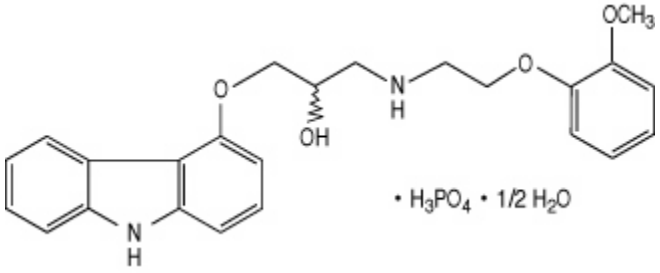
PRESCRIBING INFORMATION

COREG CR™

(carvedilol phosphate) Extended-release Capsules

DESCRIPTION

Carvedilol phosphate is a nonselective β-adrenergic blocking agent with α_1-blocking activity. It is (2*RS*)-1-(9*H*-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol phosphate salt (1:1) hemihydrate. It is a racemic mixture with the following structure:



Carvedilol phosphate is a white to almost-white solid with a molecular weight of 513.5 (406.5 carvedilol free base) and a molecular formula of $C_{24}H_{26}N_2O_4 \bullet H_3PO_4 \bullet 1/2\ H_2O$.

COREG CR is available for once-a-day administration as controlled-release oral capsules containing 10, 20, 40, or 80 mg carvedilol phosphate. COREG CR hard gelatin capsules are filled with carvedilol phosphate immediate-release and controlled-release microparticles that are drug-layered and then coated with methacrylic acid copolymers. Inactive ingredients include crospovidone, hydrogenated castor oil, hydrogenated vegetable oil, magnesium stearate, methacrylic acid copolymers, microcrystalline cellulose, and povidone.

CLINICAL PHARMACOLOGY

Carvedilol is a racemic mixture in which nonselective β-adrenoreceptor blocking activity is present in the S(-) enantiomer and α_1-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency. Carvedilol has no intrinsic sympathomimetic activity.

Pharmacokinetics: Absorption: Carvedilol is rapidly and extensively absorbed following oral administration of immediate-release carvedilol tablets, with an absolute bioavailability of approximately 25% to 35% due to a significant degree of first-pass metabolism. COREG CR extended-release capsules have approximately 85% of the bioavailability of immediate-release carvedilol tablets. For corresponding dosages (see DOSAGE AND ADMINISTRATION), the exposure (area under the curve [AUC], C_{max}, trough concentration) of carvedilol as COREG CR extended-release capsules is equivalent to those of immediate-release carvedilol tablets when both are administered with food. The absorption of carvedilol from COREG CR is slower and more prolonged compared to the immediate-release carvedilol tablet with peak concentrations achieved approximately 5 hours after administration. Plasma concentrations of carvedilol increase in a dose-proportional manner over the dosage range of COREG CR 10 to 80 mg. Within-subject and between-subject variability for AUC and C_{max} is similar for COREG CR and immediate-release carvedilol.

Effect of Food: Administration of COREG CR with a high-fat meal resulted in increases (~20%) in AUC and C_{max} compared to COREG CR administered with a standard meal. Decreases in AUC (27%) and C_{max} (43%) were observed when COREG CR was administered in the fasted state compared to administration after a standard meal. COREG CR should be taken with food.

In a study with adult subjects, sprinkling the contents of the COREG CR capsule on applesauce did not appear to have a significant effect on overall exposure (AUC) compared to administration of the intact capsule following a standard meal but did result in a decrease in C_{max} (18%).

Distribution: Carvedilol is more than 98% bound to plasma proteins, primarily with 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, indicating substantial distribution into extravascular tissues.

Metabolism and Excretion: Carvedilol is extensively metabolized. Following oral administration of radiolabelled carvedilol to healthy volunteers, carvedilol accounted for only about 7% of the total radioactivity in plasma as measured by AUC. Less than 2% of the dose was excreted unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile into the feces. Demethylation and hydroxylation at the phenol ring produce 3 active metabolites with β-receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol for β-blockade.

Compared to carvedilol, the 3 active metabolites exhibit weak vasodilating activity. Plasma concentrations of the active metabolites are about one-tenth of those observed for carvedilol and have pharmacokinetics similar to the parent.

Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R(+)-carvedilol approximately 2 to 3 times higher than S(-)-carvedilol following oral administration of COREG CR in healthy subjects. Apparent clearance is 90 L/h and 213 L/h for R(+)- and S(-)-carvedilol, respectively.

The primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4’- and 5’-hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be of primary importance in the O-methylation pathway of S(-)-carvedilol.

Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared to extensive metabolizers. In contrast, plasma levels of S(-)-carvedilol are increased only about 20% to 25% in poor metabolizers, indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol. The

pharmacokinetics of carvedilol do not appear to be different in poor metabolizers of S-mephenytoin (patients deficient in cytochrome P450 2C19).

Heart Failure: Following administration of immediate-release carvedilol tablets, steady-state plasma concentrations of carvedilol and its enantiomers increased proportionally over the dose range in patients with heart failure. Compared to healthy subjects, heart failure patients had increased mean AUC and C_{max} values for carvedilol and its enantiomers, with up to 50% to 100% higher values observed in 6 patients with NYHA class IV heart failure. The mean apparent terminal elimination half-life for carvedilol was similar to that observed in healthy subjects.

For corresponding dose levels (see DOSAGE AND ADMINISTRATION), the steady-state pharmacokinetics of carvedilol (AUC, C_{max}, trough concentrations) observed after administration of COREG CR to chronic heart failure patients (mild, moderate, and severe) were similar to those observed after administration of immediate-release carvedilol tablets.

Hypertension: For corresponding dose levels (see DOSAGE AND ADMINISTRATION), the pharmacokinetics (AUC, C_{max}, and trough concentrations) observed with administration of COREG CR were equivalent (±20%) to those observed with immediate-release carvedilol tablets following repeat dosing in patients with essential hypertension.

Pharmacokinetic Drug-Drug Interactions: Since carvedilol undergoes substantial oxidative metabolism, the metabolism and pharmacokinetics of carvedilol may be affected by induction or inhibition of cytochrome P450 enzymes.

The following drug interaction studies were performed with immediate-release carvedilol tablets.

Rifampin: In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin (600 mg daily for 12 days) decreased the AUC and C_{max} of carvedilol by about 70%.

Cimetidine: In a pharmacokinetic study conducted in 10 healthy male subjects, cimetidine (1,000 mg/day) increased the steady-state AUC of carvedilol by 30% with no change in C_{max}.

Glyburide: In 12 healthy subjects, combined administration of carvedilol (25 mg once daily) and a single dose of glyburide did not result in a clinically relevant pharmacokinetic interaction for either compound.

Hydrochlorothiazide: A single oral dose of carvedilol 25 mg did not alter the pharmacokinetics of a single oral dose of hydrochlorothiazide 25 mg in 12 patients with hypertension. Likewise, hydrochlorothiazide had no effect on the pharmacokinetics of carvedilol.

Digoxin: Following concomitant administration of carvedilol (25 mg once daily) and digoxin (0.25 mg once daily) for 14 days, steady-state AUC and trough concentrations of digoxin were increased by 14% and 16%, respectively, in 12 hypertensive patients (see PRECAUTIONS, Drug Interactions).

Torsemide: In a study of 12 healthy subjects, combined oral administration of carvedilol 25 mg once daily and torsemide 5 mg once daily for 5 days did not result in any significant differences in their pharmacokinetics compared with administration of the drugs alone.

Warfarin: Carvedilol (12.5 mg twice daily) did not have an effect on the steady-state prothrombin time ratios and did not alter the pharmacokinetics of R(+)- and S(-)-warfarin following concomitant administration with warfarin in 9 healthy volunteers.

Special Populations: ***Elderly:*** Plasma levels of carvedilol average about 50% higher in the elderly compared to young subjects after administration of immediate-release carvedilol.

Hepatic Impairment: No studies have been performed with COREG CR in patients with hepatic impairment. Compared to healthy subjects, patients with cirrhotic liver disease exhibit significantly higher concentrations of carvedilol (approximately 4- to 7-fold) following single-dose therapy with immediate-release carvedilol.

Renal Insufficiency: No studies have been performed with COREG CR in patients with renal insufficiency. Although carvedilol is metabolized primarily by the liver, plasma concentrations of carvedilol have been reported to be increased in patients with renal impairment after dosing with immediate-release carvedilol. Based on mean 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 mean peak plasma levels were less pronounced, approximately 12% to 26% higher in patients with impaired renal function.

Consistent with its high degree of plasma protein binding, carvedilol does not appear to be cleared significantly by hemodialysis.

Pharmacodynamics: ***Heart Failure and Left Ventricular Dysfunction Following Myocardial Infarction:*** The basis for the beneficial effects of carvedilol in patients with heart failure and in patients with left ventricular dysfunction following an acute myocardial infarction is not known. The concentration-response relationship for β_1-blockade following administration of COREG CR is equivalent (±20%) to immediate-release carvedilol tablets.

Hypertension: The mechanism by which β-blockade produces an antihypertensive effect has not been established.

β-adrenoreceptor blocking activity has been demonstrated in animal and human studies showing that carvedilol (1) reduces cardiac output in normal subjects; (2) reduces exercise- and/or isoproterenol-induced tachycardia; and (3) reduces reflex orthostatic tachycardia. Significant β-adrenoreceptor blocking effect is usually seen within 1 hour of drug administration.

α_1-adrenoreceptor blocking activity has been demonstrated in human and animal studies, showing that carvedilol (1) attenuates the pressor effects of phenylephrine; (2) causes vasodilation; and (3) reduces peripheral vascular resistance. These effects contribute to the reduction of blood pressure and usually are seen within 30 minutes of drug administration.

Due to the α_1-receptor blocking activity of carvedilol, blood pressure is lowered more in the standing than in the supine position, and symptoms of postural hypotension (1.8%), including rare instances of syncope, can occur. Following oral administration, when postural hypotension has occurred, it has been transient and is uncommon when immediate-release carvedilol is

administered with food at the recommended starting dose and titration increments are closely followed (see DOSAGE AND ADMINISTRATION).

In a randomized, double-blind, placebo-controlled trial, the β_1-blocking effect of COREG CR, as measured by heart rate response to submaximal bicycle ergometry, was shown to be equivalent to that observed with immediate-release carvedilol at steady state in adult patients with essential hypertension.

In hypertensive patients with normal renal function, therapeutic doses of carvedilol decreased renal vascular resistance with no change in glomerular filtration rate or renal plasma flow. Changes in excretion 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 catecholamines, plasma aldosterone, or electrolyte levels, but it does significantly reduce plasma renin activity when given for at least 4 weeks. It also increases levels of atrial natriuretic peptide.

CLINICAL TRIALS

Support for the use of COREG CR extended-release capsules for the treatment of mild-to-severe heart failure and for patients with left ventricular dysfunction following myocardial infarction is based on the equivalence of pharmacokinetic and pharmacodynamic (β_1-blockade) parameters between COREG CR and immediate-release carvedilol (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Pharmacodynamics).

The clinical trials performed with immediate-release carvedilol in heart failure and left ventricular dysfunction following myocardial infarction are presented below.

Heart Failure: A total of 6,975 patients with mild-to-severe heart failure were evaluated in placebo-controlled and active-controlled studies of immediate-release carvedilol.

Trials in Mild-to-Moderate Heart Failure: Carvedilol was studied in 5 multicenter, placebo-controlled studies, and in 1 active-controlled study (COMET study) involving patients with mild-to-moderate heart failure.

Four US multicenter, double-blind, placebo-controlled studies enrolled 1,094 patients (696 randomized to carvedilol) with NYHA class II-III heart failure and ejection fraction ≤0.35. The vast majority were on digitalis, diuretics, and an ACE inhibitor at study entry. Patients were assigned to the studies based upon exercise ability. An Australia-New Zealand double-blind, placebo-controlled study enrolled 415 patients (half randomized to immediate-release carvedilol) with less severe heart failure. All protocols excluded patients expected to undergo cardiac transplantation during the 7.5 to 15 months of double-blind follow-up. All randomized patients had tolerated a 2-week course on immediate-release carvedilol 6.25 mg twice daily.

In each study, there was a primary end point, either progression of heart failure (1 US study) or exercise tolerance (2 US studies meeting enrollment goals and the Australia-New Zealand study). There were many secondary end points specified in these studies, including NYHA classification, patient and physician global assessments, and cardiovascular hospitalization. Other analyses not prospectively planned included the sum of deaths and total cardiovascular

hospitalizations. In situations where the primary end points of a trial do not show a significant benefit of treatment, assignment of significance values to the other results is complex, and such values need to be interpreted cautiously.

The results of the US and Australia-New Zealand trials were as follows:

Slowing Progression of Heart Failure: One US multicenter study (366 subjects) had as its primary end point the sum of cardiovascular mortality, cardiovascular hospitalization, and sustained increase in heart failure medications. Heart failure progression was reduced, during an average follow-up of 7 months, by 48% ($p = 0.008$).

In the Australia-New Zealand study, death and total hospitalizations were reduced by about 25% over 18 to 24 months. In the 3 largest US studies, death and total hospitalizations were reduced by 19%, 39%, and 49%, nominally statistically significant in the last 2 studies. The Australia-New Zealand results were statistically borderline.

Functional Measures: None of the multicenter studies had NYHA classification as a primary end point, but all such studies had it as a secondary end point. There was at least a trend toward improvement in NYHA class in all studies. Exercise tolerance was the primary end point in 3 studies; in none was a statistically significant effect found.

Subjective Measures: Quality of life, as measured with a standard questionnaire (a primary end point in 1 study), was unaffected by carvedilol. However, patients' and investigators' global assessments showed significant improvement in most studies.

Mortality: Death was not a pre-specified end point in any study, but was analyzed in all studies. Overall, in these 4 US trials, mortality was reduced, nominally significantly so in 2 studies.

The COMET Trial: In this double-blind trial, 3,029 patients with NYHA class II-IV heart failure (left ventricular ejection fraction ≤35%) were randomized to receive either carvedilol (target dose: 25 mg twice daily) or immediate-release metoprolol tartrate (target dose: 50 mg twice daily). The mean age of the patients was approximately 62 years, 80% were males, and the mean left ventricular ejection fraction at baseline was 26%. Approximately 96% of the patients had NYHA class II or III heart failure. Concomitant treatment included diuretics (99%), ACE inhibitors (91%), digitalis (59%), aldosterone antagonists (11%), and "statin" lipid-lowering agents (21%). The mean duration of follow-up was 4.8 years. The mean dose of carvedilol was 42 mg per day.

The study had 2 primary end points: all-cause mortality and the composite of death plus hospitalization for any reason. The results of COMET are presented in Table 1 below. All-cause mortality carried most of the statistical weight and was the primary determinant of the study size. All-cause mortality was 34% in the patients treated with carvedilol and was 40% in the immediate-release metoprolol group ($p = 0.0017$; hazard ratio = 0.83, 95% CI 0.74–0.93). The effect on mortality was primarily due to a reduction in cardiovascular death. The difference between the 2 groups with respect to the composite end point was not significant ($p = 0.122$). The estimated mean survival was 8.0 years with carvedilol and 6.6 years with immediate-release metoprolol.

Table 1. Results of COMET

End point	Carvedilol N = 1,511	Metoprolol N = 1,518	Hazard ratio	(95% CI)
All cause mortality	34%	40%	0.83	0.74 – 0.93
Mortality + all hospitalization	74%	76%	0.94	0.86 – 1.02
Cardiovascular death	30%	35%	0.80	0.70 – 0.90
Sudden death	14%	17%	0.81	0.68 – 0.97
Death due to circulatory failure	11%	13%	0.83	0.67 – 1.02
Death due to stroke	0.9%	2.5%	0.33	0.18 – 0.62

It is not known whether this formulation of metoprolol at any dose or this low dose of metoprolol in any formulation has any effect on survival or hospitalization in patients with heart failure. Thus, this trial extends the time over which carvedilol manifests benefits on survival in heart failure, but it is not evidence that carvedilol improves outcome over the formulation of metoprolol (TOPROL-XL®) with benefits in heart failure.

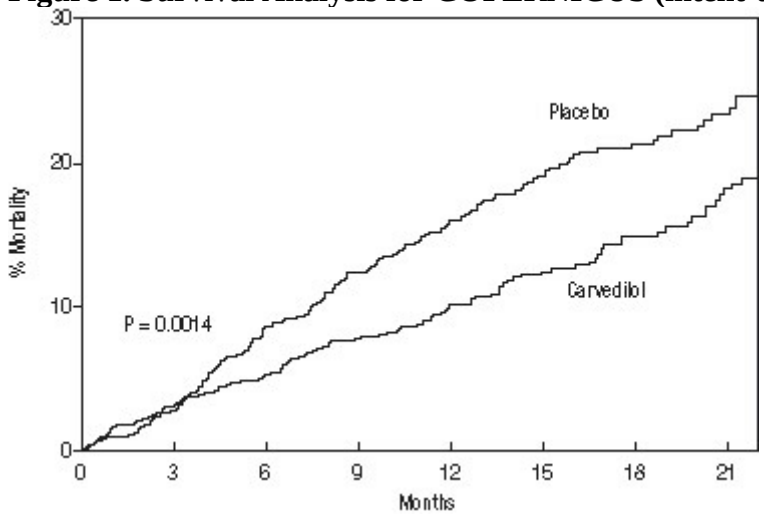
Trials in Severe Heart Failure: In a double-blind study (COPERNICUS), 2,289 patients with heart failure at rest or with minimal exertion and left ventricular ejection fraction <25% (mean 20%), despite digitalis (66%), diuretics (99%), and ACE inhibitors (89%) were randomized to placebo or carvedilol. Carvedilol was titrated from a starting dose of 3.125 mg twice daily to the maximum tolerated dose or up to 25 mg twice daily over a minimum of 6 weeks. Most subjects achieved the target dose of 25 mg. The study was conducted in Eastern and Western Europe, the United States, Israel, and Canada. Similar numbers of subjects per group (about 100) withdrew during the titration period.

The primary end point of the trial was all-cause mortality, but cause-specific mortality and the risk of death or hospitalization (total, cardiovascular [CV], or congestive heart failure [CHF]) were also examined. The developing trial data were followed by a data monitoring committee, and mortality analyses were adjusted for these multiple looks. The trial was stopped after a median follow-up of 10 months because of an observed 35% reduction in mortality (from 19.7% per patient year on placebo to 12.8% on carvedilol, hazard ratio 0.65, 95% CI 0.52 – 0.81, p = 0.0014, adjusted) (see Figure 1). The results of COPERNICUS are shown in Table 2.

Table 2. Results of COPERNICUS

End point	Placebo N = 1,133	Carvedilol N = 1,156	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
Mortality + 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	0.000004

Figure 1. Survival Analysis for COPERNICUS (intent-to-treat)



The effect on mortality was principally the result of a reduction in the rate of sudden death among patients without worsening heart failure.

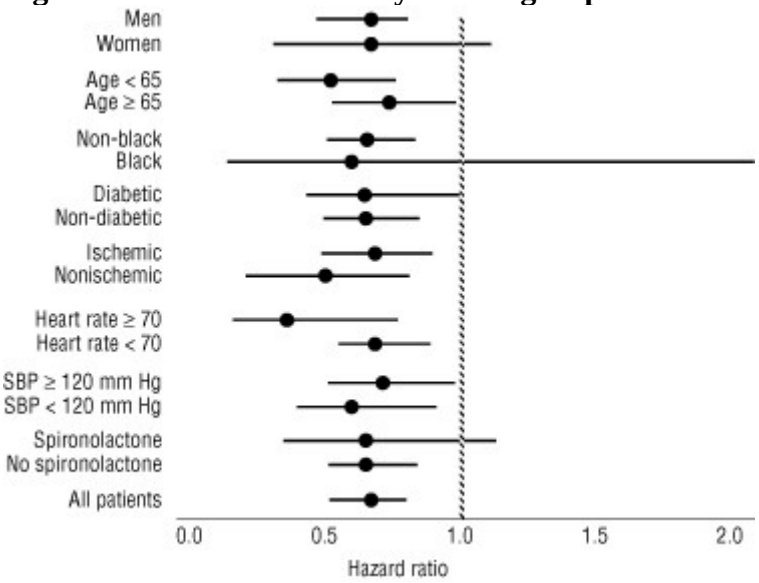
Patients' global assessments, in which carvedilol-treated patients were compared to placebo, were based on pre-specified, periodic patient self-assessments regarding whether clinical status post-treatment showed improvement, worsening, or no change compared to baseline. Patients treated with carvedilol showed significant improvements in global assessments compared with those treated with placebo in COPERNICUS.

The protocol also specified that hospitalizations would be assessed. Fewer patients on immediate-release carvedilol than on placebo were hospitalized for any reason (372 vs. 432, $p = 0.0029$), for cardiovascular reasons (246 vs. 314, $p = 0.0003$), or for worsening heart failure (198 vs. 268, $p = 0.0001$).

Immediate-release carvedilol had a consistent and beneficial effect on all-cause mortality as well as the combined end points of all-cause mortality plus hospitalization (total, CV, or for heart failure) in the overall study population and in all subgroups examined, including men and

women, elderly and non-elderly, blacks and non-blacks, and diabetics and non-diabetics (see Figure 2).

Figure 2. Effects on Mortality for Subgroups in COPERNICUS



Although the clinical trials used twice-daily dosing, clinical pharmacologic and pharmacokinetic data provide a reasonable basis for concluding that once-daily dosing with COREG CR should be adequate in the treatment of heart failure.

Left Ventricular Dysfunction Following Myocardial Infarction: CAPRICORN was a double-blind study comparing carvedilol and placebo in 1,959 patients with a recent myocardial infarction (within 21 days) and left ventricular ejection fraction of ≤40%, with (47%) or without symptoms of heart failure. Patients given carvedilol received 6.25 mg twice daily, titrated as tolerated to 25 mg twice daily. Patients had to have a systolic blood pressure >90 mm Hg, a sitting heart rate >60 beats/minute, and no contraindication to β-blocker use. Treatment of the index infarction included aspirin (85%), IV or oral β-blockers (37%), nitrates (73%), heparin (64%), thrombolytics (40%), and acute angioplasty (12%). Background treatment included ACE inhibitors or angiotensin receptor blockers (97%), anticoagulants (20%), lipid-lowering agents (23%), and diuretics (34%). Baseline 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. Mean dosage achieved of carvedilol was 20 mg twice daily; mean 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% risk reduction in patients treated with carvedilol (95% CI 2% to 40%, p = 0.03), as shown in Figure 3. The effects on mortality in various subgroups are shown in Figure 4. Nearly all deaths were cardiovascular (which were reduced by 25% by carvedilol), and most of these deaths were sudden or related to pump failure (both types of death were reduced by carvedilol). Another

study end point, total mortality and all-cause hospitalization, did not show a significant improvement.

There was also a significant 40% reduction in fatal or non-fatal myocardial infarction observed in the group treated with carvedilol (95% CI 11% to 60%, p = 0.01). A similar reduction in the risk of myocardial infarction was also observed in a meta-analysis of placebo-controlled trials of carvedilol in heart failure.

Figure 3. Survival Analysis for CAPRICORN (intent-to-treat)

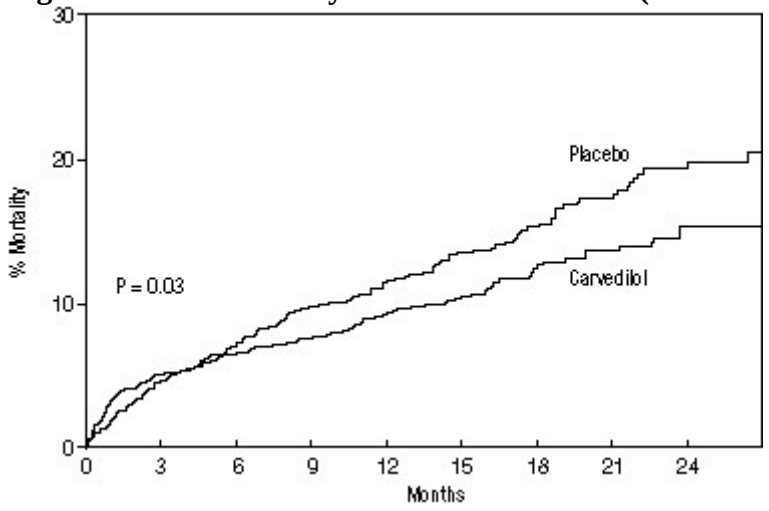
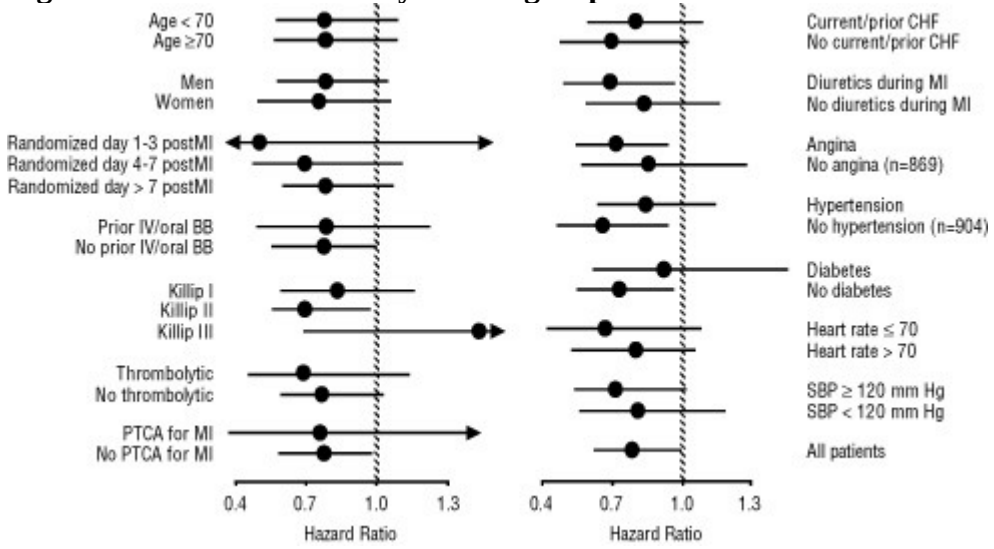


Figure 4. Effects on Mortality for Subgroups in CAPRICORN

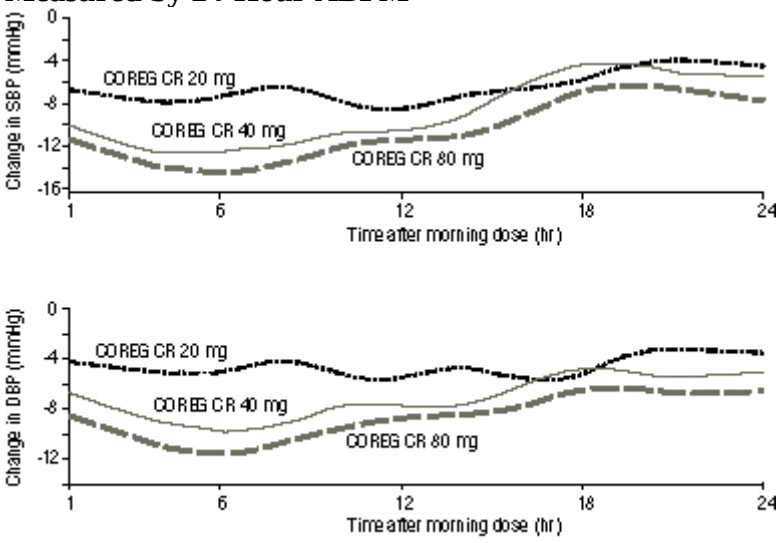


Although the clinical trials used twice-daily dosing, clinical pharmacologic and pharmacokinetic data provide a reasonable basis for concluding that once-daily dosing with COREG CR should be adequate in the treatment of left ventricular dysfunction following myocardial infarction.

Hypertension: A double-blind, randomized, placebo-controlled, 8-week trial evaluated the blood pressure lowering effects of COREG CR 20 mg, 40 mg, and 80 mg once daily in 338 patients with essential hypertension (sitting diastolic blood pressure [DBP] ≥90 and ≤109 mm Hg). Of 337 evaluable patients, a total of 273 patients (81%) completed the study. Of the 64 (19%) patients withdrawn from the study, 10 (3%) were due to adverse events, 10 (3%) were due to lack of efficacy; the remaining 44 (13%) withdrew for other reasons. The mean age of the patients was approximately 53 years, 66% were male, and the mean sitting systolic blood pressure (SBP) and DBP at baseline were 150 mm Hg and 99 mm Hg, respectively. Dose titration occurred at 2-week intervals.

Statistically significant reductions in blood pressure as measured by 24-hour ambulatory blood pressure monitoring (ABPM) were observed with each dose of COREG CR compared to placebo. Placebo-subtracted mean changes from baseline in mean SBP/DBP were -6.1/-4.0 mm Hg, -9.4/-7.6 mm Hg, and -11.8/-9.2 mm Hg for COREG CR 20 mg, 40 mg, and 80 mg, respectively. Placebo-subtracted mean changes from baseline in mean trough (average of hours 20-24) SBP/DBP were -3.3/-2.8 mm Hg, -4.9/-5.2 mm Hg, and -8.4/-7.4 mm Hg for COREG CR 20 mg, 40 mg, and 80 mg, respectively. The placebo-corrected trough to peak (3-7 hr) ratio was approximately 0.6 for COREG CR 80 mg. In this study, assessments of 24-hour ABPM monitoring demonstrated statistically significant blood pressure reductions with COREG CR throughout the dosing period (Figure 5).

Figure 5. Changes from Baseline in Systolic Blood Pressure and Diastolic Blood Pressure Measured by 24-Hour ABPM



Lines smoothed using locally weighted regression smoothing methodology.

Immediate-release carvedilol was studied in 2 placebo-controlled trials that utilized twice-daily dosing, at total daily doses of 12.5 to 50 mg. In these and other studies, the starting dose did not exceed 12.5 mg. At 50 mg/day, COREG reduced sitting 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

of trough-to-peak blood pressure showed a trough-to-peak ratio for blood pressure response of about 65%. Heart rate fell by about 7.5 beats/minute at 50 mg/day. In general, as is true for other β-blockers, responses were smaller in black than non-black patients. There were no age- or gender-related differences in response. The dose-related blood pressure response was accompanied by a dose-related increase in adverse effects (see ADVERSE REACTIONS).

Hypertensive Patients with Type 2 Diabetes Mellitus (GEMINI): In a double-blind study, carvedilol, added to an ACE inhibitor or angiotensin receptor blocker, was evaluated in a population with mild-to-moderate hypertension and well-controlled type 2 diabetes mellitus. The mean HbA1c at baseline was 7.2%. COREG was titrated to a mean dose of 17.5 mg twice daily and maintained for 5 months. COREG had no adverse effect on glycemic control, based on HbA1c measurements (mean change from baseline of 0.02%, 95% CI -0.06 to 0.10, p = NS) (see PRECAUTIONS, Effects on Glycemic Control in Type 2 Diabetic Patients).

INDICATIONS AND USAGE

Heart Failure: COREG CR is indicated for the treatment of mild-to-severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitor, and digitalis, to increase survival and, also, to reduce the risk of hospitalization (see CLINICAL TRIALS and PRECAUTIONS, Drug Interactions).

Left Ventricular Dysfunction Following Myocardial Infarction: COREG CR is indicated to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of ≤40% (with or without symptomatic heart failure) (see CLINICAL TRIALS).

Hypertension: COREG CR is indicated for the treatment of essential hypertension. It can be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics (see PRECAUTIONS, Drug Interactions).

CONTRAINDICATIONS

COREG CR is contraindicated in patients with bronchial asthma (2 cases of death from status asthmaticus have been reported in patients receiving single doses of immediate-release carvedilol) or related bronchospastic conditions, second- or third-degree AV block, sick sinus syndrome or severe bradycardia (unless a permanent pacemaker is in place), or in patients with cardiogenic shock or who have decompensated heart failure requiring the use of intravenous inotropic therapy. Such patients should first be weaned from intravenous therapy before initiating COREG CR.

Use of COREG CR in patients with clinically manifest hepatic impairment is not recommended.

COREG CR is contraindicated in patients with hypersensitivity to any component of the product.

WARNINGS

Cessation of Therapy with COREG CR: Patients with coronary artery disease, who are being treated with COREG CR, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with β-blockers. The last 2 complications may occur with or without preceding exacerbation of the angina pectoris. As with other β-blockers, when discontinuation of COREG CR is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. COREG CR should be discontinued over 1 to 2 weeks whenever possible. If the angina worsens or acute coronary insufficiency develops, it is recommended that COREG CR be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue COREG CR therapy abruptly even in patients treated only for hypertension or heart failure (see DOSAGE AND ADMINISTRATION).

Peripheral Vascular Disease: β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

Anesthesia and Major Surgery: If treatment with COREG CR is to be continued perioperatively, particular care should be taken when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used. See OVERDOSAGE for information on treatment of bradycardia and hypertension.

Diabetes and Hypoglycemia: In general, β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective β-blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned about these possibilities. In heart failure patients, there is a risk of worsening hyperglycemia (see PRECAUTIONS, Effects on Glycemic Control in Type 2 Diabetic Patients).

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.

PRECAUTIONS

General: In clinical trials of COREG CR in patients with hypertension (338 subjects) and in patients with left ventricular dysfunction following a myocardial infarction or heart failure (187 subjects), the profile of adverse events observed with carvedilol phosphate was generally similar to that observed with the administration of immediate-release carvedilol. Therefore, the information included within this section is based on data from controlled clinical trials with COREG CR as well as immediate-release carvedilol.

In clinical trials with immediate-release carvedilol, bradycardia was reported in about 2% of hypertensive patients, 9% of heart failure patients, and 6.5% of myocardial infarction patients

with left ventricular dysfunction. Bradycardia was reported in 0.5% of patients receiving COREG CR in a study of heart failure patients and myocardial infarction patients with left ventricular dysfunction. There were no reports of bradycardia in the clinical trial of COREG CR in hypertension. However, if pulse rate drops below 55 beats/minute, the dosage of COREG CR should be reduced.

In clinical trials of primarily mild-to-moderate heart failure with immediate-release carvedilol, hypotension and postural hypotension occurred in 9.7% and syncope in 3.4% of patients receiving carvedilol compared to 3.6% and 2.5% of placebo patients, respectively. The risk for these events was highest during the first 30 days of dosing, corresponding to the up-titration period and was a cause for discontinuation of therapy in 0.7% of carvedilol patients, compared to 0.4% of placebo patients. In a long-term, placebo-controlled trial in severe heart failure (COPERNICUS), hypotension and postural hypotension occurred in 15.1% and syncope in 2.9% of heart failure patients receiving carvedilol compared to 8.7% and 2.3% of placebo patients, respectively. These events were a cause for discontinuation of therapy in 1.1% of carvedilol patients, compared to 0.8% of placebo patients.

In the clinical trial of COREG CR in hypertensive patients, syncope was reported in 0.3% of patients receiving COREG CR compared to 0% of patients receiving placebo. There were no reports of postural hypotension in this trial. Postural hypotension occurred in 1.8% and syncope in 0.1% of hypertensive patients receiving immediate-release carvedilol, primarily following the initial dose or at the time of dose increase and was a cause for discontinuation of therapy in 1% of patients.

In the CAPRICORN study of survivors of an acute myocardial infarction with left ventricular dysfunction, hypotension or postural hypotension occurred in 20.2% of patients receiving carvedilol compared to 12.6% of placebo patients. Syncope was reported in 3.9% and 1.9% of patients, respectively. These events were a cause for discontinuation of therapy in 2.5% of patients receiving carvedilol, compared to 0.2% of placebo patients.

To decrease the likelihood of syncope or excessive hypotension, treatment with COREG CR should be initiated with 10 mg once daily for heart failure patients, and at 20 mg once daily for hypertensive patients and survivors of an acute myocardial infarction with left ventricular dysfunction. Dosage should then be increased slowly, according to recommendations in the DOSAGE AND ADMINISTRATION section, and the drug should be taken with food. During initiation of therapy, the patient should be cautioned to avoid situations such as driving or hazardous tasks, where injury could result should syncope occur.

Rarely, use of carvedilol in patients with heart failure has resulted in deterioration of renal function. Patients at risk appear to be those with low blood pressure (systolic blood pressure <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 COREG CR and the drug discontinued or dosage reduced if worsening of renal function occurs.

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 COREG CR should not be advanced until clinical stability resumes (see DOSAGE AND ADMINISTRATION). Occasionally it is necessary to lower the dose of COREG CR or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of, or a favorable response to, COREG CR. In a placebo-controlled trial of patients with severe heart failure, worsening heart failure during the first 3 months was reported to a similar degree with immediate-release carvedilol and with placebo. 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.

In patients with pheochromocytoma, an α-blocking agent should be initiated prior to the use of any β-blocking agent. Although carvedilol has both α- and β-blocking pharmacologic activities, there has been no experience with its use in this condition. Therefore, caution should be taken in the administration of carvedilol to patients suspected of having pheochromocytoma.

Agents with non-selective β-blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There has been no clinical experience with carvedilol in these patients although the α-blocking activity may prevent such symptoms. However, caution should be taken in the administration of COREG CR to patients suspected of having Prinzmetal's variant angina.

Effects on Glycemic Control in Type 2 Diabetic Patients: In heart failure patients with diabetes, carvedilol therapy may lead to worsening hyperglycemia, which responds to intensification of hypoglycemic therapy. It is recommended that blood glucose be monitored when dosing with COREG CR is initiated, adjusted, or discontinued. Studies designed to examine the effects of carvedilol on glycemic control in patients with diabetes and heart failure have not been conducted.

In a study designed to examine the effects of immediate-release carvedilol on glycemic control in a population with mild-to-moderate hypertension and well-controlled type 2 diabetes mellitus, carvedilol had no adverse effect on glycemic control, based on HbA1c measurements (see CLINICAL TRIALS, Hypertensive Patients with Type 2 Diabetes Mellitus [GEMINI]).

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

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema): Patients with bronchospastic disease should, in general, not receive β-blockers. COREG CR may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if COREG CR is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous β-agonists is minimized.

In clinical trials of patients with 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 COREG CR 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.

Information for Patients: Patients taking COREG CR should be advised of the following:

- They should not interrupt or discontinue using COREG CR without a physician's advice.
- Heart failure patients should consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath.
- They 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 lowered blood pressure occur.
- If patients experience dizziness or fatigue, they should avoid driving or hazardous tasks.
- They should consult a physician if they experience dizziness or faintness, in case the dosage should be adjusted.
- They should not crush or chew COREG CR capsules.
- They should take COREG CR with food.
- Diabetic patients should report any changes in blood sugar levels to their physician.
- Contact lens wearers may experience decreased lacrimation.

Drug Interactions: (Also see CLINICAL PHARMACOLOGY, Pharmacokinetic Drug-Drug Interactions.)

Inhibitors of CYP2D6: poor metabolizers of debrisoquin: Interactions of carvedilol with strong inhibitors of CYP2D6 (such as quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would be expected to increase blood levels of the R(+) enantiomer of carvedilol (see CLINICAL PHARMACOLOGY). Retrospective analysis of side effects in clinical trials showed that poor 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the α-blocking R(+) enantiomer.

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

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

Digitalis Glycosides: Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Therefore, increased monitoring of digoxin is recommended when initiating, adjusting, or discontinuing COREG CR (see CLINICAL PHARMACOLOGY, Pharmacokinetic Drug-Drug Interactions).

Inducers and inhibitors of hepatic metabolism: Rifampin reduced plasma concentrations of carvedilol by about 70%. Cimetidine increased AUC by about 30% but caused no change in C_{max}.

Calcium channel blockers: Isolated cases of conduction disturbance (rarely with hemodynamic compromise) have been observed when carvedilol is co-administered with diltiazem. As with other agents with β-blocking properties, if COREG CR is to be administered orally with calcium channel blockers of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored.

Insulin or oral hypoglycemics: Agents with β-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.

Proton Pump Inhibitors: There is no clinically meaningful increase in AUC and C_{max} with concomitant administration of carvedilol extended-release capsules with pantoprazole.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In 2-year studies conducted in rats given carvedilol at doses up to 75 mg/kg/day (12 times the maximum recommended human dose [MRHD] when compared on a mg/m^2 basis) or in mice given up to 200 mg/kg/day (16 times the MRHD on a mg/m^2 basis), carvedilol had no carcinogenic effect.

Carvedilol was negative when tested in a battery of genotoxicity assays, including the Ames and the CHO/HGPRT assays for mutagenicity and the in vitro hamster micronucleus and in vivo human lymphocyte cell tests for clastogenicity.

At doses ≥200 mg/kg/day (≥32 times the MRHD as mg/m^2) carvedilol was toxic to adult rats (sedation, reduced weight gain) and was associated with a reduced number of successful matings, prolonged mating time, significantly fewer corpora lutea and implants per dam, and complete resorption of 18% of the litters. The no-observed-effect dose level for overt toxicity and impairment of fertility was 60 mg/kg/day (10 times the MRHD as mg/m^2).

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Studies performed in pregnant rats and rabbits given carvedilol revealed increased post-implantation loss in rats at doses of 300 mg/kg/day (50 times the MRHD as mg/m^2) and in rabbits at doses of 75 mg/kg/day (25 times the MRHD as mg/m^2). In the rats, there was also a decrease in fetal body weight at the maternally toxic dose of 300 mg/kg/day (50 times the MRHD as mg/m^2), which was

accompanied by an elevation in the frequency of fetuses with delayed skeletal development (missing or stunted 13th rib). In rats the no-observed-effect level for developmental toxicity was 60 mg/kg/day (10 times the MRHD as mg/m^2); in rabbits it was 15 mg/kg/day (5 times the MRHD as mg/m^2). There are no adequate and well-controlled studies in pregnant women. COREG CR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug 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 at one week post partum in neonates from rats treated with 60 mg/kg/day (10 times the MRHD as mg/m^2) and above during the last trimester through day 22 of lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from β-blockers, especially bradycardia, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. The effects of other α- and β-blocking agents have included perinatal and neonatal distress.

Pediatric Use: Effectiveness of carvedilol in patients younger than 18 years of age has not been established.

In a double-blind trial, 161 children (mean age 6 years, range 2 months to 17 years; 45% less than 2 years old) with chronic heart failure [NYHA class II-IV, left ventricular ejection fraction <40% for children with a systemic left ventricle (LV), and moderate-severe ventricular dysfunction qualitatively by echo for those with a systemic ventricle that was not an LV] who were receiving standard background treatment were randomized to placebo or to 2 dose levels of carvedilol. These dose levels produced placebo-corrected heart rate reduction of 4-6 heart beats per minute, indicative of β-blockade activity. Exposure appeared to be lower in pediatric subjects than adults. After 8 months of follow-up, there was no significant effect of treatment on clinical outcomes. Adverse reactions in this trial that occurred in greater than 10% of patients treated with immediate-release carvedilol and at twice the rate of placebo-treated patients included chest pain (17% versus 6%), dizziness (13% versus 2%), and dyspnea (11% versus 0%).

Geriatric Use: The clinical studies of carvedilol in patients with hypertension, heart failure, and left ventricular dysfunction following myocardial infarction did not include sufficient numbers of subjects 65 years of age or older to determine whether they respond differently from younger patients.

The following information is available for trials with immediate-release carvedilol. Of the 765 patients with heart failure randomized to carvedilol in US clinical trials, 31% (235) were 65 years of age or older, and 7.3% (56) were 75 years of age or older. Of the 1,156 patients randomized to carvedilol in a long-term, placebo-controlled trial in severe heart failure, 47% (547) were 65 years of age or older, and 15% (174) were 75 years of age or older. Of 3,025 patients receiving carvedilol in heart failure trials worldwide, 42% were 65 years of age or older. Of the 975 myocardial infarction patients randomized to carvedilol in the CAPRICORN trial, 48% (468) were 65 years of age or older, and 11% (111) were 75 years of age or older. Of

the 2,065 hypertensive patients in US clinical trials of efficacy or safety who were treated with carvedilol, 21% (436) were 65 years of age or older. Of 3,722 patients receiving immediate-release carvedilol in hypertension clinical trials conducted worldwide, 24% were 65 years of age 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 the safety or effectiveness (see Figures 2 and 4) were observed between the older subjects and younger subjects in each of these populations. Similarly, other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Carvedilol has been evaluated for safety in patients with heart failure (mild, moderate, and severe heart failure), in patients with left ventricular dysfunction following myocardial infarction, and in hypertensive patients. The observed adverse event profile was consistent with the pharmacology of the drug and the health status of the patients in the clinical trials. Adverse events reported for each of these patient populations reflecting the use of either COREG CR or immediate-release carvedilol are provided below. Excluded are adverse events considered too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population. Rates of adverse events were generally similar across demographic subsets (men and women, elderly and non-elderly, blacks and non-blacks). COREG CR has been evaluated for safety in a 4-week (2 weeks of immediate-release carvedilol and 2 weeks of COREG CR) clinical study (n = 187) which included 157 patients with stable mild, moderate, or severe chronic heart failure and 30 patients with left ventricular dysfunction following acute myocardial infarction. The profile of adverse events observed with COREG CR in this small, short-term study was generally similar to that observed with immediate-release carvedilol. Differences in safety would not be expected based on the similarity in plasma levels for COREG CR and immediate-release carvedilol.

Heart Failure: The following information describes the safety experience in heart failure with immediate-release carvedilol.

Carvedilol has been evaluated for safety in heart failure in more than 4,500 patients worldwide of whom more than 2,100 participated in placebo-controlled clinical trials. Approximately 60% of the total treated population in placebo-controlled clinical trials received carvedilol for at least 6 months and 30% received carvedilol for at least 12 months. In the COMET trial, 1,511 patients with mild-to-moderate heart failure were treated with carvedilol for up to 5.9 years (mean 4.8 years). Both in US clinical trials in mild-to-moderate heart failure that compared carvedilol in daily doses up to 100 mg (n = 765) to placebo (n = 437), and in a multinational clinical trial in severe heart failure (COPERNICUS) that compared carvedilol in daily doses up to 50 mg (n = 1,156) with placebo (n = 1,133), discontinuation rates for adverse

experiences were similar in carvedilol and placebo patients. In placebo-controlled clinical trials, the only cause of discontinuation >1%, and occurring more often on carvedilol was dizziness (1.3% on carvedilol, 0.6% on placebo in the COPERNICUS trial).

Table 3 shows adverse events reported in patients with mild-to-moderate heart failure enrolled in US placebo-controlled clinical trials, and with severe heart failure enrolled in the COPERNICUS trial. Shown are adverse events that occurred more frequently in drug-treated patients than placebo-treated patients with an incidence of >3% in patients treated with carvedilol regardless of causality. Median study medication exposure was 6.3 months for both carvedilol and placebo patients in the trials of mild-to-moderate heart failure, and 10.4 months in the trial of severe heart failure patients. The adverse event profile of carvedilol observed in the long-term COMET study was generally similar to that observed in the US Heart Failure Trials.

Table 3. Adverse Events (% Occurrence) Occurring More Frequently With Immediate-Release Carvedilol Than With Placebo in Patients With Mild-to-Moderate Heart Failure Enrolled in US Heart Failure Trials or in Patients With Severe Heart Failure in the COPERNICUS Trial (Incidence >3% in Patients Treated With Carvedilol, Regardless of Causality)

	Mild-to-Moderate Heart Failure		Severe Heart Failure	
	Carvedilol	Placebo	Carvedilol	Placebo
	(n = 765)	(n = 437)	(n = 1,156)	(n = 1,133)
Body as a Whole				
Asthenia	7	7	11	9
Fatigue	24	22	-	-
Digoxin level increased	5	4	2	1
Edema generalized	5	3	6	5
Edema dependent	4	2	-	-
Cardiovascular				
Bradycardia	9	1	10	3
Hypotension	9	3	14	8
Syncope	3	3	8	5
Angina pectoris	2	3	6	4
Central Nervous System				
Dizziness	32	19	24	17
Headache	8	7	5	3
Gastrointestinal				
Diarrhea	12	6	5	3
Nausea	9	5	4	3
Vomiting	6	4	1	2
Metabolic				
Hyperglycemia	12	8	5	3
Weight increase	10	7	12	11
BUN increased	6	5	-	-
NPN increased	6	5	-	-
Hypercholesterolemia	4	3	1	1
Edema peripheral	2	1	7	6
Musculoskeletal				
Arthralgia	6	5	1	1
Respiratory				
Cough increased	8	9	5	4
Rales	4	4	4	2
Vision				
Vision abnormal	5	2	-	-

Cardiac failure and dyspnea were also reported in these studies, but the rates were equal or greater in patients who received placebo.

The following adverse events were reported with a frequency of >1% but ≤3% and more frequently with carvedilol in either the US placebo-controlled trials in patients with mild-to-moderate heart failure, or in patients with severe heart failure in the COPERNICUS trial.

Incidence >1% to ≤3%

Body as a Whole: Allergy, malaise, hypovolemia, fever, leg edema.

Cardiovascular: Fluid overload, postural hypotension, aggravated angina pectoris, AV block, palpitation, hypertension.

Central and Peripheral Nervous System: Hypesthesia, vertigo, paresthesia.

Gastrointestinal: Melena, periodontitis.

Liver and Biliary System: SGPT increased, SGOT increased.

Metabolic and Nutritional: Hyperuricemia, hypoglycemia, hyponatremia, increased alkaline phosphatase, glycosuria, hypervolemia, diabetes mellitus, GGT increased, weight loss, hyperkalemia, creatinine increased.

Musculoskeletal: Muscle cramps.

Platelet, Bleeding and Clotting: Prothrombin decreased, purpura, thrombocytopenia.

Psychiatric: Somnolence.

Reproductive, male: Impotence.

Special Senses: Blurred vision.

Urinary System: Renal insufficiency, albuminuria, hematuria.

Left Ventricular Dysfunction Following Myocardial Infarction: The following information describes the safety experience in left ventricular dysfunction following acute myocardial infarction with immediate-release carvedilol.

Carvedilol has been evaluated for safety in survivors of an acute myocardial infarction with left ventricular dysfunction in the CAPRICORN trial which involved 969 patients who received carvedilol and 980 who received placebo. Approximately 75% of the 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 with carvedilol and placebo, respectively.

The most common adverse events reported with carvedilol in the CAPRICORN trial were consistent with the profile of the drug in the US heart failure trials and the COPERNICUS trial. The only additional adverse events reported in CAPRICORN in >3% of the patients and more commonly on carvedilol were dyspnea, anemia, and lung edema. The following adverse events were reported with a frequency of >1% but ≤3% and more frequently with carvedilol: Flu syndrome, cerebrovascular accident, peripheral vascular disorder, hypotonia, depression, gastrointestinal pain, arthritis, and gout. The overall rates of discontinuations due to adverse events were similar in both groups of patients. In this database, the only cause of discontinuation >1%, and occurring more often on carvedilol was hypotension (1.5% on carvedilol, 0.2% on placebo).

Hypertension: COREG CR was evaluated for safety in an 8-week double-blind trial in 337 subjects with essential hypertension. The profile of adverse events observed with COREG CR

was generally similar to that observed with immediate-release carvedilol. The overall rates of discontinuations due to adverse events were similar between COREG CR and placebo.

Table 4. Adverse Events (% Occurrence) Occurring More Frequently With COREG CR Than With Placebo in Patients With Hypertension (Incidence ≥1% in Patients Treated With Carvedilol, Regardless of Causality)

	Placebo (n = 84)	COREG CR (n = 253)
Nasopharyngitis	0	4
Dizziness	1	2
Nausea	0	2
Edema peripheral	1	2
Nasal congestion	0	1
Paresthesia	0	1
Sinus congestion	0	1
Diarrhea	0	1
Insomnia	0	1

The following information describes the safety experience in hypertension with immediate-release carvedilol.

Carvedilol has been evaluated for safety in hypertension in more than 2,193 patients in US 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. In general, carvedilol was well tolerated at doses up to 50 mg daily. Most adverse events reported during carvedilol therapy were of mild to moderate severity. In US controlled clinical trials directly comparing carvedilol monotherapy in doses up to 50 mg (n = 1,142) to placebo (n = 462), 4.9% of carvedilol patients discontinued for adverse events vs. 5.2% of placebo patients. Although there was no overall difference in discontinuation rates, discontinuations were more common in the carvedilol group for postural hypotension (1% vs. 0). The overall incidence of adverse events in US placebo-controlled trials was found to increase with increasing dose of carvedilol. For individual adverse events this could only be distinguished for dizziness, which increased in frequency from 2% to 5% as total daily dose increased from 6.25 mg to 50 mg as single or divided doses.

Table 5 shows adverse events in US placebo-controlled clinical trials for hypertension that occurred with an incidence of ≥1% regardless of causality, and that were more frequent in drug-treated patients than placebo-treated patients.

Table 5. Adverse Events (% Occurrence) in US Placebo-Controlled Hypertension Trials With Immediate-Release Carvedilol (Incidence ≥1% in Patients Treated With Carvedilol, Regardless of Causality)*

	Placebo (n = 462)	Carvedilol (n = 1,142)
Cardiovascular		
Bradycardia	—	2
Postural hypotension	—	2
Peripheral edema	—	1
Central Nervous System		
Dizziness	5	6
Insomnia	1	2
Gastrointestinal		
Diarrhea	1	2
Hematologic		
Thrombocytopenia	—	1
Metabolic		
Hypertriglyceridemia	—	1

* Shown are events with rate >1% to nearest integer.

Dyspnea and fatigue were also reported in these studies, but the rates were equal or greater in patients who received placebo.

The following adverse events not described above were reported as possibly or probably related to carvedilol in worldwide open or controlled trials with carvedilol in patients with hypertension or heart failure.

Incidence >0.1% to ≤1%

Cardiovascular: Peripheral ischemia, tachycardia.

Central and Peripheral Nervous System: Hypokinesia.

Gastrointestinal: Bilirubinemia, increased hepatic enzymes (0.2% of hypertension patients and 0.4% of heart failure patients were discontinued from therapy because of increases in hepatic enzymes; see Laboratory Abnormalities.)

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

Respiratory System: Asthma (see CONTRAINDICATIONS).

Reproductive: Male: Decreased libido.

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

Special Senses: Tinnitus.

Urinary System: Micturition frequency increased.

Autonomic Nervous System: Dry mouth, sweating increased.

Metabolic and Nutritional: Hypokalemia, hypertriglyceridemia.

Hematologic: Anemia, leukopenia.

The following events were reported in ≤0.1% of patients 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, increased BUN, decreased HDL, pancytopenia, and atypical lymphocytes.

Laboratory Abnormalities: Reversible elevations in serum transaminases (ALT or AST) have been observed during treatment with carvedilol. Rates of transaminase elevations (2- to 3-times the upper limit of normal) observed during controlled clinical trials have generally been similar between patients treated with carvedilol and those treated with placebo. However, transaminase elevations, confirmed by rechallenge, have been observed with carvedilol. In a long-term, placebo-controlled trial in severe heart failure, patients treated with carvedilol had lower values for hepatic transaminases than patients treated with placebo, possibly because carvedilol-induced improvements in cardiac function led to less hepatic congestion and/or improved hepatic blood flow.

Carvedilol therapy has not been associated with clinically significant changes in serum potassium, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine. No clinically relevant changes were noted in fasting serum glucose in hypertensive patients; fasting serum glucose was not evaluated in the heart failure clinical trials.

Postmarketing Experience: Reports of aplastic anemia and severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme) have been rare and received only when carvedilol was administered concomitantly with other medications associated with such reactions. Urinary incontinence in women (which resolved upon discontinuation of the medication) and interstitial pneumonitis have been reported rarely.

OVERDOSAGE

The acute oral LD50 doses in male and female mice and male and female rats are over 8,000 mg/kg. Overdosage may cause severe hypotension, bradycardia, cardiac insufficiency, 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, where necessary, kept under observation and treated under intensive-care conditions. Gastric lavage or pharmacologically induced emesis may be used shortly after ingestion. The following agents may be administered:

For excessive bradycardia: atropine, 2 mg IV.

To support cardiovascular function: glucagon, 5 to 10 mg IV rapidly over 30 seconds, followed by a continuous infusion of 5 mg/hour; sympathomimetics (dobutamine, isoprenaline, adrenaline) at doses according to body weight and effect.

If peripheral vasodilation dominates, it may be necessary to administer adrenaline or noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant

bradycardia, pacemaker therapy should be performed. For bronchospasm, β-sympathomimetics (as aerosol or IV) or aminophylline IV should be given. In the event of seizures, slow IV injection of diazepam or clonazepam is recommended.

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

There is no experience of overdosage with COREG CR. Cases of overdosage with carvedilol alone or in combination with other drugs have been reported. Quantities ingested in some cases exceeded 1,000 milligrams. Symptoms experienced included low blood pressure and heart rate. Standard supportive treatment was provided and individuals recovered.

DOSAGE AND ADMINISTRATION

General: COREG CR is an extended-release capsule intended for once-daily administration. Patients controlled with immediate-release carvedilol tablets alone or in combination with other medications may be switched to COREG CR extended-release capsules based on the total daily doses shown in Table 6. Subsequent titration to higher or lower doses may be necessary as clinically warranted.

Table 6. Dosing Conversion

Daily Dose of Immediate-Release Carvedilol Tablets	Daily Dose of COREG CR Capsules
6.25 mg (3.125 mg twice daily)	10 mg once daily
12.5 mg (6.25 mg twice daily)	20 mg once daily
25 mg (12.5 mg twice daily)	40 mg once daily
50 mg (25 mg twice daily)	80 mg once daily

COREG CR should be taken once daily in the morning with food. COREG CR should be swallowed as a whole capsule. COREG CR and/or its contents should not be crushed, chewed, or taken in divided doses.

Alternative Administration: The capsules may be carefully opened and the beads sprinkled over a spoonful of applesauce. The applesauce should not be warm because it could affect the modified-release properties of this formulation. The mixture of drug and applesauce should be consumed immediately in its entirety. The drug and applesauce mixture should not be stored for future use. Absorption of the beads sprinkled on other foods has not been tested.

Heart Failure: DOSAGE MUST BE INDIVIDUALIZED AND CLOSELY MONITORED BY A PHYSICIAN DURING UP-TITRATION. Prior to initiation of COREG CR, it is recommended that fluid retention be minimized. The recommended starting dose of COREG CR is 10 mg once daily for 2 weeks. Patients who tolerate a dose of 10 mg once daily may have their dose increased to 20, 40, and 80 mg over successive intervals of at least 2 weeks. Patients should be maintained on lower doses if higher doses are not tolerated.

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 hour after dosing. Thus during these periods they should avoid situations such as driving or hazardous tasks, where symptoms could result in injury. Vasodilatory symptoms often do not require treatment, but it may be useful to separate the time of dosing of COREG CR from that of the ACE inhibitor or to reduce temporarily the dose of the ACE inhibitor. The dose of COREG CR should not be increased until symptoms of worsening heart failure or vasodilation have been stabilized.

Fluid retention (with or without transient worsening heart failure symptoms) should be treated by an increase in the dose of diuretics.

The dose of COREG CR should be reduced if patients experience bradycardia (heart rate <55 beats/minute).

Episodes of dizziness or fluid retention during initiation of COREG CR can generally be managed without discontinuation of treatment and do not preclude subsequent successful titration of, or a favorable response to, COREG CR.

Left Ventricular Dysfunction Following Myocardial Infarction: DOSAGE MUST BE INDIVIDUALIZED AND MONITORED DURING UP-TITRATION. Treatment with COREG CR may be started as an inpatient or outpatient and should be started after the patient is hemodynamically stable and fluid retention has been minimized. It is recommended that COREG CR be started at 20 mg once daily and increased after 3 to 10 days, based on tolerability to 40 mg once daily, then again to the target dose of 80 mg once daily. A lower starting dose may be used (10 mg once daily) and/or, the rate of up-titration may be slowed if clinically indicated (e.g., due to low blood pressure or heart rate, or fluid retention). Patients should be maintained on lower doses if higher doses are not tolerated. The recommended dosing regimen need not be altered in patients who received treatment with an IV or oral β-blocker during the acute phase of the myocardial infarction.

Hypertension: DOSAGE MUST BE INDIVIDUALIZED. The recommended starting dose of COREG CR is 20 mg once daily. If this dose is tolerated, using standing systolic pressure measured about one hour after dosing as a guide, the dose should be maintained for 7 to 14 days, and then increased to 40 mg once daily if needed, based on trough blood pressure, again using standing systolic pressure one hour after dosing as a guide for tolerance. This dose should also be maintained for 7 to 14 days and can then be adjusted upward to 80 mg once daily if tolerated and needed. Although not specifically studied, it is anticipated the full antihypertensive effect of COREG CR would be seen within 7 to 14 days as had been demonstrated with immediate-release carvedilol. Total daily dose should not exceed 80 mg.

Addition of a diuretic to COREG CR, or COREG CR to a diuretic can be expected to produce additive effects and exaggerate the orthostatic component of COREG CR action.

Use in Patients with Hepatic Impairment: COREG CR should not be given to patients with severe hepatic impairment (see CONTRAINDICATIONS).

HOW SUPPLIED

Capsules: The hard gelatin capsules are filled with white to off-white microparticles and are available in the following strengths:

10 mg – white and green capsule shell printed with GSK COREG CR and 10 mg
20 mg – white and yellow capsule shell printed with GSK COREG CR and 20 mg
40 mg – yellow and green capsule shell printed with GSK COREG CR and 40 mg
80 mg – white capsule shell printed with GSK COREG CR and 80 mg

10 mg 30's: NDC 0007-3370-13
10 mg 90's: NDC 0007-3370-59
20 mg 30's: NDC 0007-3371-13
20 mg 90's: NDC 0007-3371-59
40 mg 30's: NDC 0007-3372-13
40 mg 90's: NDC 0007-3372-59
80 mg 30's: NDC 0007-3373-13
80 mg 90's: NDC 0007-3373-59

STORAGE

Store at 25°C (77°F); excursions 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container.

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TOPROL-XL is a registered trademark of the AstraZeneca group of companies.

GlaxoSmithKline
Research Triangle Park, NC 27709

Month YEAR CCR:XPI

PATIENT INFORMATION LEAFLET

COREG CR™ (Co-REG)

(carvedilol phosphate) Extended-release Capsules

Read the Patient Information that comes with COREG CR before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about COREG CR, ask your doctor or pharmacist.

What is the most important information I should know about COREG CR?

It is important for you to take your medicine every day as directed by your doctor. If you stop taking COREG CR suddenly, you could have chest pain and a heart attack. If your doctor decides that you should stop taking COREG CR, your doctor may slowly lower your dose over time before stopping it completely.

What is COREG CR?

COREG CR is a prescription medicine that belongs to a group of medicines called "beta-blockers". COREG CR is used, often with other medicines, for the following conditions:

- to treat patients with high blood pressure (hypertension)
- to treat patients who had a heart attack that worsened how well the heart pumps
- to treat patients with certain types of heart failure

COREG CR is not approved for use in children under 18 years of age.

Who should not take COREG CR?

Do not take COREG CR if you:

- have severe heart failure and require certain intravenous medicines that help support circulation.
- have asthma or other breathing problems.
- have a slow heartbeat or certain conditions that cause your heart to skip a beat (irregular heartbeat).
- have liver problems.
- are allergic to any of the ingredients in COREG CR. *See "What are the ingredients in COREG CR?"*

What should I tell my doctor before taking COREG CR?

Tell your doctor about all of your medical conditions, including if you:

- have asthma or other lung problems (such as bronchitis or emphysema).

- have problems with blood flow in your feet and legs (peripheral vascular disease). COREG CR can make some of your symptoms worse.
- have diabetes.
- have thyroid problems.
- have a condition called pheochromocytoma.
- have had severe allergic reactions.
- are scheduled for surgery and will be given anesthetic agents.
- are pregnant or trying to become pregnant. It is not known if COREG CR is safe for your unborn baby. You and your doctor should talk about the best way to control your high blood pressure during pregnancy.
- are breastfeeding. It is not known if COREG CR passes into your breast milk. You should not breastfeed while using COREG CR.

Tell your doctor about all of the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. COREG CR and certain other medicines can affect each other and cause serious side effects. COREG CR may affect the way other medicines work. Also, other medicines may affect how well COREG CR works.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist before you start a new medicine.

How should I take COREG CR?

- Take COREG CR exactly as prescribed. Take COREG CR **one** time each day with food. **It is important that you take COREG CR only one time each day.** To lessen possible side effects, your doctor might begin with a low dose and then slowly increase the dose.
- Swallow COREG CR capsules whole. Do not chew or crush COREG CR capsules.
- If you have trouble swallowing COREG CR whole:
  - The capsule may be carefully opened and the beads sprinkled over a spoonful of applesauce which should be eaten right away. The applesauce should not be warm.
  - Do not sprinkle beads on foods other than applesauce.
- **Do not stop taking COREG CR and do not change the amount of COREG CR you take without talking to your doctor.**
- If you miss a dose of COREG CR, take your dose as soon as you remember, unless it is time to take your next dose. Take your next dose at the usual time. Do not take 2 doses at the same time.
- If you take too much COREG CR, call your doctor or poison control center right away.

What should I avoid while taking COREG CR?

COREG CR can cause you to feel dizzy, tired, or faint. Do not drive a car, use machinery, or do anything that needs you to be alert if you have these symptoms.

What are possible side effects of COREG CR?

Serious side effects of COREG CR include:

- **chest pain and heart attack if you suddenly stop taking COREG CR.** *See "What is the most important information I should know about COREG CR?"*
- **slow heart beat.**
- **low blood pressure (which may cause dizziness or fainting when you stand up).** If these happen, sit or lie down, and tell your doctor right away.
- **worsening heart failure.** Tell your doctor right away if you have signs and symptoms that your heart failure may be worse, such as weight gain or increased shortness of breath.
- **changes in your blood sugar. If you have diabetes, tell your doctor if you have any changes in your blood sugar levels.**
- masking (hiding) the symptoms of low blood sugar, especially a fast heartbeat.
- **new or worsening symptoms of peripheral vascular disease.**
  - leg pain that happens when you walk, but goes away when you rest
  - no feeling (numbness) in your legs or feet while you are resting
  - cold legs or feet
- masking the symptoms of hyperthyroidism (overactive thyroid), such as a fast heartbeat.
- **worsening of severe allergic reactions.** Medicines to treat a severe allergic reaction may not work as well while you are taking COREG CR.

Common side effects of COREG CR include shortness of breath, weight gain, diarrhea, and tiredness. If you wear contact lenses, you may have fewer tears or dry eyes that can become bothersome.

Call your doctor if you have any side effects that bother you or don't go away.

How should I store COREG CR?

Store COREG CR at less than 86°F (30°C).

Safely throw away COREG CR that is out of date or no longer needed.

Keep COREG CR and all medicines out of the reach of children.

General information about COREG CR

Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use COREG CR for a condition for which it was not prescribed. Do not give COREG CR to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about COREG CR. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information

about COREG CR that is written for healthcare professionals. You can also find out more about COREG CR by visiting the website www.COREGCR.com or calling 1-888-825-5249. This call is free.

What are the ingredients in COREG CR?

Active ingredient: carvedilol phosphate

Inactive ingredients: crospovidone, hydrogenated castor oil, hydrogenated vegetable oil, magnesium stearate, methacrylic acid copolymers, microcrystalline cellulose, and povidone

COREG CR capsules come in the following strengths: 10 mg, 20 mg, 40 mg, 80 mg.

COREG CR is a trademark of GlaxoSmithKline.

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