PRODUCT MONOGRAPH

NU-CARVEDILOL

Carvedilol Tablets

3.125 mg, 6.25, 12.5 mg and 25 mg

Congestive Heart Failure Agent

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THERAPEUTIC CLASSIFICATION

Congestive Heart Failure Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Carvedilol is a cardiovascular agent for the treatment of congestive heart failure that combines beta-adrenoceptor blockade and vasodilation in a single racemic mixture. Nonselective beta-adrenoceptor blocking activity is present in the S(-) enantiomer and $alpha_1$-adrenoceptor blocking activity is present at equal potency in both the R(+) and S(-) enantiomers. Carvedilol has no intrinsic sympathomimetic activity. Its action on beta-receptors is 10 times stronger than on $alpha_1$-receptors.

Carvedilol reduces peripheral vascular resistance by vasodilation, thereby causing a fall in systemic blood pressure after acute administration, predominantly mediated through selective $alpha_1$-antagonism. Beta blockade prevents reflex tachycardia with the net result that heart rate is unchanged or decreased. Carvedilol reduces renin release through beta blockade.

In two studies that compared the acute hemodynamic effects of carvedilol to baseline measurements in patients with congestive heart failure, there were significant reductions in systemic blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and heart rate. Initial effects on cardiac output, stroke volume index and systemic vascular resistance were small and variable.

In terms of chronic hemodynamic effects (12 to 14 weeks), carvedilol significantly reduced systemic blood pressure, pulmonary artery pressure, right atrial pressure, systemic vascular resistance and heart rate while stroke volume index was increased.

The mechanism for the beneficial effects of carvedilol in congestive heart failure has not been established.

In a US multicentre program, 1197 patients with stable symptomatic congestive heart failure, NYHA class II to IV, were challenged with a low dose of carvedilol (3.125 or 6.25 mg twice daily) for 2 to 4 weeks to determine tolerability. Of these patients, 1094 were then randomized to double-blind treatment with carvedilol (n=696) or placebo (n=398) and stratified to one of four studies based on baseline exercise performance, with the prestated objective to evaluate total mortality. The average duration of therapy on carvedilol was 6.5 months in this program. Patients entering the program had symptomatic congestive heart failure due to ischemic or non-ischemic cardiomyopathy with an ejection fraction $\leq$35%. All patients received conventional therapy, i.e. diuretics, angiotensin-converting enzyme (ACE) inhibitors, if tolerated, with or without digoxin.

On an intent-to-treat basis, total mortality in this program was 3.2% in the carvedilol group and 7.8% in the placebo group. Thus a relative risk reduction of 65% (95% confidence limits 39 and 80%, p=0.001) was observed. Treatment with carvedilol was associated with a significant decrease in the relative risk of death from progressive pump failure (81%, p=0.001) and the relative risk of sudden death (56%, p=0.033). The incidence of cardiovascular hospitalizations was 13% in the carvedilol group and 21% in the placebo group, with a relative risk reduction of 36% (95% confidence limits: 14% and 53%, p=0.004).

Improved patient well-being was observed with carvedilol treatment in the US multicentre program, as indicated by a change in the NYHA class from baseline to endpoint for the four US phase III placebo-controlled studies. The overall between-group difference in distributions, stratified by protocol and baseline classification, was significant ($p<0.001$) and as also indicated by patient and physician global assessments during US Phase III trials, 78% of patients in the carvedilol group rated their condition as improved compared to 63% in the placebo group (p values over four studies from 0.001 to 0.032). However, exercise tolerance was not improved.

In a large multicentre trial of carvedilol, performed in Australia and New Zealand, 443 patients with stable symptomatic congestive heart failure NYHA Class I to III, were challenged with a low dose of carvedilol (3.125 mg or 6.25 mg twice daily) for 2-4 weeks to determine tolerability. Of these patients 415 were then randomized to double-blind treatment with carvedilol (n=207) or placebo (n=208). The average duration of therapy on carvedilol was 16.1 months in this study. Patients entering the program had symptomatic congestive heart failure due to ischemic cardiomyopathy with an ejection fraction $\leq$45%. All patients received conventional therapy, i.e., diuretics, angiotensin-converting enzyme (ACE) inhibitors, if tolerated, with or without digoxin.

On an intent-to-treat basis, total mortality in this Australia and New Zealand trial was 10.1% in the carvedilol group and 13.9% in the placebo group, a non-statistically significant relative risk reduction of 29% (confidence limits -24% and 59%, p=0.231). Cardiovascular hospitalizations were 31% in the carvedilol group and 40% in the placebo group, a relative risk reduction of 28% (95% confidence limits: 1% and 48%, p=0.044). Patient well-being as judged by NYHA class or Specific Activity Scale rating, as well as exercise tolerance were no different in the carvedilol group compared to the placebo group.

In the COPERNICUS trial, 2289 patients with severe heart failure were randomly assigned to treatment with placebo or carvedilol for up to 29 months. Patients had symptoms at rest or on minimal exertion and had a left ventricular ejection fraction <25% (mean 20%), despite treatment with diuretics (99%), an ACE inhibitor (89%), and digitalis (66% worldwide, 85% within Canada) for more than 2 months. Patients with cardiac impairment not related to left ventricular dysfunction were excluded as were patients with prior cardiac transplant, cardioplasty, unstable angina, myocardial infarction, destabilizing cardiac arrhythmias, or treatment within 1 month with an α-adrenoceptor antagonist (except for prostatism), a calcium channel blocker or a class I antiarrhythmic agent. The trial was followed by a data safety monitoring committee, which stopped the trial early after a median follow-up of 10.4 months because of an observed reduction in total mortality, the primary endpoint, from 19.7% per patient-year on placebo to 12.8% per patient-year on carvedilol, (a relative risk reduction of 35%; hazard ratio 0.65, 95% CI 0.52 and 0.81, and a P value adjusted for interim analyses of 0.0014). The results are summarized as follows.

End Point	**Placebo N=1133**	**Carvedilol N=1156**	**Hazard Ratio (95% CI)**	**% Reduction**	**Nominal P value**
Mortality	190	130	0.65 (0.52-0.81)	35	0.00013
Mortality + all hospitalization	507	425	0.76 0.67-0.87)	24	0.00004
Martality + CV hospitalization	395	314	0.73 0.63-0.84)	27	0.00002
Mortality + CHF hospitalization	357	271	0.69 (0.59-0.81)	31	0.00004

Pharmacokinetics

Carvedilol is rapidly absorbed following oral administration, with peak plasma concentrations of carvedilol observed at 1 hour post-dose in fasting subjects. Despite being well absorbed, absolute bioavailability is approximately 25% to 35% due to a significant degree of first-pass metabolism.

Plasma concentrations achieved are proportional to the oral dose administered. When administered with food, the rate of absorption is slowed, as evidenced by a delay in time to reach peak plasma concentrations (about 2.3 hours post-dose), with no significant difference in extent of bioavailability.

Carvedilol is highly bound to plasma proteins, (greater than 98%) primarily to albumin. The plasma-protein binding is independent of concentration over the therapeutic range. Carvedilol is a basic, lipophilic compound with a steady-state volume of distribution of approximately 115 L.

Following oral administration, the apparent mean terminal elimination half-life of carvedilol ranges from 7 to 10 hours. Plasma clearance ranges from 500 to 700 mL/min. Carvedilol is extensively metabolized with less than 2% of the dose excreted unchanged in the urine. Carvedilol is metabolized mainly by glucuronidation and aromatic ring oxidation by the cytochrome P450 system (primarily CYP2D6 and CYP2C9 isozymes). The metabolites of carvedilol are excreted mainly via the bile into the feces. Elimination is mainly biliary. The primary route of excretion is via the feces. A minor part is eliminated via the kidneys in the form of various metabolites.

Carvedilol undergoes stereo selective first-pass metabolism with plasma levels of R(+)-carvedilol approximately 2- to 3-fold higher than S(-)-carvedilol following oral administration in healthy

subjects. The mean apparent terminal elimination half-life for R(+)-carvedilol ranges from 5 to 9 hours compared with 7 to 11 hours for the S(-) enantiomer.

Carvedilol is subject to genetic polymorphism with poor metabolizers of debrisoquin (deficient in CYP2D6) exhibiting 2- to 3-fold higher plasma concentrations of the R(+)-carvedilol compared to extensive metabolizers. In contrast, plasma levels of S(-)-carvedilol are increased only about 20% to 25% in poor metabolizers, indicating that the metabolism of this enantiomer is affected to a lesser extent by CYP2D6 than R(+)-carvedilol. The Pharmacokinetics of carvedilol enantiomers do not appear to be different in poor metabolizers of 5-mephenytoin, i.e. deficient in CYP 2C19.

There are at least 5 pharmacologically active metabolites of carvedilol: desmethyl, 4'-hydroxyphenyl, 5'-hydroxyphenyl, 1-hydroxycarbazolyl and 8-hydroxycarbazolyl metabolites. Each of these metabolites has two enantiomeric forms and each metabolite possesses different relative potencies with regard to alpha-and beta-receptor blocking activities. Plasma concentrations of these metabolites are 10 to 50-fold lower than those observed for the parent compound. Therefore, even for metabolites that are more active, or at least as active as carvedilol itself, they are present at such low concentrations that they would produce effects less than, or at least not greater than, the parent compound.

In patients with cirrhotic liver disease, the absolute bioavailability of carvedilol was 4 times greater as compared to healthy subjects with median C_{max} and AUC values for carvedilol 4 to 7 times higher in patients with liver disease following oral administration (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS).

Although carvedilol is metabolized primarily by the liver, plasma concentrations of carvedilol have been reported to be increased in patients with renal impairment. Based on AUC data,

approximately 40% to 50% higher plasma concentrations of carvedilol 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 ranges of AUC values were similar for both groups. Changes in C_{max} data were less pronounced, approximately 12% to 26% higher in patients with impaired renal function.

The pharmacokinetics of carvedilol are not altered by hemodialysis.

Steady-state plasma concentrations of carvedilol and its enantiomers increased proportionally over the 6.25 to 50 mg b.i.d. dose range in patients with congestive heart failure. Compared to healthy subjects, patients with Class IV congestive heart failure had increased mean AUC and C_{max} values for carvedilol and its enantiomers with up to 50% to 100% higher values than normal volunteers. The mean apparent terminal elimination half-life for carvedilol was similar to that observed in healthy subjects.

Compared to young subjects (18-43 years old), AUC values for carvedilol were, on average, 38% higher in elderly (65-76 years old) subjects . Moreover, AUC values were 50% higher for S(-)-carvedilol and 23% for R(+)-carvedilol in the elderly compared to the young subjects. Changes in C_{max} values for carvedilol and its enantiomers were less pronounced, approximately 8% to 17% higher in elderly subjects with no apparent change in T_{max}. Although the terminal elimination half-lives of carvedilol were similar in both young and elderly subjects, the initial decline in plasma concentrations in the elderly appeared to be slower than in the young subjects, suggesting a decrease in systemic clearance of carvedilol in the elderly (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).

Comparative Bioavailability

A comparative bioavailability study was performed on healthy volunteers. The rate and extent of absorption of carvedilol was measured and compared following oral administration of 1 x 25 mg of either NU-CARVEDILOL 25 mg tablets or Coreg 25 mg tablets. The results from measured data are summarized below:

Summary Table of the Comparative Bioavailability Data

Carvedilol (Dose: 1 x 25 mg) From Measured Data - Under Fed Conditions

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	NU-CARVEDILOL	Coreg®†	
AUC_T (ng •hr/mL)	329 362 (46)	306 344 (51)	107.5
AUC_I (ng •hr/mL)	336 370 (47)	321 359 (50)	109.3
C_{max} (ng/mL)	65.0 73.5 (55)	70.2 82.3 (61)	92.6
T_{max} (hr)*	2.62 (52.9)	1.84 (60.1)	
$t_{1/2}$ (hr)*	9.99 (34)	10.0 (43)	

* Arithmetic means (CV%).

** Based on the least squares estimate.

† Coreg® is manufactured by Hoffmann-La Roche Limited, marketed by SmithKlineBeecham and was purchased in Canada.

INDICATIONS AND CLINICAL USE

NU-CARVEDILOL (carvedilol) is indicated for treatment of mild, moderate or severe heart failure of ischemic or non-ischemic origin to increase survival and also, to reduce the combined risk of all-cause mortality and cardiovascular or non-cardiovascular hospitalizations.

In general, NU-CARVEDILOL is used in conjunction with diuretics and an ACE inhibitor, with or without digitalis.

NU-CARVEDILOL should be prescribed by a physician experienced in the treatment of heart failure.

Beta blockers can cause worsening heart failure (see PRECAUTIONS). Since carvedilol has beta-blocking properties, care must be taken during initiation and up-titration of the drug in heart failure patients, since worsening heart failure has been observed during this phase of treatment. In order to minimize the risk of these events, it is critical to carefully follow the recommended dosing for carvedilol in patients with congestive heart failure (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

NU-CARVEDILOL (carvedilol) is contraindicated in patients with:

- decompensated cardiac failure requiring intravenous inotropic therapy with sympathomimetic agents
- bronchial asthma or related bronchospastic conditions (see PRECAUTIONS)

- second- or third- degree AV block, or sick sinus syndrome (unless a permanent pacemaker is in place)
- cardiogenic shock
- severe hypotension (see WARNINGS)
- severe bradycardia (see WARNINGS)
- primary obstructive valvular heart disease
- clinically manifest hepatic impairment (jaundice, ascites, spider angiomata, esophageal varices, etc.)
- mental incapacity (eg. severe Alzheimer's, alcoholism, drug abuse), unless closely supervised by an appropriate caregiver
- hypersensitivity to carvedilol or any component of NU-CARVEDILOL

WARNINGS

Hypotension

Hypotension and postural hypotension in congestive heart failure patients occurred with a higher incidence in carvedilol-treated than in placebo-treated patients (see ADVERSE REASONS). The risk of these events was highest during initiation of therapy and during the first 30 days of dosing corresponding to the up-titration period. Therefore, it is of critical importance that the dosing recommendation be followed (see DOSAGE AND ADMINISTRATION).

Sinus Bradycardia

Severe sinus bradycardia may occur with the use of carvedilol. In such cases, dosage should be discontinued.

In clinical trials, patients with a resting heart rate of less than or equal to 68 beats/minute prior to initiation of carvedilol were not studied.

Hepatic Injury

Hepatocellular injury, confirmed by rechallenge, has occurred rarely with carvedilol therapy.

Hepatic injury has been reversible and has occurred after short-and/or long-term therapy with minimal clinical symptomatology. No deaths due to liver function abnormalities have been reported in association with the use of carvedilol.

At the first symptom/sign of liver dysfunction (e.g. pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness or unexplained "flu-like" symptoms) laboratory testing should be performed. If the patient has laboratory evidence of liver injury or jaundice, NU-CARVEDILOL (carvedilol) should be stopped and not restarted.

Abrupt Cessation of Therapy

In patients with heart failure treated chronically with carvedilol, abrupt cessation of therapy may lead to deterioration. Therefore discontinuation of carvedilol should be done gradually, if possible.

Patients with ischemic heart disease should be warned against abrupt discontinuation of beta-adrenergic blocking agents. There have been reports of severe exacerbation of angina, and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris, following abrupt discontinuation of beta-blocker therapy.

The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuing NU-CARVEDILOL in patients with angina pectoris, the dosage should be gradually reduced over a period of about 2 weeks and the patient should be carefully observed. The same frequency of administration should be maintained. In situations of greater urgency, carvedilol therapy should be discontinued stepwise and under conditions of closer observation. If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with the drug be re-instituted promptly, at least temporarily.

Oculomucocutaneous Syndrome

Various skin rashes and conjunctival xerosis have been reported with beta-blockers. A severe syndrome (oculomucocutaneous syndrome) whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one beta-adrenergic blocking agent (practolol). This syndrome has not been observed in association with carvedilol or any other such agent. However, physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

Uveal Binding

Animal studies have shown that carvedilol binds to the melanin of the uveal tract. The significance of this in humans is not known but periodic ophthalmic examinations are advisable while the patient is taking NU-CARVEDILOL.

Hyperthyroidism

In patients with thyrotoxicosis, possible deleterious effects from long-term use of carvedilol have not been appraised. Beta-blockade, in general, may mask the clinical signs of continuing hyperthyroidism or complications, and give a false impression of improvement. Therefore, abrupt withdrawal of carvedilol may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

Pheochromocytoma

The effect of carvedilol in patients with pheochromocytoma has not been studied. Since paradoxical hypertensive responses have been reported in a few patients with this tumor when treated with beta-blockers, physicians should use caution when administering carvedilol to patients with pheochromocytoma.

PRECAUTIONS

Cardiac Failure

Worsening cardiac failure may occur during initiation and up-titration of NU-CARVEDILOL (carvedilol). Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta blockade may further depress myocardial contractility.

Cardiac failure should be controlled for at least 4 weeks before NU-CARVEDILOL treatment is initiated. In clinical trials of mild to moderate heart failure, patients were required to be on stable doses of diuretics and ACE inhibitors (if tolerated) prior to the initiation of carvedilol. Despite these steps to ensure stability, a small number of patients developed worsening heart failure. During the initiation of therapy (doses of 3.125-6.25 mg b.i.d over 2-4 weeks) 6.0 % of patients developed worsening congestive heart failure. During up-titration (12.5-50 mg b.i.d over 2-6 weeks), worsening heart failure was reported in 5.1% of patients treated with carvedilol and in 4.1% of placebo patients.

In a placebo-controlled trial of patients with severe heart failure (COPERNICUS trial), worsening heart failure occurred during up-titration although the frequency reported during the first 3 months was similar with carvedilol (15.4%) and with placebo (14.8%). When treatment was maintained beyond 3 months, worsening heart failure was reported less frequently in patients treated with carvedilol than with placebo. Worsening heart failure observed during long-term therapy is more likely to be related to the patients' underlying disease than to treatment with carvedilol.

Administration of NU-CARVEDILOL to patients with controlled heart failure must be carried out under careful supervision. If symptoms occur, diuretics should be increased and the carvedilol

dose not advanced or even lowered until clinical stability resumes (see DOSAGE AND ADMINISTRATION). However, it may be necessary to discontinue NU-CARVEDILOL. Such episodes may not preclude subsequent successful titration of the drug or a favourable response to carvedilol.

Renal Function

Rarely, use of NU-CARVEDILOL in patients with congestive heart failure has resulted in acute renal failure and deterioration of renal function, likely on a pre-renal basis. Patients at risk appear to be those with low blood pressure (systolic BP<100 mm Hg), ischemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency. Renal function has returned to baseline when carvedilol was stopped. In patients with these risk factors it is recommended that renal function be monitored during up-titration of NU-CARVEDILOL and the drug discontinued or dosage reduced if worsening of renal function occurs (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment:

Since carvedilol undergoes first-pass metabolism in the liver, reduced hepatic metabolism could lead to greater systemic bioavailability of carvedilol in patients with hepatic impairment. Care should be taken in selecting an appropriate dosage regimen for these patients (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION). Physicians should be aware of the potential for increased manifestations of vasodilation (dizziness, postural hypotension, hypotension, syncope) or beta-blockade (bradycardia, AV block) in patients with mild hepatic impairment receiving NU-CARVEDILOL (see DOSAGE AND ADMINISTRATION).

Bronchospasm (e.g. chronic bronchitis and emphysema)

Patients with bronchospastic disease should, in general, not receive beta-blockers (see CONTRAINDICATIONS).

In clinical trials of patients with congestive heart failure, patients with bronchospastic disease were enrolled if they did not require oral or inhaled medication to treat their bronchospastic disease. In such patients, it is recommended that carvedilol be used with caution. The dosing recommendations should be followed closely and the dose should be lowered if any evidence of bronchospasm is observed during up-titration.

Allergic Reaction

There may be increased difficulty in treating an allergic-type reaction in patients on beta-blockers. In these patients, the reaction may be more severe due to pharmacological effects of beta-blockers and problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis.

On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other, these doses can be associated with excessive alpha-adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of beta agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm and norepinephrine to overcome hypotension.

Prinzmetal's Angina:

Beta-blocking agents may provoke chest pain in patients with Prinzmetal's angina. There has been no clinical experience with carvedilol in these patients. Caution should be taken in the administration of NU-CARVEDILOL to patients suspected of having Prinzmetal's variant angina.

Primary Regurgitative Valvular Heart Disease

NU-CARVEDILOL should be used with caution in patients with primary regurgitative valvular disease as experienced in this patient population is limited.

Patients with Diabetes

NU-CARVEDILOL should be administered with caution to patients subject to spontaneous hypoglycemia, or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic blocking drugs may enhance hypoglycemia in patients prone to this condition. Also, diabetics on insulin or oral hypoglycemic medication may have an increased tendency towards hypoglycemia when treated with these drugs. It may also be necessary to adjust the dosage of oral hypoglycemics or insulin. Early signs of acute hypoglycemia, especially tachycardia, may be masked or attenuated. Regular monitoring of blood glucose is therefore recommended when carvedilol is initiated, adjusted or discontinued.

Thyrotoxicosis

β-adrenergic blockade may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of β-blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate thyroid storm.

Peripheral Vascular Disease

Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

Patients and General Surgery

Because of the synergistic negative inotropic and vasodilating effects of carvedilol and anaesthetic drugs, the potential for pronounced hypotension during anesthesia exists. If treatment with NU-CARVEDILOL is to be continued perioperatively, particular care should be taken when anesthetic agents which depress myocardial function are used.

Contact Lens Use

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

Use in the Elderly

Pharmacokinetic studies indicate that AUC and T_{max} values are increased in elderly patients. Plasma levels of carvedilol averaged about 38% higher in elderly compared to young subjects.

Therefore, dosage adjustments should be made with particular caution (see DOSAGE and ADMINISTRATION).

Use During Pregnancy

There have been no clinical studies carried out to specifically examine the use of carvedilol in pregnant women. Beta-blockers reduce placental perfusion, which may result in intrauterine fetal death, immature and premature deliveries. In addition, adverse effects (especially hypoglycemia and bradycardia) may occur in the fetus and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period.

Animal reproduction studies have revealed no teratogenic potential for carvedilol. Embryotoxicity was observed only after large doses in rabbits. The relevance of these findings for humans is uncertain.

NU-CARVEDILOL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use During Lactation

Carvedilol and/or its metabolites are excreted in breast milk. Therefore, breast feeding is not recommended during administration of NU-CARVEDILOL.

Use in Children

Safety and efficacy in children have not been established.

Drug Interactions

Antihypertensive Agents: When administered concomitantly with other drugs that are anti-hypertensive in action or have hypotension as part of their adverse effect profile, carvedilol may have additive effects to excessively lower blood pressure.

Catecholamine-depleting agents: Patients taking both agents with beta-blocking properties and a drug that can deplete catecholamines (e.g., *reserpine* and *monoamine oxidase inhibitors)* should be observed closely for evidence of hypotension and/or marked bradycardia.

Antiarrhythmics and Calcium Channel Blockers: Isolated cases of conduction disturbance (rarely with hemodynamic compromise) have been observed when carvedilol is co-administered with anti-arrhythmic agents or calcium channel blockers such as *diltiazem* and *verapamil* that can slow cardiac conduction. As with other agents with beta-blocking properties, if NU-CARVEDILOL is to be administered orally with antiarrhythmics that slow conduction or calcium channel blockers of the *verapamil* or *diltiazem* type, it is recommended that ECG and blood pressure be monitored.

Digoxin: Following concomitant administration of carvedilol and *digoxin,* peak concentration of digoxin increased by approximately 30% and steady-state trough concentrations of digoxin were increased by about 15%. Both *digoxin* and carvedilol slow AV conduction. Therefore, increased monitoring of *digoxin* levels is recommended when initiating, adjusting or discontinuing NU-CARVEDILOL.

Clonidine: Concomitant administration of *clonidine* with agents with beta-blocking properties may potentiate blood pressure and heart rate lowering effects. When concomitant treatment with agents with beta-blocking properties and *clonidine* is to be terminated, the beta-blocking agent

should be discontinued first. *Clonidine* therapy can then be discontinued several days later by gradually decreasing the dosage.

Cyclosporine: Modest increases in mean trough cyclosporine concentrations were observed following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30% of patients, the dose of cyclosporine had to be reduced in order to maintain cyclosporine concentrations within the therapeutic range, while in the remainder no adjustment was needed. On the average for the group, the dose of cyclosporine was reduced about 20% in these patients. Due to wide inter-individual variability in the dose adjustment required, it is recommended that cyclosporine concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporine be adjusted as appropriate.

Inducers and Inhibitors of Cytochrome P450: Since carvedilol undergoes substantial oxidative metabolism, care may be required in patients receiving inducers or inhibitors of cytochrome P450, as plasma concentrations may be altered. Pre-treatment with *rifampin* (600 mg daily for 12 days) decreased the AUC and C_{max} for carvedilol approximately 70% following a single oral dose of carvedilol. Co-administration of carvedilol and *cimetidine* (1000 mg/day) resulted in a 30% increase in median AUC for carvedilol. Despite the reduction in oral clearance, peak plasma concentrations of carvedilol were unchanged due to an apparent decrease in rate of absorption.

Grapefruit Juice: Following simultaneous administration of a single dose of 25 mg of carvedilol with 300 mL of grapefruit juice (an inhibitor of CYP3A4 and CYP1A2), AUC for carvedilol was approximately 16% higher than following administration of carvedilol with 300 mL of water.

Nitroglycerin: The effect of carvedilol co-administration with *nitroglycerin* has not been studied. Carvedilol could blunt the reflex tachycardia produced by *nitroglycerin* through its beta-adrenergic

blocking activity. When it is used with *nitroglycerin* in patients with angina pectoris, additional decreases in blood pressure may occur.

Insulin or Oral Hypoglycemics: Agents with beta-blocking properties may enhance the blood-sugar reducing effect of insulin and oral hypoglycemics. Therefore, in patients taking insulin or oral hypoglycemics, regular monitoring of blood glucose is recommended.

Tricyclic Antidepressants: The effect of carvedilol co-administration with tricyclic antidepressants has not been studied. As an increased incidence of tremor has been observed with other drugs of this class upon co-administration of tricyclic antidepressants, the possibility of a drug interaction cannot be excluded.

Warfarin: Carvedilol (12.5 mg twice daily for 7 days) did not have an effect on warfarin-induced increase in steady-state prothrombin time ratios and did not alter the pharmacokinetics of both enantiomers of warfarin following concomitant administration with warfarin in healthy volunteers.

ADVERSE REACTIONS

Mild to Moderate Heart Failure – Controlled Trials

In six US placebo controlled trials, 1313 patients were challenged with carvedilol over a 2-4 week period. Of these patients, 1202 were randomized to double blind treatment with carvedilol (n= 765) or placebo (n =437). 92.5% of those treated with carvedilol reported at least one adverse experience.

During the double-blind phase of these trials, adverse experiences rated as serious were reported in 22.4% of patients treated with carvedilol and 31.8% in the placebo group. The most serious adverse experiences reported with carvedilol were cardiac failure (5.6%), syncope

(1.8%), bradycardia (1.6%), hypotension (1.3%), myocardial infarction (0.9%), acute renal failure (0.8%), and AV block (0.7%).

Adverse experiences rated as severe in intensity during the double-blind phase of these trials were reported in 24.3% of patients treated with carvedilol. The most frequent severe adverse experiences were cardiac failure (2.9%), fatigue (2.2%), dizziness (2.0%), dyspnea (1.8%), and syncope (1.7%).

The most common adverse experiences reported in the double-blind phase of the US clinical trial experience (see Table 1) with carvedilol were dizziness (32.4%), fatigue (23.9%), dyspnea (21.3%), upper respiratory infection (18.3%) cardiac failure (15.3%) and chest pain (14.4%).

Of the 1202 patients who received randomized treatment in these trials, 5.4% of patients treated with carvedilol withdrew because of adverse experiences compared with 8.0% of placebo patients. Bradycardia, fatigue, hypotension, dizziness and dyspnea were the most commonly reported adverse experiences leading to discontinuation in patients treated with carvedilol (see Table 1).

Six deaths occurred in 1319 patients enrolled in the screening phase (3-4 weeks), eleven deaths occurred in 1313 patients challenged with carvedilol (2-4 weeks). There were 8 deaths (3/765 carvedilol; 5/437 placebo) during up titration phase (2-6 weeks) and 47 deaths (20/765 carvedilol; 27/437 placebo) during the maintenance phase (up to 12 months) of the studies.

Withdrawals due to worsening heart failure in U.S. placebo controlled trials were as follows: during challenge 1.4% of patients (18/1313 for 24 weeks); during up-titration 0.9% (7/765) of patients treated with carvedilol and 0% (0/437) of placebo patients (2-6 weeks); during the

maintenance phase 0.7% (5/765) of patients treated with carvedilol and 2.3% (10/437) of placebo patients (up to 12 months).

Worsening renal function, including acute renal failure (see Table 1), has been seen in some patients (carvedilol 9.5% and placebo 7.6%). Patients at greatest risk include those with pre-existing renal insufficiency, hypotension and ischemic cardiomyopathy, previous renal insufficiency due to ACE inhibitors, diffuse vascular disease, or evidence of renal artery stenosis.

Table 1 shows adverse events reported in patients with mild to moderate heart failure enrolled in U.S. placebo-controlled clinical trials. Shown are adverse events that occurred more frequently in carvedilol-treated patients than placebo-treated patients with an incidence >1% regardless of causality. Median study medication exposure was 6.3 months for carvedilol and placebo patients.

TABLE 1

Adverse Events in (% Occurrence and % Withdrawal) Occurring More Frequently with Carvedilol than with Placebo in Patients with Mild to Moderate Heart Failure Enrolled in U.S. Heart Failure Trials (Incidence >1%, Regardless of Causality; Withdrawal Rates due to Adverse Events)

	Adverse Reactions		**Withdrawals**	
	Carvedilol (n=765) % occurrence	Placebo (n=437) % occurrence	Carvedilol (n=765) % withdrawals	Placebo (n=437) % withdrawals
Autonomic Nervous System				
Sweating increased	2.9	2.1		
Body as a whole				
Fatigue	23.9	22.4	0.7	0.7
Chest Pain	14.4	14.2	0.1	
Pain	8.6	7.6		0.2
Injury	5.9	5.5		
Drug level increased	5.1	3.7		0.2
Edema generalized	5.1	2.5		
Edema dependent	3.7	1.8		
Fever	3.1	2.3		
Edema legs	2.2	0.2	0.1	0.2
Edema peripheral	1.6	0.7		
Allergy	1.4	0.2		
Sudden death	1.3	1.1		
Malaise	1.3	0.7		

	Adverse Reactions		Withdrawals	
	Carvedilol (n=765) % occurrence	Placebo (n=437) % occurrence	Carvedilol (n=765) % withdrawals	Placebo (n=437) % withdrawals
Hypovolemia	1.2	0.2		
Cardiovascular				
Bradycardia	8.8	0.9	0.8	
Hypotension	8.5	3.4	0.4	0.2
Syncope	3.4	2.5	0.3	0.2
Hypertension	2.9	2.5	0.1	
AV block	2.9	0.5		
Angina pectoris aggravated	2.0	1.1		
Fluid overload	1.7	1.6		
Postural hypotension	1.2	0.2		
Central Nervous System				
Dizziness	32.4	19.2	0.4	
Headache	8.1	7.1	0.3	
Paresthesia	2.0	1.8	0.1	
Hypesthesia	1.7	1.1		
Vertigo	1.4	1.1		
Confusion	1.3	0.9		
Somnolence	1.2	0.9		0.2
Gastrointestinal				
Diarrhea	11.8	5.9	0.3	
Nausea	8.5	4.8		
Abdominal pain	7.2	7.1	0.3	
Vomiting	6.3	4.3	0.1	
Melena	1.4	1.1		
Periodontitis	1.3	0.7		
Hematologic				
Thrombocytopenia	2.0	0.5	0.1	
Prothrombin decreased	1.3	1.1		
Purpura	1.3	0.2		
Metabolic				
Hyperglycemia	12.2	7.8	0.1	
Weight increase	9.7	6.9	0.1	0.5
Gout	6.3	6.2		
BUN increased	6.0	4.6	0.3	0.2
NPN increased	5.8	4.6	0.3	0.2
Hypocholesterolemia	4.1	2.5		
Dehydration	2.1	1.6		
Hypervolernia	2.0	0.9		
Hyperuricaemia	1.8	1.6		
Hypoglycaemia	1.6	1.4	0.1	
SGPT increased	1.4	0.9		
Hyponatremia	1.3	1.1		
Phosphatase alkaline increase	1.2	1.1		
SGOT increased	1.2	0.9		
Glycosuria	1.2	0.7		
Musculoskeletal				
Back Pain	6.9	6.6		
Arthralgia	6.4	4.8	0.1	0.2
Myalgia	3.4	2.7		
Resistance Mechanism				
Upper respiratory tract infection	18.3	17.6		

	Adverse Reactions		Withdrawals	
	Carvedilol (n=765) % occurrence	Placebo (n=437) % occurrence	Carvedilol (n=765) % withdrawals	Placebo (n=437) % withdrawals
Infection	2.2	0.9		
Reproductive Male				
Impotence	1.7	0.9		
Respiratory				
Sinusitis	5.4	4.3		
Bronchitis	5.4	3.4		0.2
Pharyngitis	3.1	2.7		
Urinary/Renal				
Urinary tract infection	3.1	2.7		
Hematuria	2.9	2.1		
Renal function abnormal	1.7	1.4	0.3	
Albuminuria	1.6	1.1		
Acute renal failure	1.2	0.5	0.3	
Vision				
Vision abnormal	5.0	1.8	0.1	

In addition to the events in Table 1, the following events occurred in more than 1% of carvedilol-treated patients but rates were equal to, or more common in, placebo-treated patients: asthenia, cardiac failure, flatulence, anorexia, dyspepsia, palpitation, ventricular tachycardia, atrial fibrillation, extrasystoles, bilirubinemia, hyperkalemia, arthritis, angina pectoris, insomnia, depression, amnesia, anemia, viral infection, dyspnea, coughing, respiratory disorder, pneumonia, rhinitis, rash, pruritus, and leg cramps.

Adverse experiences related to laboratory parameters reported in greater than 1% of patients are in Table 1. Adverse experiences related to laboratory parameters reported in $\leq$1% but more than 0.1% of patients included increased hepatic enzymes (0.4% of congestive heart failure patients were discontinued from therapy because of increases in hepatic enzymes; see PRECAUTIONS, Hepatic Impairment), hypokalemia, hypertriglyceridemia, anemia, leukopenia.

Severe Heart Failure – Controlled Trial

In a clinical trial in severe heart failure that compared carvedilol in daily doses of 50 mg (n=1156) with placebo (n=1133), 9.4% of patients treated with carvedilol discontinued treatment for adverse experiences versus 11.2% of placebo patients.

The most common adverse experiences reported with carvedilol were dizziness (24.1%), hypotension (13.9%) and upper respiratory infection (see Table 2). Median study exposure was 10.4 months for both carvedilol and placebo patients.

Table 2 shows adverse events reported in patients with severe heart failure enrolled in multinational placebo-controlled clinical trial. Shown are adverse events that occurred more frequently in carvedilol-treated patients than placebo-treated patients with an incidence >1% regardless of causality.

TABLE 2
Adverse Events in (% Occurrence and % Withdrawal) Occurring More Frequently with Carvedilol than with Placebo in Patients with Severe Heart Failure (Incidence >1%, Regardless of Causality)

	Adverse Reactions		**Withdrawals**	
	Carvedilol (n=1156) % occurrence	Placebo (n=1133) % occurrence	Carvedilol (n=1156) % withdrawals	Placebo (n=1133) % withdrawals
Body as a whole				
Asthenia	10.9	9.4	0.4	0.7
Infection	2.5	2.4		
Back pain	2.9	1.4		
Cardiovascular				
Hypotension	13.9	8.2	0.6	0.4
Bradycardia	10.3	2.7	0.6	
Syncope	7.6	5.0	0.4	0.4
Angina pectoris	5.5	4.1	0.1	0.1
Hypertension	2.6	2.2		0.1
Postural hypotension	1.8	1.0	0.1	0.1
Sinus bradycardia	1.7	0.4		
Palpitation	1.6	1.5		0.1
Gastrointestinal				
Diarrhea	4.8	3.1	0.3	
Nausea	3.8	3.3		0.1
Gastrointestinal disorder	1.6	1.1	0.1	0.1
Hematologic				
Anemia	2.4	2.0		
Metabolic and Nutritional				
Weight gain	11.7	10.7	0.1	0.1
Peripheral edema	7.0	6.4	0.2	0.1
Generalized edema	6.0	4.9	0.2	0.2
Hyperglycemia	4.5	3.3	0.0	0.1
Gout	3.5	2.7		
Hyperkalemia	3.3	1.9	0.2	0.1
Creatinine increased	2.9	1.4		0.1
Diabetes mellitus	2.0	1.7		
Weight loss	1.4	1.1		
CGT increased	1.3	1.1		
Nervous System				
Dizziness	24.1	16.8	1.3	0.6
Headache	4.8	3.0		0.1
Paresthesia	1.7	1.4		
Respiratory				
Upper respiratory tract infection	13.6	12.6	0.1	
Dyspnea	11.2	11.0	0.5	0.3
Bronchitis	5.2	4.5	0.1	
Cough increased	4.5	4.2	0.1	0.2
Lung disorder	4.0	3.2	0.1	
Sinusitis	1.6	1.1		
Special Senses				
Blurred vision	2.8	2.2	0.2	0.1
Urogenital				
Kidney failure	1.6	1.3	0.1	

In addition to the events in Table 2, when compared with placebo, carvedilol-treated patients had fewer of the following adverse events related to the cardiovascular system and occurring in or equal to 2% of patients: sudden death, atrial fibrillation, chest pain, congestive heart failure, heart failure, peripheral vascular disorder, unstable angina pectoris and ventricular tachycardia. Other adverse experiences occurring in greater or equal to 2% but reported less frequently in carvedilol-treated patients include: abdominal pain, pain in the extremity, hypokalemia, lung edema, pneumonia, abnormal kidney function and urinary tract infection.

Hypertension and Heart Failure – Open and Controlled Trials

The following adverse events were reported as possibly or probably related in worldwide open or controlled trials with carvedilol in patients with hypertension or congestive heart failure at an incidence of >0.1% to $\leq$1%:

Cardiovascular: Peripheral ischemia, tachycardia.

Central and Peripheral Nervous System: Hypokinesia.

General: Substernal chest pain, edema.

Psychiatric: Sleep disorder, aggravated depression, impaired concentration, abnormal thinking, paroniria, emotional lability.

Respiratory System: Asthma

Reproductive, Male: Decreased libido.

Skin and Appendages: Pruritus, rash erythematous, rash maculopapular, rash psoriaform, photosensitivity reaction.

Special Senses: Tinnitus.

Urinary System: Micturition frequency.

Autonomic Nervous System: Dry mouth, sweating increased.

Metabolic and Nutritional: Diabetes mellitus.

The following adverse events were reported as possibly or probably related in worldwide open or controlled trials with carvedilol in patients with hypertension or congestive heart failure at an incidence of $\leq$0.1%, and are potentially important: complete AV block, bundle branch block, myocardial ischemia, cerebrovascular disorder, convulsions, migraine, neuralgia, paresis, anaphylactoid reaction, alopecia, exfoliative dermatitis, amnesia, GI hemorrhage, bronchospasm, pulmonary edema, decreased hearing, respiratory alkalosis, decreased HDL, pancytopenia, and atypical lymphocytes.

Post-Marketing Experience

The following adverse reaction has been reported in post-marketing experience: reports of aplastic anemia have been rare and received only when carvedilol was administered concomitantly with other medications associated with the event.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Cases of overdosage with carvedilol alone or in combination with other drugs have been reported. Quantities ingested in some cases exceeded 1000 mg. Clinical signs experienced included low blood pressure and heart rate. Standard supportive treatment was provided and individuals recovered.

In the event of inadvertent or intentional overdosage with carvedilol, there may be severe hypotension, excessive bradycardia, heart failure, cardiogenic shock, and cardiac arrest due to its pharmacologic activities. There may also be respiratory distress, bronchospasm, vomiting, disturbed consciousness, and generalized seizures.

Patients who have taken an overdose of carvedilol should be placed supine, with their legs raised. For removal of the drug shortly after ingestion, gastric lavage or pharmacologically induced emesis may be useful. Carvedilol is not removed by hemodialysis. In addition to these general procedures, the patient's vital signs should be monitored under intensive care conditions with continuous monitoring, if necessary.

The following additional supportive therapies can be used:

If excessive hypotension occurs, vasopressors, norepinephrine or noradrenaline should be administered with continuous monitoring of the circulatory system. Digitalis, diuretics, and if necessary, dopamine or dobutamine should be administered if cardiac failure occurs.

For excessive bradycardia, atropine 0.5 to 2 mg should be given intravenously. In addition, glucagon 1 to 10 mg given intravenously over 30 seconds initially, followed by a continuous infusion of 2 to 2.5 mg/h, has been shown to be effective when severe overdosage of beta blockers causes hypotension and or bradycardia. For therapy-resistant bradycardia, pacemaker therapy may be necessary.

For bronchospasm, beta-sympathomimetics (as aerosol or intravenously) or intravenous aminophylline should be given.

In the event of seizures, slow intravenous injection of diazepam or clonazepam is recommended.

NOTE: In the event of severe intoxication where there are symptoms of shock, treatment must be continued for a sufficiently long period of time consistent with the 7-10 hour elimination half-life of carvedilol.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED AND PATIENTS CLOSELY MONITORED DURING INITIATION AND UP-TITRATION BY A PHYSICIAN EXPERIENCED IN THE TREATMENT OF HEART FAILURE.

ALL PATIENTS IN WHOM NU-CARVEDILOL (CARVEDILOL) THERAPY IS TO BE CONSIDERED MUST BE CLINICALLY STABLE FOR 4 WEEKS PRIOR TO INITIATION OF NU-CARVEDILOL.

PRIOR TO INITIATION OF THERAPY WITH NU-CARVEDILOL, PATIENTS SHOULD BE ON STABLE DOSES OF DIURETICS AND ANGIOTENSIN CONVERTING ENZYME INHIBITORS, WITH OR WITHOUT DIGITALIS. IN CLINICAL TRIALS, PATIENTS WERE ON THE ABOVE REGIMEN UNLESS THEY WERE INTOLERANT TO AN ACE INHIBITOR.

The recommended starting dose of NU-CARVEDILOL is 3.125 mg twice daily for two weeks. If this dose is tolerated, it can then be increased to 6.25, 12.5 and 25 mg twice daily over successive intervals of at least 2 weeks. Patients should be maintained on the highest tolerated dose. The maximum recommended dose is 25 mg twice daily. The dose of NU-CARVEDILOL should not be increased until symptoms of worsening heart failure or vasodilation have stabilized.

Patients should be advised that initiation of treatment and, to a lesser extent, dosage increases may be associated with transient symptoms of dizziness or lightheadedness, and rarely syncope, within the first 2 hours after dosing. During these periods, they should avoid situations such as driving or dangerous tasks where symptoms could result in injury. In addition, NU-CARVEDILOL should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects, especially during up-titration. Symptoms of hypotension do not often require treatment, but it may be useful to separate the time of dosing of NU-CARVEDILOL from that of the ACE inhibitor, or to reduce temporarily the dose of the ACE inhibitor.

The risk/benefit of carvedilol therapy in clinically stable heart failure patients with a heart rate lower than 68 beats per minute should be carefully considered prior to initiation of carvedilol since carvedilol has not been studied in these patients (see WARNINGS).

Before each dose increase the patient should be seen in the office and evaluated for symptoms of worsening heart failure, vasodilation (dizziness, lightheadedness, symptomatic hypotension) or bradycardia, in order to determine tolerability of NU-CARVEDILOL. Transient worsening of heart failure may be treated with increased doses of diuretics, lowering the dose of NU-CARVEDILOL or, if necessary, discontinuation of NU-CARVEDILOL. Symptoms of vasodilation such as dizziness, lightheadedness or decreasing blood pressure may respond to a reduction in the dose of diuretics. If these changes do not relieve symptoms, the dose of NU-CARVEDILOL should be decreased. If the dose of NU-CARVEDILOL was decreased, it should not be increased again until symptoms of worsening heart failure or vasodilation have been stabilized for 2 weeks. Initial difficulty with titration may not preclude later attempts to re-introduce or resume titration of NU-CARVEDILOL, however caution is required in these circumstances. If congestive heart failure patients experience bradycardia (pulse rate below 55 beats/min.), the dose of NU-CARVEDILOL should be reduced, or may require discontinuation.

Elderly

The frequency and pattern of adverse reactions in patients ≥65 years was similar to that in younger patients. However, plasma levels of carvedilol are higher in older patients compared to younger patients (see PRECAUTIONS). Therefore, after initiating NU-CARVEDILOL at the same dose in the elderly as in younger patients, up-titration should be done more cautiously in the elderly. A lower total daily dose may be reached at the end of up-titration in such patients compared to younger patients.

Hepatic Impairment

NU-CARVEDILOL is contraindicated in patients with clinically manifest liver disease (see CONTRAINDICATIONS). In patients with milder hepatic impairment, there is a potential for increased manifestations of vasodilation and beta-blockade (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, and PRECAUTIONS). Therefore, after initiating NU-CARVEDILOL at the same dose in patients with hepatic impairment as in other patients, up-titration should be done more cautiously in patients with hepatic impairment. A lower total daily dose may be reached at the end of up-titration in such patients compared to other patients.

Renal Impairment

Acute, reversible renal failure has been seen in some patients treated with NU-CARVEDILOL, particularly those with underlying renal impairment (see PRECAUTIONS). Therefore, after initiating NU-CARVEDILOL at the same dose in patients with renal impairment as in other patients, up-titration should be done more cautiously in patients with renal impairment. Renal function (BUN and creatinine) should be checked in such patients as appropriate. If renal function has deteriorated, the dose of NU-CARVEDILOL may need to be reduced or discontinued.

Discontinuation

NU-CARVEDILOL should be gradually reduced over a period of about 2 weeks, if possible, and the patient should be carefully observed (see WARNINGS, Abrupt Cessation of Therapy).

PHARMACEUTICAL INFORMATION

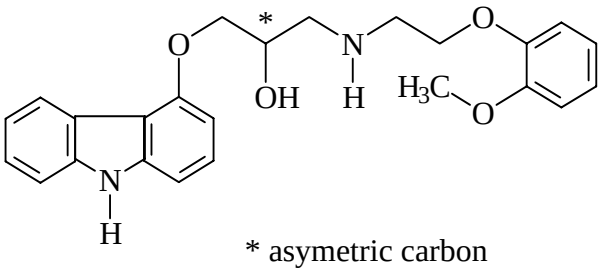
Drug Substance

Proper Name: Carvedilol

Chemical Name: (±)-1-(carbazol-4-yloxy)-3-{[2-(methoxyphenoxy) ethyl] amino}-2-propanol

Molecular Formula: $C_{24}N_{26}N_2O_4$

Structural Formula:



* asymetric carbon

Molecular Weight: 406.49

Description: White to off-white (pale yellowish) crystalline powder.

Physico-Chemical Properties: Racemic form, melting point 115.0 - 116.50°C, insoluble in water, soluble in chloroform, ethanol, acetone, ether, dimethylformamide and methanol; pK_a value may vary between 7.7 and 7.9 (25°C).

Composition

In addition to carvedilol, each tablet contains the non-medicinal ingredients lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hydroxyethyl cellulose, polyethylene glycol, and titanium dioxide.

Stability and Storage Recommendations

Store at room temperature between (15˚ and 30˚C). Protect from heat and moisture. Dispense in a tight, light-resistant container.

AVAILABILITY OF DOSAGE FORMS

NU-CARVEDILOL 3.125 mg: Each oval, white, film-coated tablet engraved ‘APO’ on one side and ‘C3’ on the other contains 3.125 mg carvedilol. Available in bottles of 100.

NU-CARVEDILOL 6.25 mg: Each oval, white, film-coated tablet engraved ‘APO’ on one side and ‘6.25’ on the other contains 6.25 mg carvedilol. Available in bottles of 100.

NU-CARVEDILOL 12.5 mg: Each oval, white, film-coated tablet engraved ‘APO’ on one side and ’12.5’ on the other contains12.5 mg carvedilol. Available in bottles of 100.

NU-CARVEDILOL 25 mg: Each oval, white, film-coated tablet engraved ‘APO’ on one side and ‘C25’ on the other contains 25 mg carvedilol. Available in bottles of 100.

INFORMATION FOR THE PATIENT

Please read this information before you start to take your medicine. Keep this leaflet until you have finished all your tablets as you may need to read it again. If you are helping someone take NU-CARVEDILOL (carvedilol) tablets, read this leaflet before you give the first tablet. This leaflet does not contain all information about your medicine. **FOR FURTHER INFORMATION OR ADVICE, PLEASE SEE YOUR DOCTOR OR PHARMACIST.**

What you should know about NU-CARVEDILOL

- NU-CARVEDILOL is used in the treatment of heart failure.
- NU-CARVEDILOL has been prescribed to you by your doctor to help manage your symptoms of heart failure.

What you should tell your doctor before taking NU-CARVEDILOL

- all your medical conditions, including a history of heart, kidney or liver problems, asthma or breathing difficulties;
- if you suffer from diabetes, thyroid problems, Raynaud's phenomenon (coldness/spasm in the hands or feet) or cramping pains in the leg when exercising;
- if you suffer or have suffered from psoriasis (scaly red patches on the skin);
- any medications (prescription or non prescription) which you are taking, especially anti-hypertensives, digoxin, insulin, hypoglycaemics, stomach medication, tricyclic antidepressants, clonidine, and rifampin;

- tell the doctor if you change the amount of any other medicine you are taking;

- if you see another physician other than your heart doctor for another condition tell this physician that you are taking NU-CARVEDILOL;

- if you are pregnant or thinking about becoming pregnant, or if you are breast feeding.

How to take NU-CARVEDILOL

- **It Is very important that you take NU-CARVEDILOL exactly as your doctor has instructed.** The doctor will decide how many tablets you need to take each day, when and for how long. It may be necessary for the doctor to increase or decrease the dose.

- You should swallow the tablets whole with water. Do not chew or break your tablet.

- Take your tablets at the same time each day. You should take NU-CARVEDILOL with food.

- If you forget to take a tablet, take it as soon as you remember. If possible, take your next dose at the normal time, but do not take two doses within 6 hours of each other.

- If you miss more than two doses of NU-CARVEDILOL, contact your doctor for instructions. Do not re-start NU-CARVEDILOL until you have spoken to the doctor.

- Do NOT stop taking NU-CARVEDILOL without first consulting with your doctor.

Remember: This medicine is for the person named by the doctor. Do not give it to anybody else.

When not to use NU-CARVEDILOL

- You should not take this medicine if you are pregnant or if you plan on being pregnant unless the doctor tells you to.

- Do not use NU-CARVEDILOL if you are allergic to it or any of the components of its formulation (see list of components at the end of this section). If you become unwell while taking NU-CARVEDILOL tell your doctor at once.

Precautions when taking NU-CARVEDILOL

- Some people may have unwanted effects when taking NU-CARVEDILOL. Dizziness, headache and tiredness are the most common and often occur when NU-CARVEDILOL is started or when the dose of NU-CARVEDILOL is changed. These symptoms generally go away with continued use. If they do not or appear to become more severe, then tell your doctor.

- Other possible effects are: stomach complaints such as diarrhea, constipation, nausea and vomiting, allergic reactions such as rashes and hot or itching skin, pain in the side, passing water more or less frequently, breathing problems such as wheezing, breathlessness and stuffy nose, depressed mood, sleep disturbance, dry mouth, slowing of heart rate, dizziness when standing up, fainting, cold or painful hands and feet, general swelling of parts of the body, weight gain, impotence, blurred vision, cramping pain on exercise.

- If suffering from Raynaud's phenomenon (cold hands or feet with changes in color) an increase in symptoms of coldness/spasms in the hands may be seen.

- Psoriasis (scaly patches on the skin) may occur or, if you already have psoriasis, it may become worse.

- If you are diabetic you could become less aware of symptoms of hypoglycemia. You should monitor your blood sugar more carefully. Tell your doctor if you see any appreciable changes.

- If you wear contact lenses you may suffer from dryness of the eyes while taking your tablets.

- If you develop any unusual discomfort, tell the doctor as soon as possible, especially if you have unusual dizziness, ankle swelling, tiredness or breathlessness when your dose is being increased.

- If you experience dizziness or fatigue while taking your tablets, do not drive or operate machinery.

- You should be especially careful when starting or changing the dose of NU-CARVEDILOL.

- NU-CARVEDILOL should not be taken with alcohol.

What to do in case of overdose

- If you have taken more tablets than the recommended dose, tell your doctor or the nearest hospital emergency department immediately. Show the doctor your bottle of tablets and any other medications you are taking.

How to store NU-CARVEDILOL

- Store your tablets at room temperature (15-30˚C) in a dry place. Protect from high humidity and light.
- Keep container tightly closed.
- Do not use the medicine if it has expired.
- Keep out of reach of children.

What does NU-CARVEDILOL contain

NU-CARVEDILOL (carvedilol) is available is 3.125 mg, 6.25 mg, 12.5 mg and 25 mg oval white tablets. Carvedilol is the active ingredient. Non-medicinal ingredients include: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hydroxyethyl cellulose, polyethylene glycol, and titanium dioxide. They do not contain tartrazine or any other azo dyes.

Who manufactures NU-CARVEDILOL

- NU-CARVEDILOL tablets are manufactured by: NU-PHARM INC.

PHARMACOLOGY

Beta-adrenoceptor blocking activity has been demonstrated in animal and human studies by showing that carvedilol 1) reduces exercise- and/or isoproterenol-induced tachycardia; and 2) reduces reflex orthostatic tachycardia. Significant beta-adrenoceptor blocking effect is usually seen within 1 hour of oral drug administration (in the fasting state). Carvedilol is not cardioselective, does not have intrinsic sympathomimetic activity, and possesses some membrane stabilizing activity.

Alpha$_1$-adrenoceptor blocking activity has been demonstrated in animal and human studies by showing that carvedilol 1) attenuates the pressor effects of phenylephrine but not of angiotensin II, 2) causes vasodilation; and 3) reduces peripheral vascular resistance. The onset of these effects is usually seen within 30 minutes of oral drug administration (in the fasting state).

In animal *in vivo* studies, and in human *in vitro* studies, carvedilol has been shown to have antioxidant activity. Some metabolites are ten-fold more potent than carvedilol in this regard, although these metabolites are found at serum concentrations ten-fold lower than those of carvedilol. The carbazole portion of the molecule is responsible for this antioxidant activity, which is found to be equally potent in each enantiomer; the beta-blocking and vasodilating actions reside in other parts of the molecular structure and both enantiomers of carvedilol are equally potent as antioxidants. The clinical significance of the antioxidant effect has not been established.

TOXICOLOGY

LD_{50} values in mg/kg after 14 days observation time (n=10 for all groups):

Species	Sex	Oral	I.P. (range)	I.V. (range)
Mouse	F	>8000	363 (273-445)	36(31-40)
Mouse	M	>8000	568 (419-787)	27(21-33)
Rat	F	>8000	769 (697-837)	25(24-26)
Rat	M	>8000	1244 (1004-1430)	27(26-28)

Almost all deaths occurred one to two days after dosing. No systemic clinical signs were observed in the animals treated orally. Animals dosed parenterally (except doses intraperitoneally) showed transient apathy and ptosis.

Long-Term Toxicity

Carvedilol was administered daily for 12 months to 5 dogs/sex/group at 0, 10, 30, 100, and 300 mg/kg given orally in two divided doses. Carvedilol was also administered daily in the feed for 12 months to 30 rats/sex/group at doses of 30, 100, or 300 mg/kg and in another study for 18 months to 30 rats/sex/group at doses of 10, 31, 89, 261 mg/kg. Following oral administration, no toxic effects were seen at 10 mg/kg in the dog and at 30 mg/kg in the rat. These no-effect doses are 14 and 42 times higher than a relatively high therapeutic dose in humans (based on a daily dose of 50 mg in a 70 kg patient).

TERATOLOGY STUDIES

Teratology studies show no evidence of carvedilol having teratogenic effects. In the fertility study, high doses resulted in reduced fertility and diminished general reproductive capacity in the F_0-generation and retardation in physical development in the F_1 generation. These adverse effects are regarded as nonspecific effects due to loading the parental generation with toxic dosages.

MUTAGENICITY STUDIES

No mutagenic potential of carvedilol was demonstrated in several *in vitro* and *in vivo* test systems.

CARCINOGENICITY STUDIES

Two-year carcinogenicity studies were conducted in both mice and rats. In the mouse study, groups of 50 mice/sex/group received daily doses of 20, 65 or 200 mg/kg in the diet. A group of 100 mice/sex/group were untreated and served as controls. In the rat study, groups of 50 rats/sex/group received 0, 200, 400, 800, or 1600 ppm carvedilol in the diet. These concentrations corresponded to daily dosages at the start of the study up to 21.7, 43, 86.7 and 169.5 mg/kg. Since the carvedilol dietary concentration did not change throughout the study and the animals gained weight, by the end of the study the actual daily dosages decreased to 9.5, 18.8, 38.1 and 74.7 mg/kg.

The results of the histopathologic examinations from these carcinogenicity studies indicated that carvedilol does not have either a tumorigenic or a carcinogenic potential.

REFERENCES

1. de Mey C, Breithaupt K, Schloos J, Neugebauer G, Palm D, Belz GG. Dose-effect and pharmacokinetic-pharmacodynamic relationships of the beta-1-adrenergic receptor blocking properties of various doses of carvedilol in healthy humans. Clin Pharmacol Ther l994; 55(3): 329-37.

2. Harder S, Merz PG, Rietbrock N. Lack of pharmacokinetic interaction between carvedilol and digitoxin, phenprocoumon or glibenclamide. Cardiovasc Drugs Ther 1993; 7(Suppl 2): 447.

3. Nichols AJ, Gallai M, Ruffolo RR Jr. Studies on the mechanism of arterial vasodilation produced by the novel antihypertensive agent, carvedilol. Fundam Clin Pharmacol 1991; 5/1: 25-38.

4. Packer M. How should physicians view heart failure? The philosophical and physiological evolution of three conceptual models of the disease. Am J Cardiol 1991; 71: 3C-11C.

5. Packer M, Bristow M, Cohen J, Colucci W, Fowler MB, Gilbert E and Shusterman N. The effect of Carvedilol on survival and hospitalization for cardiovascular complications in patients with chronic heart failure. N Engl J Med 1996; 334:1349-55.

6. Packer M, Coats AJS, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001; 344: 1651-8.

7. Schocken DD, Arrieta MI, Leaverton PE. Prevalence and mortality rate of congestive heart failure in the United States. J Am Coll Cardiol 1992; 20: 301-6.

8. Sponer G, Bartsch W, Strein K. Pharmacological profile of beta-adrenoceptor blockers with vasodilating properties, especially Carvedilol - Rationale for clinical use. Clin Invest 1992; 70(2): S20-S26.

9. van Zwieten PA. Pharmacodynamic profile of carvedilol. Cardiology 1993; 82(Suppl 3): 19-23.

10. Yue TL, Cheng HY, Lysko PG, et al. Carvedilol, a new vasodilator and beta-adrenoceptor antagonist, is an antioxidant and free radical scavenger. J Pharm Experimental Ther 1992; 263: 92-8.