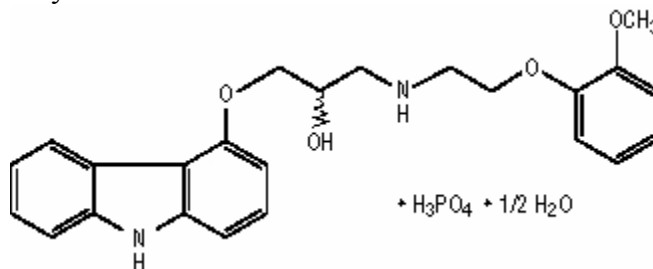


## PRESCRIBING INFORMATION

**COREG CR™**  
**(carvedilol phosphate) Extended-Release Capsules****DESCRIPTION**

Carvedilol phosphate is a nonselective  $\beta$ -adrenergic blocking agent with  $\alpha_1$ -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  $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_4 \cdot \text{H}_3\text{PO}_4 \cdot 1/2 \text{H}_2\text{O}$ .

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  $\beta$ -adrenoreceptor blocking activity is present in the S(-) enantiomer and  $\alpha_1$ -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],  $C_{\text{max}}$ , 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

1 increase in a dose-proportional manner over the dosage range of COREG CR 10 to 80 mg.  
2 Within-subject and between-subject variability for AUC and  $C_{max}$  is similar for COREG CR and  
3 immediate-release carvedilol.

4 **Effect of Food:** Administration of COREG CR with a high-fat meal resulted in increases  
5 (~20%) in AUC and  $C_{max}$  compared to COREG CR administered with a standard meal.  
6 Decreases in AUC (27%) and  $C_{max}$  (43%) were observed when COREG CR was administered in  
7 the fasted state compared to administration after a standard meal. COREG CR should be taken  
8 with food.

9 In a study with adult subjects, sprinkling the contents of the COREG CR capsule on  
10 applesauce did not appear to have a significant effect on overall exposure (AUC) compared to  
11 administration of the intact capsule following a standard meal but did result in a decrease in  $C_{max}$   
12 (18%).

13 **Distribution:** Carvedilol is more than 98% bound to plasma proteins, primarily with albumin.  
14 The plasma-protein binding is independent of concentration over the therapeutic range.  
15 Carvedilol is a basic, lipophilic compound with a steady-state volume of distribution of  
16 approximately 115 L, indicating substantial distribution into extravascular tissues.

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

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

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

33 The primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-carvedilol in  
34 human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19,  
35 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and 5'-hydroxylation of  
36 carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be of primary  
37 importance in the O-methylation pathway of S(-)-carvedilol.

38 Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of  
39 debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma  
40 concentrations of R(+)-carvedilol compared to extensive metabolizers. In contrast, plasma levels

1 of S(-)-carvedilol are increased only about 20% to 25% in poor metabolizers, indicating this  
2 enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol. The  
3 pharmacokinetics of carvedilol do not appear to be different in poor metabolizers of  
4 S-mephenytoin (patients deficient in cytochrome P450 2C19).

5 **Heart Failure:** Following administration of immediate-release carvedilol tablets, steady-state  
6 plasma concentrations of carvedilol and its enantiomers increased proportionally over the dose  
7 range in patients with heart failure. Compared to healthy subjects, heart failure patients had  
8 increased mean AUC and  $C_{max}$  values for carvedilol and its enantiomers, with up to 50% to  
9 100% higher values observed in 6 patients with NYHA class IV heart failure. The mean apparent  
10 terminal elimination half-life for carvedilol was similar to that observed in healthy subjects.

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

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

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

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

24 **Rifampin:** In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin  
25 (600 mg daily for 12 days) decreased the AUC and  $C_{max}$  of carvedilol by about 70%.

26 **Cimetidine:** In a pharmacokinetic study conducted in 10 healthy male subjects, cimetidine  
27 (1,000 mg/day) increased the steady-state AUC of carvedilol by 30% with no change in  $C_{max}$ .

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

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

34 **Digoxin:** Following concomitant administration of carvedilol (25 mg once daily) and digoxin  
35 (0.25 mg once daily) for 14 days, steady-state AUC and trough concentrations of digoxin were  
36 increased by 14% and 16%, respectively, in 12 hypertensive patients.

37 **Torsemide:** In a study of 12 healthy subjects, combined oral administration of carvedilol  
38 25 mg once daily and torsemide 5 mg once daily for 5 days did not result in any significant  
39 differences in their pharmacokinetics compared with administration of the drugs alone.

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

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

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

10 **Renal Insufficiency:** No studies have been performed with COREG CR in patients with  
11 renal insufficiency. Although carvedilol is metabolized primarily by the liver, plasma  
12 concentrations of carvedilol have been reported to be increased in patients with renal impairment  
13 after dosing with immediate-release carvedilol. Based on mean AUC data, approximately 40% to  
14 50% higher plasma concentrations of carvedilol were observed in hypertensive patients with  
15 moderate to severe renal impairment compared to a control group of hypertensive patients with  
16 normal renal function. However, the ranges of AUC values were similar for both groups.  
17 Changes in mean peak plasma levels were less pronounced, approximately 12% to 26% higher in  
18 patients with impaired renal function.

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

21 **Pharmacodynamics: Heart Failure and Left Ventricular Dysfunction Following**  
22 **Myocardial Infarction:** The basis for the beneficial effects of carvedilol in patients with heart  
23 failure and in patients with left ventricular dysfunction following an acute myocardial infarction  
24 is not known. The concentration-response relationship for  $\beta_1$ -blockade following administration  
25 of COREG CR is equivalent ( $\pm 20\%$ ) to immediate-release carvedilol tablets.

26 **Hypertension:** The mechanism by which  $\beta$ -blockade produces an antihypertensive effect  
27 has not been established.

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

32  $\alpha_1$ -adrenoreceptor blocking activity has been demonstrated in human and animal studies,  
33 showing that carvedilol (1) attenuates the pressor effects of phenylephrine; (2) causes  
34 vasodilation; and (3) reduces peripheral vascular resistance. These effects contribute to the  
35 reduction of blood pressure and usually are seen within 30 minutes of drug administration.

36 Due to the  $\alpha_1$ -receptor blocking activity of carvedilol, blood pressure is lowered more in the  
37 standing than in the supine position, and symptoms of postural hypotension (1.8%), including  
38 rare instances of syncope, can occur. Following oral administration, when postural hypotension  
39 has occurred, it has been transient and is uncommon when immediate-release carvedilol is

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

3 In a randomized, double-blind, placebo-controlled trial, the  $\beta_1$  blocking effect of COREG CR,  
4 as measured by heart rate response to submaximal bicycle ergometry, was shown to be  
5 equivalent to that observed with immediate-release carvedilol at steady state in adult patients  
6 with essential hypertension.

7 In hypertensive patients with normal renal function, therapeutic doses of carvedilol decreased  
8 renal vascular resistance with no change in glomerular filtration rate or renal plasma flow.  
9 Changes in excretion of sodium, potassium, uric acid, and phosphorus in hypertensive patients  
10 with normal renal function were similar after carvedilol and placebo.

11 Carvedilol has little effect on plasma catecholamines, plasma aldosterone, or electrolyte  
12 levels, but it does significantly reduce plasma renin activity when given for at least 4 weeks. It  
13 also increases levels of atrial natriuretic peptide.

## 14 **CLINICAL TRIALS**

15 Support for the use of COREG CR extended-release capsules for the treatment of mild to  
16 severe heart failure and for patients with left ventricular dysfunction following myocardial  
17 infarction is based on the equivalence of pharmacokinetic and pharmacodynamic ( $\beta_1$ -blockade)  
18 parameters between COREG CR and immediate-release carvedilol (see CLINICAL  
19 PHARMACOLOGY, Pharmacokinetics and Pharmacodynamics).

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

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

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

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

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

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

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

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

9 In the Australia-New Zealand study, death and total hospitalizations were reduced by about  
10 25% over 18 to 24 months. In the 3 largest US studies, death and total hospitalizations were  
11 reduced by 19%, 39%, and 49%, nominally statistically significant in the last 2 studies. The  
12 Australia-New Zealand results were statistically borderline.

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

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

20 *Mortality:* Death was not a pre-specified end point in any study, but was analyzed in all  
21 studies. Overall, in these 4 US trials, mortality was reduced, nominally significantly so in  
22 2 studies.

23 **The COMET Trial:** In this double-blind trial, 3,029 patients with NYHA class II-IV heart  
24 failure (left ventricular ejection fraction  $\leq 35\%$ ) were randomized to receive either carvedilol  
25 (target dose: 25 mg twice daily) or immediate-release metoprolol tartrate (target dose: 50 mg  
26 twice daily). The mean age of the patients was approximately 62 years, 80% were males, and the  
27 mean left ventricular ejection fraction at baseline was 26%. Approximately 96% of the patients  
28 had NYHA class II or III heart failure. Concomitant treatment included diuretics (99%), ACE  
29 inhibitors (91%), digitalis (59%), aldosterone antagonists (11%), and "statin" lipid-lowering  
30 agents (21%). The mean duration of follow-up was 4.8 years. The mean dose of carvedilol was  
31 42 mg per day.

32 The study had 2 primary end points: all-cause mortality and the composite of death plus  
33 hospitalization for any reason. All-cause mortality carried most of the statistical weight and was  
34 the primary determinant of the study size. All-cause mortality was 34% in the patients treated  
35 with carvedilol and was 40% in the immediate-release metoprolol group ( $p = 0.0017$ ; hazard  
36 ratio = 0.83, 95% CI 0.74–0.93). The difference between the 2 groups with respect to the  
37 composite end point was not significant ( $p = 0.122$ ). The estimated mean survival was 8.0 years  
38 with carvedilol and 6.6 years with immediate-release metoprolol.

39 It is not known whether this formulation of metoprolol at any dose or this low dose of  
40 metoprolol in any formulation has any effect on survival or hospitalization in patients with heart

1 failure. Thus, this trial extends the time over which carvedilol manifests benefits on survival in  
 2 heart failure, but it is not evidence that carvedilol improves outcome over the formulation of  
 3 metoprolol (Toprol XL) with benefits in heart failure.

4 ***Trials in Severe Heart Failure:*** In a double-blind study (COPERNICUS), 2,289 patients  
 5 with heart failure at rest or with minimal exertion and left ventricular ejection fraction <25%  
 6 (mean 20%), despite digitalis (66%), diuretics (99%), and ACE inhibitors (89%) were  
 7 randomized to placebo or carvedilol. Carvedilol was titrated from a starting dose of 3.125 mg  
 8 twice daily to the maximum tolerated dose or up to 25 mg twice daily over a minimum of  
 9 6 weeks. Most subjects achieved the target dose of 25 mg. The study was conducted in Eastern  
 10 and Western Europe, the United States, Israel, and Canada. Similar numbers of subjects per  
 11 group (about 100) withdrew during the titration period.

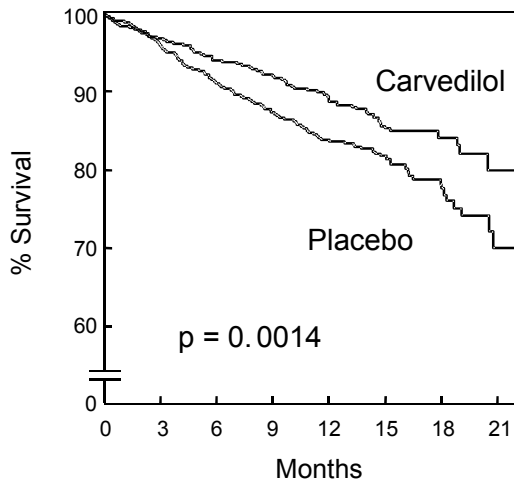
12 The primary end point of the trial was all-cause mortality, but cause-specific mortality and the  
 13 risk of death or hospitalization (total, cardiovascular [CV], or congestive heart failure [CHF])  
 14 were also examined. The developing trial data were followed by a data monitoring committee,  
 15 and mortality analyses were adjusted for these multiple looks. The trial was stopped after a  
 16 median follow-up of 10 months because of an observed 35% reduction in mortality (from 19.7%  
 17 per patient year on placebo to 12.8% on carvedilol, hazard ratio 0.65, 95% CI 0.52 – 0.81,  
 18  $p = 0.0014$ , adjusted) (see Figure 1). The results of COPERNICUS are shown in Table 1.  
 19

20 **Table 1. 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

21

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



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

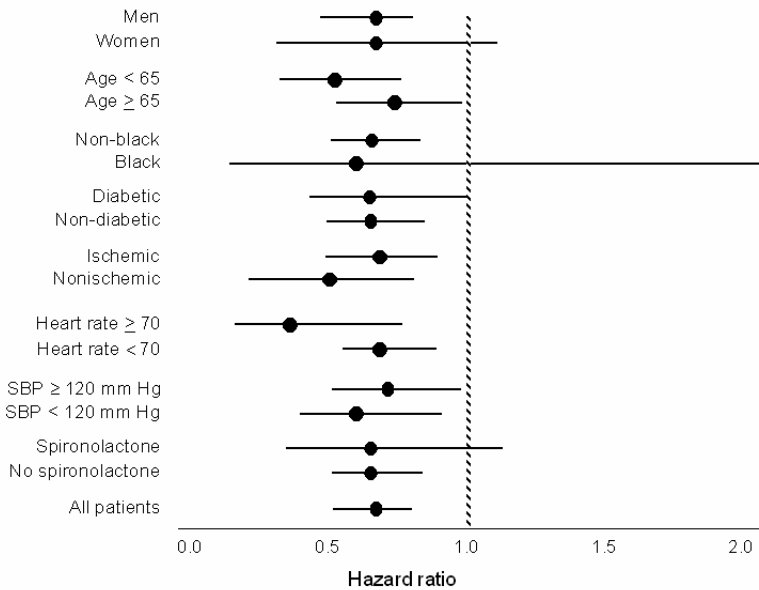
Patients' global assessments, in which carvedilol-treated patients were compared to placebo, were based on pre-specified, periodic patient self-assessments regarding whether clinical status post-treatment showed improvement, worsening, or no change compared to baseline. Patients treated with carvedilol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



1 **Figure 2. Effects on Mortality for Subgroups in COPERNICUS**



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

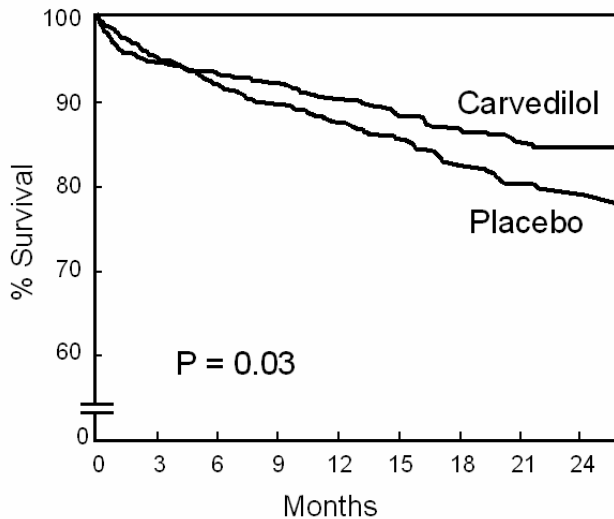
7 **Left Ventricular Dysfunction Following Myocardial Infarction:** CAPRICORN was a  
8 double-blind study comparing carvedilol and placebo in 1,959 patients with a recent myocardial  
9 infarction (within 21 days) and left ventricular ejection fraction of  $\leq 40\%$ , with (47%) or without  
10 symptoms of heart failure. Patients given carvedilol received 6.25 mg twice daily, titrated as  
11 tolerated to 25 mg twice daily. Patients had to have a systolic blood pressure  $>90$  mm Hg, a  
12 sitting heart rate  $>60$  beats/minute, and no contraindication to  $\beta$ -blocker use. Treatment of the  
13 index infarction included aspirin (85%), IV or oral  $\beta$ -blockers (37%), nitrates (73%), heparin  
14 (64%), thrombolytics (40%), and acute angioplasty (12%). Background treatment included ACE  
15 inhibitors or angiotensin receptor blockers (97%), anticoagulants (20%), lipid-lowering agents  
16 (23%), and diuretics (34%). Baseline population characteristics included an average age of  
17 63 years, 74% male, 95% Caucasian, mean blood pressure 121/74 mm Hg, 22% with diabetes,  
18 and 54% with a history of hypertension. Mean dosage achieved of carvedilol was 20 mg twice  
19 daily; mean duration of follow-up was 15 months.

20 All-cause mortality was 15% in the placebo group and 12% in the carvedilol group, indicating  
21 a 23% risk reduction in patients treated with carvedilol (95% CI 2% to 40%,  $p = 0.03$ ), as shown  
22 in Figure 3. The effects on mortality in various subgroups are shown in Figure 4. Nearly all  
23 deaths were cardiovascular (which were reduced by 25% by carvedilol), and most of these deaths  
24 were sudden or related to pump failure (both types of death were reduced by carvedilol). Another  
25 study end point, total mortality and all-cause hospitalization, did not show a significant  
26 improvement.

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

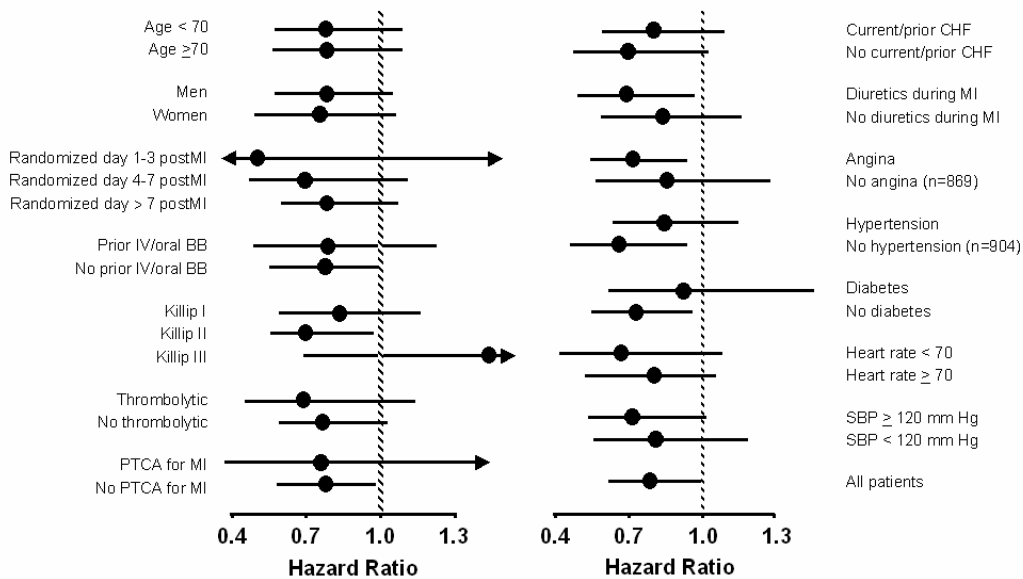
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6 **Figure 3. Survival Analysis for CAPRICORN (intent-to-treat)**



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8 **Figure 4. Effects on Mortality for Subgroups in CAPRICORN**



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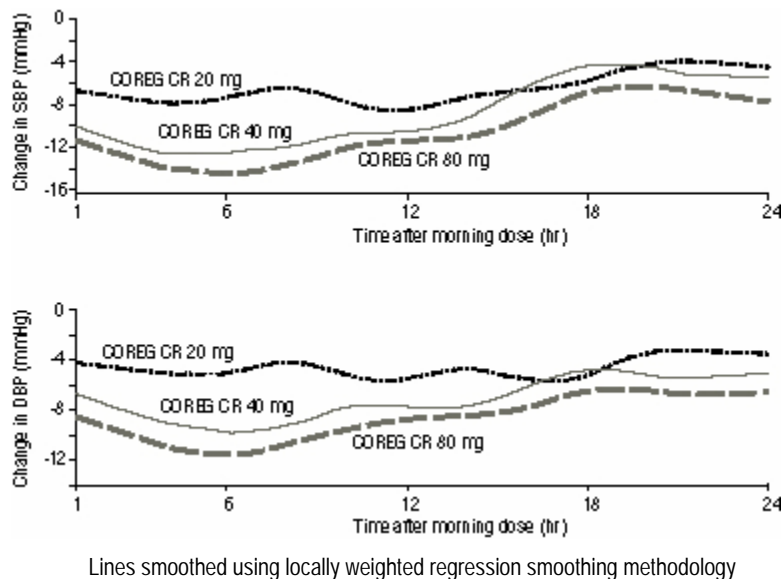
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11 Although the clinical trials used twice-daily dosing, clinical pharmacologic and  
 12 pharmacokinetic data provide a reasonable basis for concluding that once-daily dosing with  
 13 COREG CR should be adequate in the treatment of left ventricular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

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

10 Statistically significant reductions in blood pressure as measured by 24-hour ambulatory  
11 blood pressure monitoring (ABPM) were observed with each dose of COREG CR compared to  
12 placebo. Placebo-subtracted mean changes from baseline in mean SBP/DBP were  
13 -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  
14 80 mg, respectively. Placebo-subtracted mean changes from baseline in mean trough (average of  
15 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  
16 COREG CR 20 mg, 40 mg, and 80 mg, respectively. The placebo-corrected trough to peak  
17 (3-7 hr) ratio was approximately 0.6 for COREG CR 80 mg. In this study, assessments of  
18 24-hour ABPM monitoring demonstrated statistically significant blood pressure reductions with  
19 COREG CR throughout the dosing period (Figure 5).

20  
21 **Figure 5. Changes from Baseline in Systolic Blood Pressure and Diastolic Blood Pressure**  
22 **Measured by 24-Hour ABPM**



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

1 pressure by about 9/5.5 mm Hg; at 25 mg/day the effect was about 7.5/3.5 mm Hg. Comparisons  
2 of trough-to-peak blood pressure showed a trough-to-peak ratio for blood pressure response of  
3 about 65%. Heart rate fell by about 7.5 beats/minute at 50 mg/day. In general, as is true for other  
4  $\beta$ -blockers, responses were smaller in black than non-black patients. There were no age- or  
5 gender-related differences in response. The dose-related blood pressure response was  
6 accompanied by a dose-related increase in adverse effects (see ADVERSE REACTIONS).

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

## 14 INDICATIONS AND USAGE

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

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

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

## 25 CONTRAINDICATIONS

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

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

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

1 **WARNINGS**

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

15 **Peripheral Vascular Disease:**  $\beta$ -blockers can precipitate or aggravate symptoms of arterial  
16 insufficiency in patients with peripheral vascular disease. Caution should be exercised in such  
17 individuals.

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

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

28 **Thyrotoxicosis:**  $\beta$ -adrenergic blockade may mask clinical signs of hyperthyroidism, such as  
29 tachycardia. Abrupt withdrawal of  $\beta$ -blockade may be followed by an exacerbation of the  
30 symptoms of hyperthyroidism or may precipitate thyroid storm.

31 **PRECAUTIONS**

32 **General:** In clinical trials of COREG CR in patients with hypertension (338 subjects) and in  
33 patients with left ventricular dysfunction following a myocardial infarction or heart failure  
34 (187 subjects), the profile of adverse events observed with carvedilol phosphate was generally  
35 similar to that observed with the administration of immediate-release carvedilol. Therefore, the  
36 information included within this section is based on data from controlled clinical trials with  
37 COREG CR as well as immediate-release carvedilol.

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

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

6 In clinical trials of primarily mild-to-moderate heart failure with immediate-release carvedilol,  
7 hypotension and postural hypotension occurred in 9.7% and syncope in 3.4% of patients  
8 receiving carvedilol compared to 3.6% and 2.5% of placebo patients, respectively. The risk for  
9 these events was highest during the first 30 days of dosing, corresponding to the up-titration  
10 period and was a cause for discontinuation of therapy in 0.7% of carvedilol patients, compared to  
11 0.4% of placebo patients. In a long-term, placebo-controlled trial in severe heart failure  
12 (COPERNICUS), hypotension and postural hypotension occurred in 15.1% and syncope in 2.9%  
13 of heart failure patients receiving carvedilol compared to 8.7% and 2.3% of placebo patients,  
14 respectively. These events were a cause for discontinuation of therapy in 1.1% of carvedilol  
15 patients, compared to 0.8% of placebo patients.

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

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

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

34 Rarely, use of carvedilol in patients with heart failure has resulted in deterioration of renal  
35 function. Patients at risk appear to be those with low blood pressure (systolic blood pressure  
36 <100 mm Hg), ischemic heart disease and diffuse vascular disease, and/or underlying renal  
37 insufficiency. Renal function has returned to baseline when carvedilol was stopped. In patients  
38 with these risk factors it is recommended that renal function be monitored during up-titration of  
39 COREG CR and the drug discontinued or dosage reduced if worsening of renal function occurs.

1 Worsening heart failure or fluid retention may occur during up-titration of carvedilol. If such  
2 symptoms occur, diuretics should be increased and the dose of COREG CR should not be  
3 advanced until clinical stability resumes (see DOSAGE AND ADMINISTRATION).  
4 Occasionally it is necessary to lower the dose of COREG CR or temporarily discontinue it. Such  
5 episodes do not preclude subsequent successful titration of, or a favorable response to,  
6 COREG CR. In a placebo-controlled trial of patients with severe heart failure, worsening heart  
7 failure during the first 3 months was reported to a similar degree with immediate-release  
8 carvedilol and with placebo. When treatment was maintained beyond 3 months, worsening heart  
9 failure was reported less frequently in patients treated with carvedilol than with placebo.  
10 Worsening heart failure observed during long-term therapy is more likely to be related to the  
11 patients' underlying disease than to treatment with carvedilol.

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

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

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

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

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

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

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

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

- 7 • They should not interrupt or discontinue using COREG CR without a physician's advice.
- 8 • Heart failure patients should consult their physician if they experience signs or symptoms of  
9 worsening heart failure such as weight gain or increasing shortness of breath.
- 10 • They may experience a drop in blood pressure when standing, resulting in dizziness and,  
11 rarely, fainting. Patients should sit or lie down when these symptoms of lowered blood  
12 pressure occur.
- 13 • If patients experience dizziness or fatigue, they should avoid driving or hazardous tasks.
- 14 • They should consult a physician if they experience dizziness or faintness, in case the dosage  
15 should be adjusted.
- 16 • They should not crush or chew COREG CR capsules.
- 17 • They should take COREG CR with food.
- 18 • Diabetic patients should report any changes in blood sugar levels to their physician.
- 19 • Contact lens wearers may experience decreased lacrimation.

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

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

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

32 ***Clonidine:*** Concomitant administration of clonidine with agents with  $\beta$ -blocking properties  
33 may potentiate blood-pressure- and heart-rate-lowering effects. When concomitant treatment  
34 with agents with  $\beta$ -blocking properties and clonidine is to be terminated, the  $\beta$ -blocking agent  
35 should be discontinued first. Clonidine therapy can then be discontinued several days later by  
36 gradually decreasing the dosage.

37 ***Cyclosporine:*** Modest increases in mean trough cyclosporine concentrations were observed  
38 following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic  
39 vascular rejection. In about 30% of patients, the dose of cyclosporine had to be reduced in order  
40 to maintain cyclosporine concentrations within the therapeutic range, while in the remainder no



1 adjustment was needed. On the average for the group, the dose of cyclosporine was reduced  
2 about 20% in these patients. Due to wide interindividual variability in the dose adjustment  
3 required, it is recommended that cyclosporine concentrations be monitored closely after initiation  
4 of carvedilol therapy and that the dose of cyclosporine be adjusted as appropriate.

5 **Digoxin:** Digoxin concentrations are increased by about 15% when digoxin and carvedilol  
6 are administered concomitantly. Both digoxin and carvedilol slow AV conduction. Therefore,  
7 increased monitoring of digoxin is recommended when initiating, adjusting, or discontinuing  
8 COREG CR.

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

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

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

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

22 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In 2-year studies conducted in  
23 rats given carvedilol at doses up to 75 mg/kg/day (12 times the maximum recommended human  
24 dose [MRHD] when compared on a  $mg/m^2$  basis) or in mice given up to 200 mg/kg/day  
25 (16 times the MRHD on a  $mg/m^2$  basis), carvedilol had no carcinogenic effect.

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

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

34 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Studies performed in pregnant rats  
35 and rabbits given carvedilol revealed increased post-implantation loss in rats at doses of  
36 300 mg/kg/day (50 times the MRHD as  $mg/m^2$ ) and in rabbits at doses of 75 mg/kg/day  
37 (25 times the MRHD as  $mg/m^2$ ). In the rats, there was also a decrease in fetal body weight at the  
38 maternally toxic dose of 300 mg/kg/day (50 times the MRHD as  $mg/m^2$ ), which was  
39 accompanied by an elevation in the frequency of fetuses with delayed skeletal development  
40 (missing or stunted 13th rib). In rats the no-observed-effect level for developmental toxicity was

1 60 mg/kg/day (10 times the MRHD as mg/m<sup>2</sup>); in rabbits it was 15 mg/kg/day (5 times the  
2 MRHD as mg/m<sup>2</sup>). There are no adequate and well-controlled studies in pregnant women.  
3 COREG CR should be used during pregnancy only if the potential benefit justifies the potential  
4 risk to the fetus.

5 **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Studies in rats  
6 have shown that carvedilol and/or its metabolites (as well as other β-blockers) cross the placental  
7 barrier and are excreted in breast milk. There was increased mortality at one week post partum in  
8 neonates from rats treated with 60 mg/kg/day (10 times the MRHD as mg/m<sup>2</sup>) and above during  
9 the last trimester through day 22 of lactation. Because many drugs are excreted in human milk  
10 and because of the potential for serious adverse reactions in nursing infants from β-blockers,  
11 especially bradycardia, a decision should be made whether to discontinue nursing or to  
12 discontinue the drug, taking into account the importance of the drug to the mother. The effects of  
13 other α- and β-blocking agents have included perinatal and neonatal distress.

14 **Pediatric Use:** Safety and efficacy of carvedilol in patients younger than 18 years of age have  
15 not been established.

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

20 The following information is available for trials with immediate-release carvedilol. Of the  
21 765 patients with heart failure randomized to carvedilol in US clinical trials, 31% (235) were  
22 65 years of age or older, and 7.3% (56) were 75 years of age or older. Of the 1,156 patients  
23 randomized to carvedilol in a long-term, placebo-controlled trial in severe heart failure, 47%  
24 (547) were 65 years of age or older, and 15% (174) were 75 years of age or older. Of  
25 3,025 patients receiving carvedilol in heart failure trials worldwide, 42% were 65 years of age or  
26 older. Of the 975 myocardial infarction patients randomized to carvedilol in the CAPRICORN  
27 trial, 48% (468) were 65 years of age or older, and 11% (111) were 75 years of age or older. Of  
28 the 2,065 hypertensive patients in US clinical trials of efficacy or safety who were treated with  
29 carvedilol, 21% (436) were 65 years of age or older. Of 3,722 patients receiving immediate-  
30 release carvedilol in hypertension clinical trials conducted worldwide, 24% were 65 years of age  
31 or older.

32 With the exception of dizziness in hypertensive patients (incidence 8.8% in the elderly vs. 6%  
33 in younger patients), no overall differences in the safety or effectiveness (see Figures 2 and 4)  
34 were observed between the older subjects and younger subjects in each of these populations.  
35 Similarly, other reported clinical experience has not identified differences in responses between  
36 the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled  
37 out.

## 1 **ADVERSE REACTIONS**

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

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

21 Carvedilol has been evaluated for safety in heart failure in more than 4,500 patients  
22 worldwide of whom more than 2,100 participated in placebo-controlled clinical trials.  
23 Approximately 60% of the total treated population in placebo-controlled clinical trials received  
24 carvedilol for at least 6 months and 30% received carvedilol for at least 12 months. In the  
25 COMET trial, 1,511 patients with mild-to-moderate heart failure were treated with carvedilol for  
26 up to 5.9 years (mean 4.8 years). Both in US clinical trials in mild-to-moderate heart failure that  
27 compared carvedilol in daily doses up to 100 mg (n = 765) to placebo (n = 437), and in a  
28 multinational clinical trial in severe heart failure (COPERNICUS) that compared carvedilol in  
29 daily doses up to 50 mg (n = 1,156) with placebo (n = 1,133), discontinuation rates for adverse  
30 experiences were similar in carvedilol and placebo patients. In placebo-controlled clinical trials,  
31 the only cause of discontinuation >1%, and occurring more often on carvedilol was dizziness  
32 (1.3% on carvedilol, 0.6% on placebo in the COPERNICUS trial).

33 Table 2 shows adverse events reported in patients with mild-to-moderate heart failure enrolled  
34 in US placebo-controlled clinical trials, and with severe heart failure enrolled in the  
35 COPERNICUS trial. Shown are adverse events that occurred more frequently in drug-treated  
36 patients than placebo-treated patients with an incidence of >3% in patients treated with  
37 carvedilol regardless of causality. Median study medication exposure was 6.3 months for both  
38 carvedilol and placebo patients in the trials of mild-to-moderate heart failure, and 10.4 months in  
39 the trial of severe heart failure patients. The adverse event profile of carvedilol observed in the  
40 long-term COMET study was generally similar to that observed in the US Heart Failure Trials.

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**Table 2. 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 (n = 765)	Placebo (n = 437)	Carvedilol (n = 1,156)	Placebo (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	-	-

7

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

3 The following adverse events were reported with a frequency of >1% but ≤3% and more  
4 frequently with carvedilol in either the US placebo-controlled trials in patients with  
5 mild-to-moderate heart failure, or in patients with severe heart failure in the COPERNICUS trial.  
6

#### 7 **Incidence >1% to ≤3%**

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

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

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

12 **Gastrointestinal:** Melena, periodontitis.

13 **Liver and Biliary System:** SGPT increased, SGOT increased.

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

17 **Musculoskeletal:** Muscle cramps.

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

19 **Psychiatric:** Somnolence.

20 **Reproductive, male:** Impotence.

21 **Special Senses:** Blurred vision.

22 **Urinary System:** Renal insufficiency, albuminuria, hematuria.  
23

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

27 Carvedilol has been evaluated for safety in survivors of an acute myocardial infarction with  
28 left ventricular dysfunction in the CAPRICORN trial which involved 969 patients who received  
29 carvedilol and 980 who received placebo. Approximately 75% of the patients received carvedilol  
30 for at least 6 months and 53% received carvedilol for at least 12 months. Patients were treated for  
31 an average of 12.9 months and 12.8 months with carvedilol and placebo, respectively.

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

1 >1%, and occurring more often on carvedilol was hypotension (1.5% on carvedilol, 0.2% on  
2 placebo).

3 **Hypertension:** COREG CR was evaluated for safety in an 8-week double-blind trial in 337  
4 subjects with essential hypertension. The profile of adverse events observed with COREG CR  
5 was generally similar to that observed with immediate-release carvedilol. The overall rates of  
6 discontinuations due to adverse events were similar between COREG CR and placebo.  
7

8 **Table 3. Adverse Events (% Occurrence) Occurring More Frequently With COREG CR**  
9 **Than With Placebo in Patients With Hypertension (Incidence  $\geq$ 1% in Patients Treated**  
10 **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

11  
12 The following information describes the safety experience in hypertension with immediate-  
13 release carvedilol.

14 Carvedilol has been evaluated for safety in hypertension in more than 2,193 patients in US  
15 clinical trials and in 2,976 patients in international clinical trials. Approximately 36% of the total  
16 treated population received carvedilol for at least 6 months. In general, carvedilol was well  
17 tolerated at doses up to 50 mg daily. Most adverse events reported during carvedilol therapy  
18 were of mild to moderate severity. In US controlled clinical trials directly comparing carvedilol  
19 monotherapy in doses up to 50 mg (n = 1,142) to placebo (n = 462), 4.9% of carvedilol patients  
20 discontinued for adverse events vs. 5.2% of placebo patients. Although there was no overall  
21 difference in discontinuation rates, discontinuations were more common in the carvedilol group  
22 for postural hypotension (1% vs. 0). The overall incidence of adverse events in US  
23 placebo-controlled trials was found to increase with increasing dose of carvedilol. For individual  
24 adverse events this could only be distinguished for dizziness, which increased in frequency from  
25 2% to 5% as total daily dose increased from 6.25 mg to 50 mg as single or divided doses.

26 Table 4 shows adverse events in US placebo-controlled clinical trials for hypertension that  
27 occurred with an incidence of >1% regardless of causality, and that were more frequent in  
28 drug-treated patients than placebo-treated patients.  
29

1 **Table 4. Adverse Events (% Occurrence) in US Placebo-Controlled Hypertension Trials**  
 2 **With Immediate-Release Carvedilol (Incidence  $\geq 1\%$  in Patients Treated With Carvedilol,**  
 3 **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

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

5

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

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

11

12 **Incidence  $>0.1\%$  to  $\leq 1\%$**

13 **Cardiovascular:** Peripheral ischemia, tachycardia.

14 **Central and Peripheral Nervous System:** Hypokinesia.

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

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

20 **Respiratory System:** Asthma (see CONTRAINDICATIONS).

21 **Reproductive:** Male: Decreased libido.

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

24 **Special Senses:** Tinnitus.

25 **Urinary System:** Micturition frequency increased.

1 **Autonomic Nervous System:** Dry mouth, sweating increased.

2 **Metabolic and Nutritional:** Hypokalemia, hypertriglyceridemia.

3 **Hematologic:** Anemia, leukopenia.

4 The following events were reported in  $\leq 0.1\%$  of patients and are potentially important:  
5 Complete AV block, bundle branch block, myocardial ischemia, cerebrovascular disorder,  
6 convulsions, migraine, neuralgia, paresis, anaphylactoid reaction, alopecia, exfoliative  
7 dermatitis, amnesia, GI hemorrhage, bronchospasm, pulmonary edema, decreased hearing,  
8 respiratory alkalosis, increased BUN, decreased HDL, pancytopenia, and atypical lymphocytes.

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

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

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

## 27 **OVERDOSAGE**

28 The acute oral LD50 doses in male and female mice and male and female rats are over  
29 8,000 mg/kg. Overdosage may cause severe hypotension, bradycardia, cardiac insufficiency,  
30 cardiogenic shock, and cardiac arrest. Respiratory problems, bronchospasms, vomiting, lapses of  
31 consciousness, and generalized seizures may also occur.

32 The patient should be placed in a supine position and, where necessary, kept under  
33 observation and treated under intensive-care conditions. Gastric lavage or pharmacologically  
34 induced emesis may be used shortly after ingestion. The following agents may be administered:

35 *For excessive bradycardia:* atropine, 2 mg IV.

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



1 If peripheral vasodilation dominates, it may be necessary to administer adrenaline or  
2 noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant  
3 bradycardia, pacemaker therapy should be performed. For bronchospasm,  $\beta$ -sympathomimetics  
4 (as aerosol or IV) or aminophylline IV should be given. In the event of seizures, slow IV  
5 injection of diazepam or clonazepam is recommended.

6 NOTE: In the event of severe intoxication where there are symptoms of shock, treatment with  
7 antidotes must be continued for a sufficiently long period of time consistent with the 7- to  
8 10-hour half-life of carvedilol.

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

### 13 **DOSAGE AND ADMINISTRATION**

14 **General:** COREG CR is an extended-release capsule intended for once-daily administration.  
15 Patients controlled with immediate-release carvedilol tablets alone or in combination with other  
16 medications may be switched to COREG CR extended-release capsules based on the total daily  
17 doses shown in Table 5. Subsequent titration to higher or lower doses may be necessary as  
18 clinically warranted.

19  
20 **Table 5. 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

21  
22 COREG CR should be taken once daily in the morning with food. COREG CR should be  
23 swallowed as a whole capsule. COREG CR and/or its contents should not be crushed, chewed, or  
24 taken in divided doses.

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

30 **Heart Failure:** DOSAGE MUST BE INDIVIDUALIZED AND CLOSELY MONITORED BY  
31 A PHYSICIAN DURING UP-TITRATION. Prior to initiation of COREG CR, it is  
32 recommended that fluid retention be minimized. The recommended starting dose of COREG CR  
33 is 10 mg once daily for 2 weeks. Patients who tolerate a dose of 10 mg once daily may have their

1 dose increased to 20, 40, and 80 mg over successive intervals of at least 2 weeks. Patients should  
2 be maintained on lower doses if higher doses are not tolerated.

3 Patients should be advised that initiation of treatment and (to a lesser extent) dosage increases  
4 may be associated with transient symptoms of dizziness or lightheadedness (and rarely syncope)  
5 within the first hour after dosing. Thus during these periods they should avoid situations such as  
6 driving or hazardous tasks, where symptoms could result in injury. Vasodilatory symptoms often  
7 do not require treatment, but it may be useful to separate the time of dosing of COREG CR from  
8 that of the ACE inhibitor or to reduce temporarily the dose of the ACE inhibitor. The dose of  
9 COREG CR should not be increased until symptoms of worsening heart failure or vasodilation  
10 have been stabilized.

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

13 The dose of COREG CR should be reduced if patients experience bradycardia (heart rate  
14 <55 beats/minute).

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

18 **Left Ventricular Dysfunction Following Myocardial Infarction:** DOSAGE MUST BE  
19 INDIVIDUALIZED AND MONITORED DURING UP-TITRATION. Treatment with  
20 COREG CR may be started as an inpatient or outpatient and should be started after the patient is  
21 hemodynamically stable and fluid retention has been minimized. It is recommended that  
22 COREG CR be started at 20 mg once daily and increased after 3 to 10 days, based on tolerability  
23 to 40 mg once daily, then again to the target dose of 80 mg once daily. Patients should be  
24 maintained on lower doses if higher doses are not tolerated. The recommended dosing regimen  
25 need not be altered in patients who received treatment with an IV or oral  $\beta$ -blocker during the  
26 acute phase of the myocardial infarction.

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

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

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

1 **HOW SUPPLIED**

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

- 4 10 mg – white and green capsule shell printed with GSK COREG CR and 10 mg
- 5 20 mg – white and yellow capsule shell printed with GSK COREG CR and 20 mg
- 6 40 mg – yellow and green capsule shell printed with GSK COREG CR and 40 mg
- 7 80 mg – white capsule shell printed with GSK COREG CR and 80 mg

- 8
- 9 10 mg 30's: NDC 0007-3370-13
- 10 10 mg 90's: NDC 0007-3370-59
- 11 20 mg 30's: NDC 0007-3371-13
- 12 20 mg 90's: NDC 0007-3371-59
- 13 40 mg 30's: NDC 0007-3372-13
- 14 40 mg 90's: NDC 0007-3372-59
- 15 80 mg 30's: NDC 0007-3373-13
- 16 80 mg 90's: NDC 0007-3373-59

17 **STORAGE**

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

20  
21 COREG CR is a trademark of GlaxoSmithKline.



23  
24  
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26 Research Triangle Park, NC 27709  
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28  
29 Month Year

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