and safety of Carvedilol. Elderly: Elderly patients may be more susceptible to the effects of Carvedilol and should be monitored more closely. As with other betablockers and especially in coronary patients, the withdrawal of Carvedilol should be done gradually (see precautions). Methods of administration: Tablets should be taken with the appropriate fluid supply. Tablets should not be taken with a meal. However, it is recommended that heart failure patients be taken with a meal. However, it is recommended that heart failure patients take carvedilol with food to make absorption slower and the risk of orthostatic hypotension reduced. Updated Oct 6, 2007 If you are a consumer or patient visit this version. HIGHLIGHTS OF PRESCRIBING INFORMATION Carvedilol is an alpha/beta-adrenergic blocking agent indicated for treatment: (2) Left ventricle dysfunction after myocardial infarction in clinically stable patients (1,1) Hypertension (1,2) Take with food. Individualize doses and monitor during titration. (2) (3) Left ventricle dysfunction after myocardial infarction: Start at 6.25 mg twice a day and increase to 12.5 mg, then 25 mg twice a day after an interval of 3 to 10 days. A lower initial dose or slower titration may be used. (2.1) Hypertension: Start at 6.25 mg twice a day and increase if necessary to control blood pressure at 12.5 mg then 25 mg twice a day at intervals of 1 to 2 weeks. (2.2) Tablets: 3,125, 6.25, 12.5, 25 mg (3) (4) Bronchial asthma or related bronchospastic conditions (4) Second- or third-degree AV block (4) Sick sinus syndrome (4) Severe bradycardia (unless a permanent pacemaker in place) (4) Patients in cardiogenic shock or decompensated heart failure require iv inotropic therapy. (4) Severe liver damage (2,3, 4) Hypersensitivity to carvedilol (e.g. Stevens-Johnson syndrome) (4) Acute worsening of coronary artery disease after cessation of therapy: Do not stop abruptly. (5.1) Bradycardia, hypotension, worsening of heart failure/fluid retention may occur. Reduce the dose as needed. (5.2, 5.3, 5.4) Nonallergic bronchospasm (e.g. chronic bronchitis and emphysema): Avoid β blockers. (4) However, if deemed necessary, use with caution and at the lowest effective dose. (5.5) Diabetes: Monitor glucose β-blockers may mask symptoms of hypoglycemia or worsen hyperglycemia. (5.6) Most common adverse events (6.1): (7) Left ventricle dysfunction after myocardial infarction (≥10%): Dizziness, Fatigue, hypotension, diarrhea, hyperglycemia, asthenia, bradycardia, weight gain Hypertension (≥5%): Dizziness CYP P450 2D6 enzyme inhibitors may increase, and rifampine may reduce enzyme levels. (7.1, 7.5) Hypotensive agents (e.g. reserpin, MAO inhibitors, clonidine) may increase the risk of hypotension and/or severe bradycardia. (7.2) Levels of cyclosporins or digoxins may increase. (7.3, 7.4) Verapamil or diltiazem calcium channel blockers may affect ECG and/or blood pressure. (7.6) The effects of insulin and oral hypoglycemia may be intensified. (7.7) September 2007 (8) See 17 for information on patient counseling. Revised: 10/2007 Table of Contents N/A - Section title not found in database 1 INDICATIONS AND USE 1.1 Left ventricle dysfunction after myocardial infarction Carvedilol is an indication to reduce cardiovascular mortality clinically stable patients who have gotten over the acute stage of myocardial infarction and have part of the left ventricle ejection of ≤40% (with or without symptomatic heart failure) [see Clinical Studies (14.1)]. 1.2 Hypertension Carvedilol is indicated for the management of essential. It can be used alone or in combination with other antihypertensive agents, especially tiaside-type diuretics [see Drug Interactions (7.2)]. 2 Dosage and ADMINISTRATION Carvedilol should be taken with food to slow down absorption rates and reduce the frequency of orthostatic effects. 2.1 Left ventricle dysfunction after dosing myocardial infarction must be individualised and monitored during UP-TITRATION. Treatment with carvedilol can be initiated as hospital or outpatient and should be initiated after the patient is hemodynamically stable and fluid retention is kept to a minimum. It is recommended that carvedilol be started at 6.25 mg twice a day and increased after 3 to 10 days, based on tolerability, to 12.5 mg twice a day, and then again to a target dose of 25 mg twice a day. A lower starting dose (3,125 mg twice daily) may be used and/or the titration rate may be slowed down if clinically indicated (e.g. due to low blood pressure or heart rate or fluid retention). Patients should be maintained at lower doses if higher doses are not tolerated. Recommended dosing should not be changed in patients receiving IV or oral treatment with an β-blocker during the acute stage of myocardial infarction. 2.2 The dose of hypertension MUST BE INDIVIDUALISED. The recommended initial dose of carvedillol is 6.25 mg twice a day. If this dose is tolerated, using standing sistal pressure measured about 1 hour after the dose as a guide, the dose should be maintained for 7 to 14 days and then increased to 12.5 mg twice a day if necessary, based on a blood pressure trough, again using standing systalic pressure one hour after the dose as a tolerance guide. This dose should also be maintained for 7 to 14 days, and can then be adjusted upwards to 25 mg twice a day if tolerated and should. The full antihypertensive effect of carvedilol is seen within 7 to 14 days. The total daily dose should not exceed 50 mg. It can be expected that concomisal application with diuretics will produce additive effects and exaggerate the orthostatic component of the action of the disrupterole. 3 dose shape and strength 3.125 mg tablets: White on off-white, oval shape, biconvex, film coated tablets, debossed with 'RX4', on one side and plain on the other. 6.25 mg tablets: White to whitish, oval in shape, biconvex, film-coated tablets, deossed with 'RX', on one side and '824' on the other. 12.5 mg tablets: White to whitish, oval in shape, biconvex, film-coated tablets, deossed with 'RX825' on one side and plain on the other. 25 mg tablets: White to white, oval shape, biconvex, film-coated tablets, deossed with 'RX826' on one side and plain on the other. 4 CONTRAINDICATIONS Carvedilol is contraindicated under the following conditions: Bronchial asthma or related bronchospastic conditions. Deaths from astmaticus status were reported after a single dose of carvedilol. Second- or third-degree AV block Disease sinus syndrome Severe bradycardia (unless a permanent pacemaker is in place) Patients with cardiogenic shock or who have decompensated heart failure requiring intravenous inotropic therapy. Such patients should first be cut off from intravenous therapy before starting carvedillo Patients with clinical manifest liver damage Patients with a mixed hypersensitivity reaction to carvedilol (e.g. Stevens-Johnson syndrome) 5 WARNINGS AND PRECAUTIONS 5.1 Discontinuation of therapy Patients with coronary artery disease, treated with carvedilol, should be advised against abrupt discontinuation of therapy. Severe angina exacerbation and the occurrence of myocardial infarction and ventricular arrhythmias were reported in patients with angina after abrupt discontinuation of β-blockers. The last 2 complications can occur with or without prior deterioration of angina šactoris. As with β-blockers, when it is planned to discontinue the use of carvedillola, patients carefully observe and advise to limit physical activity to a minimum. Carvedilol should be discontinued for 1 to 2 weeks whenever possible. If angina worsens or acute coronary insuffication develops, it is recommended that carvedilol be reinstalled immediately, at least temporarily. Since coronary artery disease is common and may be unrecognly recognizable, it may be prudent not to discontinue carvedillol therapy abruptly even in patients treated only for hypertension or heart failure. 5.2 Bradycardia In clinical trials, carvedilol caused bradycardia in about 2% of hypertensive patients, and 6.5% of patients with myocardial infarction with left ventricle dysfunction. If the heart rate drops below 55 beats/minutes, the dose should be reduced. 5.3 Hypotension Postural hypotension occurred in 1.8% and syncope in 0.1% of hypertensive patients, primarily after the initial dose or at the time of dose increase and was the cause of discontinuation in 1% of patients. In a JARCA study in which acute myocardial infarction, hypotension or postural hypotension survived, 20.2% of patients receiving carvedilol compared to 12.6% of placebo patients occurred. Syncope was reported in 3.9% and 1.9% of patients, respectively. These events were the cause of discontinuation in 2.5% of patients receiving carvedilol, compared to 0.2% of placebo patients. Starting with low dose, food use and gradual titration should reduce the likelihood of syncope or excessive hypotension [see Dose and Administration (2.1, 2.2, 2.3)]. During the start of therapy, patients should be advised to avoid situations such as driving or dangerous tasks, whereby injury may occur. 5.4 Heart failure/Fluid retention Worsening heart failure or fluid retention may occur during up-titration of carvedilol. If such symptoms occur, diuretics should be increased and the dose of carvedillol should not be advanced until clinical stability continues [see Dose and Administration (2)]. Occasionally it is necessary to reduce the dose of carvedilol or temporarily discontinue it. Such episodes excluding subsequent successful titration or favourable response to carvedilol. 5.5 Non-allergic bronchospasm Patients with bronchospastic disease (e.g. chronic bronchitis and emphysema) should generally not receive β blockers. Carvedilol can be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if carvedilol is used, to use the smallest effective dose, so that the inhibition of endogenous or exogenous β-agonists is minimized. In clinical trials, patients with bronchospastic disease were enrolled if they did not require oral or inhalation drugs to treat their bronchospastic disease. In such patients it is recommended that carvedilol be used with caution. Dosing recommendations should be closely monitored and the dose lowered if there is evidence of observed during upwards titration. 5.6 Glycemic control of type 2 diabetes In general, β-blockers may mask some of the manifestations of hypoglycemia, especially tahidlike. Indiscriminate β-blockers may potentiate insulin-induced hypoglycemia and delay the recovery of serum glucose levels. Patients undergoing spontaneous hypoglycemia or patients with diabetics receiving insulin or oral hypoglycaemic agents should be advised of these options. Studies designed to examine the effects of carvedillol on glymetma control in patients with diabetes and heart failure were not conducted. 5.7 Peripheral vascular disease β -blockers may degrade or worsen symptoms of arterial insufficing in patients with peripheral vascular disease. In such individuals should be careful. 5.8 Worsening of kidney function Rare, use of carvedilol in patients with heart failure resulted in deterioration of renal function. At-risk patients with low blood pressure (sistalic blood pressure <100 mm Hg), ischemia heart disease and diffuse vascular disease, and/or underlying renal insufficiency appear to be at risk. The renal function returned to baseline when the carvedilol was stopped. In patients with these risk factors, it is recommended to monitor renal function during carving titration and discontinuation or dose reduction if renal function deteriorates. 5.9 Anaesthesia and major surgery If carvedillolil treatment should be continued perioperatively, special care should be taken when using anaesthetic agents that depress myocardial function, such as ether, cyclopropan and trichloroethylene[see Overdosage (10) for information on the treatment of bradyxoquine and hypertension]. 5.10 Thyroid oxycose β-adrenergic blockage may mask clinical signs of hyperthyroidism, such as tahycardia. A sudden β blockage may be followed by worsening symptoms of hyperthyroidia or may trigger a thyroid storm. 5.11 Pheochromocytoma In patients with phenochromocytoma, a life-blocking agent should be α before using any life-blocking β. Although carvedilol is α- and β-blocking pharmacological activity, there has been no experience with its use in this state. Therefore, caution should be exercised in the use of carvedilol to patients suspected of having phenochromocytoma. 5.12 Prinzmetal variant of Angina agents with non-selective β-blocking activity may cause chest pain in patients with Prinzmetal variant angina. There was no clinical experience with carvedilol in these patients, although α blocking symptoms can prevent such symptoms. However, caution should be exercised in applying carvedilol to patients suspected of having Prinzmetal's variant of angina. 5.13 The risk of anaphylactic reaction while taking β-blockers, patients with anaphylactic reaction in anaphylactic reaction to different allergens may be more reactive to a repeated challenge, whether random, diagnostic or Such patients may not respond to the usual doses of adrenaline used to treat an allergic reaction. 6 SIDE EFFECTS 6.1 Clinical Studies Experience Carvedilol was evaluated for safety in patients with left ventricle dysfunction after myocardial infarction and in hypertensive patients. The observed adverse event profile was consistent with the pharmacology of the drug and the health status of patients in clinical trials. Adverse events reported for each of these patient populations can be found below. Adverse events considered as overearing to be informative are excluded, and those that are not reasonably associated with the use of the medicine because they have been associated with a condition that is being treated or are very common in the treated population. Adverse event rates were generally similar in demographic subsets (men and women, older and non-elderly, black and non-black). Left ventricle dysfunction after myocardial infarction Carvedilol was assessed for safety in people who survived acute myocardial infarction with left ventricle dysfunction in the CAPRICORN study involving 969 patients receiving carvedilol and 980 receiving placebo. Approximately 75% of patients received carvedilol for at least 6 months and 53% received carvedilol for at least 12 months. Patients were treated for an average of 12.9 months and 12.8 months respectively with carvedilol and placebo. The following adverse events were reported with a frequency of >1%, but ≤3% and more often with carvedilol: flu syndrome, cerebrovascular accident, peripheral vascular disorder, hypotonia, depression, gastrointestinal pain, arthritis and glyte. Overall discontinuation rates for adverse events were similar in both patient groups. In this database, the only cause of interruption >1%, and occurs more often on carvedilol is hypotension (1.5% on carvedilol, 0.2% on placebo). Hypertension Carvedilol was evaluated for safety in hypertension in more than 2,193 patients in U.S. clinical trials and in 2,976 patients in international clinical trials. Approximately 36% of the total treated population received carvedilol for at least 6 months. Most adverse events reported during carvedilol therapy were mild to moderate in severity. In controlled clinical trials in the UNITED States, directly compared carvedilol in doses up to 50 mg (n = 1142) with placebo (n = 462), 4.9% of patients receiving carvedilol discontinued adverse events versus 5.2% of placebo patients. Although there was no overall difference in break rates, interruptions were more common in the postural hypotension carvedilol group (1% vs. 0). The overall incidence of adverse events in U.S. placebo-controlled trials increased with an increase in the dose of carvedilol. For individual side effects, this can only be distinguished by vertigo, which increased in frequency from 2% to 5% as the total daily dose increased from 6.25 mg to 50 mg. Table 1 shows unfavorable in the UNITED States placebo controlled clinical hypertension studies that occurred with an incidence of >1% regardless of causation, and which were more common in patients treated with drugs than patients treated with placebo. Dyspnea and fatigue were also reported in these studies, but rates were equal to or higher in patients receiving placebo. The following adverse events not described above have been reported as possibly or likely associated with carvedillol in open or controlled carvedillol studies in patients with hypertension. Incidence >0.1% to ≤1% cardiovascular system: peripheral ischemia, tahicadicalia. Central and peripheral nervous system: hypokinesis. Gastrointestinal: Bilirubinemia, increased uptic enzymes (0.2% of hypertension patients discontinued due to an increase in jep enzymes) [see Side effects (6.2)]. Psychiatric: Nervousness, sleep disorder, aggravated depression, decreased concentration, abnormal thinking, paroniria, emotional lability. Respiratory system: Asthma [see contraindications (4)]. Reproductive, male: Decreased libido. Skin and pendants: Pruritus, rash erythitemate, rash maculopapular, rash psoriaform, photoshoitivity reaction. Special senses: tinnitus. Urinary system: Increased frequency of myctura. Autonomic nervous system: Dry mouth, sweating increased. Metabolic and nutritional: Hypocalemia, hypertriglerideemia. Haematological: Anemia, leukemia. Urinary system: Increased frequency of myctura. Autonomic nervous system: Dry mouth, sweating increased. Metabolic and nutritional: Hypocalemia, hypertriglerideemia. Haematological: Anemia, leukemia. The following events have been reported in ≤0.1% of patients and are potentially important: complete AV block, block beam branches, myocardial ischemia, cerebrovascular disorder, convulsions, migraine, neuralgia, pareza, anaphylactic reaction, alopecia, exfoliation dermatitis, amnesia, GI bleeding, bronchospasm, pulmonary edema, decreased hearing, respiratory alkalosis, enlarged BUN, decreased HDL, pancytopenia and atypical lymphocytes. 6.2 Reversible elevation laboratory abnormalities in serum transaminases (ALT or AST) were observed during carvedillol treatment. Transaminasion elevation rates (2 to 3 times the upper limit of normal) observed during controlled clinical trials were generally similar between patients treated with carvedilol and those treated with placebo. However, transaminasion elevations, confirmed rechallenge, were observed with carvedilol. In a long-term, placebo-controlled study of severe heart failure, patients treated with carvedillol had lower values for hepatic transaminases than patients treated with placebo, possibly because improvements in cardiac function caused by carvedillol led to lower liver congestion and/or improved liver blood flow. Carvedilol was not associated with clinically significant changes in serum potassium, total triglycerides, total cholesterol, HDL cholesterol, kiselini, blood urei or creatinine. No clinically relevant changes were observed in serum glucose fasting in hypertensive patients. 6.3 Postmarketing experience The following side effects were identified during the use of carvedilol after approval. As these reactions are reported voluntarily from an unsafe population, it is not always possible to reliably estimate their frequency or establish a causal link to drug exposure. Reports of aplastic anaemia and severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme) were rare and received only when carvedilol was administered concurrently with other drugs associated with such reactions. Urinary incontinence in women (which was resolved after cessation of administration) and interstimial pneumonitis were reported infrequently. 7 DRUG INTERACTIONS 7.1 CYP2D6 Inhibitors and Bad Metabolisers Interactions of Carvedilol with Powerful Cyp2D6 Isoenzyme Inhibitors (such as quinidin, fluoxetine, patoksetin and propafenon) have not been studied, but these drugs are expected to increase the level of enantiomer carvedillol in the blood [see Clinical Pharmacology (12.3)]. Retrospective analysis of adverse reactions in clinical trials showed that poor 2D6 metabolisers had a higher rate of dizziness during upwards titration, which is likely due to the vasodilation effects of higher concentrations of enantiomer R(+) blocking α. 7.2 Hypotensive agents Patients taking both medicines with blocking properties β and a medicine that can deplete catecholamines (e.g. reserpin inhibitors and monoamine oxidases) should be closely observed for signs of hypotension and/or severe bradycardidide. Converse use of clonidine with β that block lives can potentiate blood pressure and heart rate-lowering effects. When it comes to breaking β with agents with door-blocking properties and clonidion, the door β to block the door. Clonidine therapy can then be discontinued a few days later by gradually reducing the dose. 7.3 Cyclosporin Modest increases in mean cyclosporin concentrations were observed after starting carvedillol treatment in 21 renal transplant patients suffering from chronic rejection of circulatory tissue. In about 30% of patients, the dose of cyclosporin had to be reduced to maintain cyclosporin concentrations within the therapeutic range, while the rest did not require adjustment. On average for the group, the dose of cyclosporin was reduced about 20% in these patients. Due to the wide interindividual variability in the required dose adjustment, it is recommended to closely monitor cyclosporin concentrations after the start of rezdididal therapy and to adjust the dose of cyclosporin as needed. 7.4 Digoxin Digoxin concentrations increase by about 15% when digoxin and carvedilol are administered contendily. Both digoxin and carvedilol slow AV Therefore, enhanced digoxin monitoring at initiation, adjustment or discontinuation of carvedilol is recommended [see Drug-Drug Interactions (12.5)]. 7.5 Inductors/Metabolism Inhibitors rifampin reduces plasma disrupterol concentrations by about 70% [see Drug-Drug Interactions (12.5)]. Cimetidine increased the AUC by about 30%, but did not cause any change in Cmax [see Drug and Drug Interactions (12.5)]. 7.6 The disruption of calcium channel blocker water decision (rarely with hemodynamic compromise) is observed when carvedilol is administered with dilciasm. As with other agents with β-blocking properties, if carvedilol should be administered with calcium channel blockers verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored. 7.7 Insulin or oral hypoglycemics agents with β-blocking properties may improve the effect of insulin and oral hypoglycemics in blood-sugar. Therefore, regular blood glucose monitoring is recommended in patients taking insulin or oral hypoglycemia [see warnings and precautions (5.6)]. 8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy Pregnancy Category C. Studies conducted in pregnant rats and rabbits with respect to carvedilol revealed increased loss after implantation in rats at doses of 300 mg/kg/day (50 times MRHD as mg/m 2) and in rabbits at doses of 75 mg/kg/day (25 times MRHD as mg/m2). In rats, there was also a decrease in foetal body weight at the maternal toxic dose of 300 mg/kg/day (50 times mrHD as mg/m2), which was accompanied by an increase in the frequency of the foetus with delayed skeletal development (missing or stunted 13th rib). In rats, the developmental toxicity adverse effect level was 60 mg/kg/day (10 times MRHD as mg/m2); in rabbits it was 15 mg/kg/day (5 times MRHD as mg/m2). There are no proper and well-controlled studies in pregnant women. Carvedilol should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus. 8.3 Nursing nursing is not known if this medicine is excreted in human milk. Studies in rats have shown that carvedilol and/or its metabolites (as well as other β-blockers) cross the placental barrier and are excreted in breast milk. There was increased mortality in one week after partuma in newborn rats treated with 60 mg/kg/day (10 times mrHD as mg/m 2) and more during the last trimester to 22. Since many drugs are excreted in human milk and due to the potential for serious side effects in nursing women from β-blockers, especially bradycides, a decision should be made on whether to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother. Effects of α and β to block the head included perinatal and neonatal stress. 8.4 Paediatric paediatrics:The effectiveness of cardiillola in patients under 18 years of age has not been established. In double-blind trial, 161 children aged 6 years, ranging from 2 months to 17 years; 45% less than 2 years old) with chronic heart failure [NYHA Class II to IV, left ventricular ejection fraction <40% for children with systemic left ventricle (L) and moderately severe ventricular dysfunction with qualitative echo for those with a systemic ventricle other than LV] receiving standard background treatment were randomised to placebo or to two levels of carvedillol dose. These dose levels produced a placebo corrective heart rate reduction of 4 to 6 heartbeats per minute, indicating beta-blockage activity. Exposure seemed to be lower in pediatric subjects than adults. After 8 months of follow-up, there was no significant effect of treatment on clinical outcomes. Side effects in this study that occurred in more than 10% of patients treated with carvedilol and twice the rate of placebo-treated patients included chest pain (17% vs. 6%), dizziness (13% vs. 2%) dyspnea (11% vs. 0%). Of the 2,065 hypertensive patients in U.S. efficacy or safety clinical trials treated with carvedilol, 21% (436) were aged 65 or older. Of the 3,722 patients receiving carvedilol in hypertension clinical trials conducted worldwide, 24% were aged 65 or older. With the exception of dizziness in hypertensive patients (incidence 8.8% in the elderly vs. 6% in younger patients), no overall differences in safety or effectiveness (see Figure 2) were observed between older subjects and younger subjects in each of these populations. Similarly, other clinical experiences reported found no differences in responses between older and younger subjects, but higher sensitivity of some elderly people cannot be excluded. 10 OVERUSE Excessive illness can cause severe hypotension, bradycardia, cardiac insuffition, cardiogenic shock and cardiac arrest. Respiratory problems, bronchospasms, vomiting, lapses of consciousness and generalized seizures may also occur. The patient should be placed in a supine position and, if necessary, kept under observation and treated in intensive care conditions. Gastric lavage or pharmacologically induced emesis can be used shortly after introduction. The following means can be applied: for excessive bradycardia: Atropine, 2 mg IV. to support cardiovascular function: glucagon, 5 to 10 mg IV quickly for 30 seconds, followed by a continuous infusion of 5 mg / hour; sympathomimetics (dobutamine, isoprenaline, adrenaline) in doses according to body weight and effect. If peripheral vasodilation dominates, it may be necessary to apply adrenaline or norepinephral with continuous monitoring of circulatory conditions. For therapy-resistant bradycelia, pacemaker therapy should be performed. For bronchospasm, β-simpatomimetics (such as or IV) or should be given aminophylline IV. In case of seizures, a slow IV injection of diazepam or clonazepam is recommended. NOTE: In case of severe intoxication where there are symptoms of shock, treatment with the antidote must continue for a sufficiently long period of time in accordance with the 7- to 10-hour half-life of the carvedillole. Cases of overuse have been reported only with carvedilol or in combination with other medicines. The amounts that are summed up in some cases exceeded 1000 million. Symptoms they experienced included low blood pressure and heart rate. Standard supportive treatment was provided and individuals recovered. 11 DESCRIPTION Carvedilol is an indiscriminate β-adrenergic blocking α 1-blocking activity. It is (±)-1-(Carbazol-4-yloxy)-3-[2-(o-methoxyphoxyphaxis)ethyl]amino]-2-propanol. Carvedilol is a racing blend with the following structure: Carvedilol is white to whitish, oval in shape, biconvex, a film-coated tablet containing 3,125 mg, 6.25 mg, 12.5 mg, or 25 mg of carvedilol. Inactive ingredients: consist of colloidal silica, chromspovidone, hydroxypropile cellulose, hypothyllosis, lactose monohydrate, magnesium steat, polysorbate 80, poilon, propylene glycol, sucrose, talc and titanium dioxide. Carvedilol is a white to whitish powder with a molecular weight of 406.5 and molecular formula C 24H26N2O4. It is freely soluble in dimethylulfoxide; soluble in metallic chloride and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in ethyl ether; and practically unsolvable in water, gastric fluid (simulated, TS, pH 1.1) and intestinal fluid (simulated, TS without pancreas, pH 7.5). 12 CLINICAL PHARMACOLOGY 12.1 The Mechanism of Action Carvedilol is a racing mixture in which indiscriminate β-adrenoreceptor blocking activity is present in S(-) enantiomer and α 1-adrenergic blocking activity is present in both R(+) and S(-) enantiomers in equal potency. Carvedilol has no intrinsic sympathetic activity. 12.2 Pharmacodynamics Left ventricular dysfunction after myocardial infarction The basis for beneficial effects of carvedilol in patients with left ventricular dysfunction after acute myocardial infarction has not been established. Hypertension The mechanism by which β-blockage produces an antihypertensive effect has not been established. β of blocking adrenoreceptors has been demonstrated in animal and human studies showing that carvedilol (1) reduces cardiac production in normal subjects; (2) reduces exercise and/or isoproterenol-induced tahycardia; and (3) reduces orthostatic tahichia reflex. Significant β-adrenoreceptor blocking effect is usually seen within 1 hour of administration of the drug. α 1-adrenoreceptor blocking activity has been proven in human and animal studies, showing that carvedilol (1) attenuates pressor effects of phenylephrin; (2) causes vasodilation; and (3) reduces peripheral vascular resistance. These effects contribute to blood pressure and are usually seen within 30 minutes of administration. Due to the activity of blocking 1-receptor α 1 receptors, blood pressure decreases more in standing position than in a supine position, and symptoms of postural hypotension (1.8%), including rare cases of syncope, may occur. After oral administration, when postural hypotension occurred, it was transient and uncommon when carvedilol is administered with food at the recommended initial dose, and titration steps are closely monitored [see Dosage and Administration (2)]. In

hypertensive patients with normal renal function, therapeutic doses of carvings reduced the resistance of renal blood processes without changing the rate of glomerular filtration or the flow of renal plasma. Changes in the secretion of sodium, potassium, uric acid and phosphorus in hypertensive patients with normal renal function were similar after carvedilol and placebo. Carvedilol has little effect on plasma catecholamine, plasma aldosterone, or electrolyte levels, but this significantly reduces plasma renin activity when given for at least 4 weeks. It also increases the level of atrial sodium peptide. 12.3 Pharmacokinetics Carvedilol is quickly and extensively absorbed after oral administration, with absolute biouravity of about 25% to 35% due to a significant degree of first pass metabolism. After oral administration, the apparent mean terminal elimination of half-life carvedillos usually ranges from 7 a.m. to 10 a.m. The plasma concentrations achieved are proportional to the oral dose administered. When administered with food, the absorption rate slows down, as demonstrated by a delay in the time to peak plasma levels, without a significant difference in the extent of bioautomatics. Taking carvedilol with food should reduce the risk of orthostatic hypotension. Carvedilol is extensively metabolized. After oral administration of radiolabelled carvedilol to healthy volunteers, carvedilol accounts for only about 7% of total plasma radioactivity measured by the surface under the curve (AUC). Less than 2% of the dose is excreted unchanged in urine. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronide. Oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfate. Metabolites of carvedillola are excreted primarily by bile in feces. Demitillation and hydroxylation in the phenono ring produce three active metabolites with β blocking receptors. Based on preclinical studies, 4'-hydroxypheneyl metabolite is about 13 times more potent than carvedilol β-blockage. Compared to carvedilol, three active metabolites show poor vasodilate activity. Concentrations of active metabolites in plasma are about one-tenth of those observed for carvedilol and have parent-like pharmacokinetics. Carvedilol undergoes stereoselective first pass metabolism with plasma levels approximately 2 to 3 times higher than S(-)-carvedillol after oral administration in healthy subjects. Intermediate apparent semi-lives for the elimination of terminals for R(+)-carvedilol range from 5 to 9 hours compared to 7 to 11 hours for S(-)-enantiomer. The primary enzymes P450 responsible for metabolism I R(+) and S(-)-carvedilola in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2 and 2E1. CYP2D6 is thought to be the main enzyme in 4'- and 5'-hydroxylation of carvediloles, with a potential contribution of 3A4. CYP2C9 is considered to be of primary importance in the path of O-methylation of S(-)-carvedilol. Carvedilol is susceptible to the effects of genetic polymorphism with poor debris metabolisers (marker for cytochrome P450 2D6) showing 2- to 3 times higher plasma concentrations of R(+)-carvedillol compared to extensive metabolisers. In contrast, levels of S(-)-chisila in plasma increase only about 20% to 25% in bad metabolisers, indicating that this enantiomer is metabolized to a lesser extent by cytoctomy P450 2D6 than R(+)-carvedillol. Pharmacokinetics of carvedilol do not seem different in poor S-mefenytoin metabolisers (patients with cytochrome deficit P450 2C19). Carvedilol is more than 98% attached to plasma protein, primarily with albumin. Plasma protein binding is independent of concentration in the therapeutic range. Carvedilol is a basic, lipophilic compound with a constant distribution volume of about 115 L, indicating a significant distribution into extravascular tissues. Plasma clearance ranges from 500 to 700 mL/min. 12.4 Specific geriatric plasma populations of carvedillol levels averaged about 50% more in the elderly compared to young subjects. Liver damage compared to healthy subjects, patients with severe liver damage (cirrhosis) show a 4 to 7 times increase in carvedilol levels. Carvedilol is contraindicated in patients with severe liver damage. Kidney damage Although carvedilol is metabolized primarily by the liver, plasma rezdidiol concentrations have been reported to have increased in patients with kidney damage. Based on mean AUC data, approximately 40% to 50% higher plasma resimele concentrations were observed in hypertensive patients with moderate to severe renal impairment compared to a control group of hypertensive patients with normal renal function. However, the AUC value ranges were similar for both groups. Changes in the mean peak plasma level were less pronounced, approximately 12% to 26% more in patients with impaired renal function. In accordance with the high degree of binding of proteins in plasma, it seems that carvedilol is not significantly cleaned by haemodialysis. 12.5 Drug and drug interactions Since carvedilol undergoes significant oxidative metabolism, metabolism and pharmacokinetics of carvedilol may be influenced by induction or inhibition of the cytochrome enzyme P450. Rifampin in A study conducted in 8 healthy male subjects, rifampine (600 mg daily for 12 days) reduced AUC and C max carvedilol by about 70% [see Drug Interactions (7.5)]. Cimetidine In a pharmacokinetic study conducted in 10 healthy male subjects, cimetidine (1000 mg/day) increased AUC carvedillola in stable condition by 30% without changing in C max[see Drug Interactions (7.5)]. Gliburid In 12 healthy subjects, combined administration of cardiillola (25 mg once a day) and one dose of glyburid did not result in clinically relevant pharmacokinetic interaction for any compound. Hydrochlorothiazid One oral dose of carvedilol 25 mg did not change the pharmacokinetics of a single oral dose of hydrochlorothiaside 25 mg in 12 patients with hypertension. Likewise, hydrochlorothiazid did not affect the pharmacokinetics of carvedilol. Digoxin After concomid administration of carvedilol (25 mg once a day) and digoxin (0.25 mg once a day) for 14 days, concentrations of auc and digoxin troughs increased by 14% and 16% respectively, in 12 hypertensive patients. Digoxin After concomid administration of carvedilol (25 mg once a day) and digoxin (0.25 mg once a day) for 14 days, concentrations of auc and digoxin troughs increased by 14% and 16% respectively, in 12 hypertensive patients. Torsemide In a study of 12 healthy subjects, combined oral administration of carvedilol 25 mg once a day and torsemis 5 mg once a day for 5 days did not result in any significant differences in their pharmacokinetics compared to the use of the drugs alone. Warfarin Carvedilol (12.5 mg twice daily) had no effect on the ratio of prothrombin time in stable condition and did not alter pharmacokinetics R(+)- and S(-)-warfarin after concomiment administration with warfarin in 9 healthy volunteers. 13 NON-CLINICAL TOXICOLOGY 13.1 Carcinogenesis and mutagenesis and fertility impairment In two-year studies conducted in rats given carvedillol at doses up to 75 mg/kg/day (12 times more than the maximum recommended human dose [MRHD] compared to mg/m 2 basis) or in mice given up to 200 mg/kg/day (16 times MRHD on mg/m2 basis), carvedilol did not have a carcinogenic effect. Carvedilol tested negative when tested in a battery of genotoxicity tests, including Ames and CHO/HGPRT tests for mutagenicity and micronucleus in vitro hamsters and in vivo human lymphocyte cell tests for clastogenicity. In doses ≥200 mg/kg/day (≥32 times MRHD as mg/m 2), carvedilol was toxic to adult rats (sedation, reduced weight gain) and was associated with reduced number of successful mating, prolonged mating time, significantly lower amount of lute corpora and implants per dam, and complete resorption of 18% of litter. The dose level with no observed effect for excessive toxicity and fertility impairment was 60 mg/kg/day (10 times mrHD as mg/m2). 14 CLINICAL TRIALS 14.1 Left ventricle dysfunction after myocardial infarction There was a double blind study comparing carvedilol and placebo in 1,959 patients with recent myocardial infarction (within 21 days) and a left ventricle ejection fraction of ≤40%, with (47%) symptoms of heart failure. Patients receiving carvedilol received 6.25 mg twice a day, titrated as tolerated at 25 mg twice a day. Patients had to have sistalic blood pressure > 90 mm Hg, a sitting heart rate >60 beats/minutes and no contraindication to β blockers. Treatment of index infarction included aspirin (85%), IV or oral β-blockers (37%), nitrates (73%), heparin (64%), thrombolytics (40%) acute angioplasty (12%). Background treatment included ACE inhibitors or angiotensin receptor blockers (97%), anticoagulant (20%), lipid-lowering agents (23%) and diuretics (34%). Initial population characteristics included an average age of 63 years, 74% male, 95% caucasian, mean blood pressure 121/74 mm Hg, 22% with diabetes and 54% with a history of hypertension. The mean dose achieved by carvedilol is 20 mg twice a day; duration of follow-up was 15 months. All-cause mortality was 15% in the placebo group and 12% in the carvedilol group, indicating a 23% reduction in risk in patients treated with carvedilol (95% CI 2 to 40%, p = 0.03), as shown in Figure 1. The effects on mortality in different subgroups are shown on 2 October 2015. Almost all deaths were cardiovascular (reduced by 25% by carvedilol), and most of these deaths were sudden or associated with pump failure (both types of deaths were reduced by carvedilol). The second endpoint of the study, overall mortality and hospitalization of all causes, showed no significant improvement. There was also a significant reduction from the 40% fatal or unsatisfacted myocardial infarction observed in the carvedilol group (95% CI 11% to 60%, p = 0.01). A similar reduction in the risk of myocardial infarction was observed in placebo-controlled placebo-controlled studies of rezdidiol in heart failure. Figure 1. Survival analysis for CAPRICORN (treatment intent) Figure 2. Effects on mortality for subgroups in JARAC 14.2 Hypertension Carvedilol has been studied in 2 placebo-controlled trials that used twice daily dosing, in total daily doses of 12.5 to 50 mg. In these and other studies, the initial dose did not exceed 12.5 mg. At 50 mg/day, carvedilol reduces sedentary trough (12-hour) blood pressure by about 9/5.5 mm Hg; At 25 mg/day the effect was about 7.5/3.5 mm Hg. Comparisons between trough and peak blood pressure showed a trough-to-peak ratio for blood pressure response of about 65%. Heart rate dropped by about 7.5 beats/minutes at 50 mg/day. In general, as for other β, responses were lower in black than non-black patients. There were no differences in age or gender in response. The peak antihypertensive effect occurred 1 to 2 hours after the dose. The dose-related blood pressure response was accompanied by dose-related adverse reactions [see side effects (6)]. 16 HOW TO AND HANDLING Carvedilol tablets are delivered as: 3,125 mg tablets: White on off-white, oval-shaped, biconveks, film coated tablets, debossed with 'RX4', on one side and plain on the other. NDC 63304-823-30 Bottles 30 NDC 63304-823-10 Bottles of 1000 6.25 mg tablets: White on off-white, oval-shaped, biconvex, film coated tablets, debossed with 'RX' on one side and '824' on the other side. NDC 63304-824-30 Bottles 30 NDC 63304-824-10 Bottles of 1000 12.5 mg tablets: White on off-white, oval shape, biconveks, film coated tablets, debossed with 'RX825' on one side and plain on the other. NDC 63304-825-30 Bottles 30 NDC 63304-825-10 Bottles of 1000 25 mg tablets: White on off-white, oval-shaped, biconvex, film coated tablets, debossed with 'RX826' on one side and plain on the other. NDC 63304-826-30 Bottles 30 NDC 63304-826-10 Bottles 1000 Trade at 20 - 25 °C (68 - 77 ° F). (See USP controlled room temperature). Protect against moisture. Spray in a narrow, lightproof container. 17 PATIENT COUNSELING INFORMATION 17.1 Patient advice Patients taking carvedilol should be advised of the following: Patients should take carvedilol with food. Patients should not discontinue or discontinue carvedilol without medical advice. Patients should consult their doctor if they have signs or symptoms of worsening heart failure such as weight gain or shortness of breath enlargement. Patients may experience a drop in blood pressure when standing, resulting in dizziness and, rarely, fainting. Patients should sit or lie down when these symptoms of lowering blood pressure occur. If you have dizziness or fatigue, patients should avoid driving or dangerous tasks. Patients should consult a doctor if they have dizziness or fainting, in case the dose is adjusted. Diabetic patients should report any changes in their blood sugar level to their doctor. Carriers of contact lenses may experience reduced variation. PHARMACIST-SEPARATE HERE AND GIVE INSTRUCTIONS TO THE PATIENT ---------- 17.2 FDA-approved patient information Rx Only Carvedilol Tablets Read the patient information that comes with the carvedilol before you start taking it and every time you get a refill. Maybe there's new information. This information does not take place to talk to your doctor about your medical condition or treatment. If you have any questions about carvedilol, ask your doctor or pharmacist. WHAT IS CARVEDILOL? Carvedilol is a prescription drug belonging to a group of medicines called beta-blockers. Carvedilol is used, often with other medicines, for the following conditions: To treat patients with high blood pressure (hypertension) To treat patients who have had a heart attack that has worsened how well the heart is pumping to treat patients with certain types of failure Carvedilol is not approved for use in under the age of 18. WHO SHOULDN'T TAKE CARVEDILOL? Do not take carvedilol if: You have severe heart failure and are hospitalized in the intensive care ward or need certain intravenous medications that help support circulation (inotropic medications) They are prone to asthma or other breathing problems They have a slow heartbeat or heart skipping heart rate (irregular heartbeat) They have liver problems They are allergic to any of the ingredients in the carvedilol. The active ingredient is carvedilol. See the end of this leaflet for a list of all the ingredients in carvedilol. WHAT DO I TELL MY DOCTOR BEFORE TAKING CARVEDILOL? Tell your doctor about all your medical conditions, including if: You have asthma or other lung problems (such as bronchitis or emphysema) You have problems with blood flow to your feet and legs (peripheral vascular disease) carvedilol can worsen some of your symptoms. They have diabetes They have thyroid problems They have a condition called phenochromocyte They had severe allergic reactions she is pregnant or trying to get pregnant. It is not known if carvedilol is safe for your unborn child. You and your doctor should discuss the best way to control high blood pressure during pregnancy. Are you breastfeeding. It is not known if the carvedilol passes into your breast milk. Do not breastfeed while using carvedilol. They are scheduled for surgery and will receive anesthetic agents taking prescription or over-the-counter medications, vitamins, and herbal supplements. Carvedilol and certain other drugs can affect each other and cause serious side effects. Carvedilol may affect the way other medicines work. Also, other medications can affect how well carvedilol works. Show this list to your doctor and pharmacist before starting a new medicine. HOW DO I GET CARVEDILOL? It is important that you take the medicine every day as directed by your doctor. If you suddenly stop taking carvedilol, you may have chest pain and/or a heart attack. If your doctor decides that you should stop taking carvedilol, your doctor may slowly reduce the dose over a period of time before stopping it completely. Take the carvedilol exactly as prescribed. Your doctor will tell you how many tablets to take and how often. To reduce possible side effects, your doctor may start with a low dose and then slowly increase the dose. Do not stop taking carvedilol and do not change the amount of carvedilol you take without talking to your doctor. Tell your doctor if you gain weight or have trouble breathing while taking carvedilol. Take carvedilol with food If you miss a dose of carvedilol, take the dose as soon as you remember, unless it is time to take the next dose. Take your next dose at the usual time. Do not take 2 doses at a time. If you take too much carvedilol, call your doctor or poison control center immediately. WHAT SHOULD I AVOID WHILE TAKING CARVEDILOL? can cause you to feel dizzy, tired, tired, Weak. Do not drive a car, use machines or do anything that should be careful if you have these symptoms. WHAT ARE THE POSSIBLE SIDE EFFECTS OF CARVEDILOL? Low blood pressure (which can cause dizziness or fainting when you get up). If this happens, sit down or lie down immediately and tell your doctor. Fatigue. If you feel tired or dizzy, you should not drive, use machines or do anything that needs you to be careful. Slow heart rate Changes in blood sugar. If you have diabetes, tell your doctor if you have any changes in your blood sugar level. Carvedilol can hide some of the symptoms of low blood sugar, especially rapid heartbeat Carvedilol can mask symptoms of hyperthyroidism (overactive thyroid). Exacerbation of severe allergic reactions. Other side effects of carvedilol include shortness of breath, weight gain, diarrhoea and fewer tears or dry eyes that become worrying if you wear contact lenses. Call your doctor if you have any side effects that bother you or do not leave. How do I store carvedilol? Store the carvedilol at less than 86 °F (30 °C). Keep the pills dry. Surely, throw away the carvedilol, which is for safety or no longer needed. Keep the carvedilol and all medicines out of the reach of children. GENERAL INFORMATION about CarveDILOL is sometimes prescribed for conditions not described in leaflets with patient information. Do not use carvedilol for a condition for which it is not prescribed. Do not give carvedilol to other people, even if they have the same symptoms as you. It could hurt them. This leaflet compresses the most important information about carvedillol. If you want more information, talk to your doctor. You can ask your doctor or pharmacist for information about carvedilol that has been written for healthcare professionals. You can also find out more about carvedilol by visiting the www.ranbaxyusa.com website or by calling 1-888-RANBAXY- (726-2299). This call is free. WHAT ARE THE INGREDIENTS IN CARVEDILOL? Active ingredient: Carvedilol Inactive ingredients: colloidal silicon dioxide, crospovidone, hydroxypropile cellulose, hypochromellosis, lactose monohydrate, magnesium stearate, polysorbate 80, povidon, propylene glycol, sucrose, talc and titanium dioxide Carvedilol tablets come in the following strengths: 3,125 mg, 6.25 mg, 12.5 mg, 25 mg. Manufatured for: Ranbaxy Pharmaceuticals Inc. Jacksonville, FL 32257 USA by: Ohm Laboratories Inc. North Brunswick, NJ 08902 USA September 2007 2007