

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**20-297/S-009**

**Approved Labeling**

- 1 **Foreword:** This document incorporated proposed changes to the existing COREG prescribing
- 2 information modified following FDA feedback on 3-25-03.

3 March 25, 2003

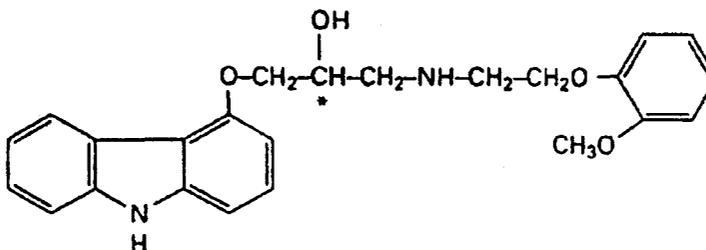
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PRESCRIBING INFORMATION

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5  
6 **COREG<sup>®</sup>**  
7 **(carvedilol)**  
8 **Tablets**

9 **DESCRIPTION**

10 Carvedilol is a nonselective  $\beta$ -adrenergic blocking agent with  $\alpha_1$ -blocking activity. It is ( $\pm$ )-1-  
11 (Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol. It is a racemic mixture  
12 with the following structure:



13

14

Carvedilol

15 **Tablets for Oral Administration:** COREG (carvedilol) is a white, oval, film-coated tablet  
16 containing 3.125 mg, 6.25 mg, 12.5 mg, or 25 mg of carvedilol. The 6.25 mg, 12.5 mg, and  
17 25 mg tablets are TILTAB<sup>®</sup> tablets. Inactive ingredients consist of colloidal silicon dioxide,  
18 crospovidone, hypromellose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80,  
19 povidone, sucrose, and titanium dioxide.

20 Carvedilol is a white to off-white powder with a molecular weight of 406.5 and a molecular  
21 formula of C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>. It is freely soluble in dimethylsulfoxide; soluble in methylene chloride  
22 and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in ethyl ether;  
23 and practically insoluble in water, gastric fluid (simulated, TS, pH 1.1), and intestinal fluid  
24 (simulated, TS without pancreatin, pH 7.5).

25 **CLINICAL PHARMACOLOGY**

26 COREG is a racemic mixture in which nonselective  $\beta$ -adrenoreceptor blocking activity is  
27 present in the S(-) enantiomer and  $\alpha$ -adrenergic blocking activity is present in both R(+) and S(-)  
28 enantiomers at equal potency. COREG has no intrinsic sympathomimetic activity.

29 **Pharmacokinetics:** COREG is rapidly and extensively absorbed following oral  
30 administration, with absolute bioavailability of approximately 25% to 35% due to a significant  
31 degree of first-pass metabolism. Following oral administration, the apparent mean terminal  
32 elimination half-life of carvedilol generally ranges from 7 to 10 hours. Plasma concentrations  
33 achieved are proportional to the oral dose administered. When administered with food, the rate of  
34 absorption is slowed, as evidenced by a delay in the time to reach peak plasma levels, with no

35 significant difference in extent of bioavailability. Taking COREG with food should minimize the  
36 risk of orthostatic hypotension.

37 Carvedilol is extensively metabolized. Following oral administration of radiolabelled  
38 carvedilol to healthy volunteers, carvedilol accounted for only about 7% of the total radioactivity  
39 in plasma as measured by area under the curve (AUC). Less than 2% of the dose was excreted  
40 unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and  
41 glucuronidation. The oxidative metabolites are further metabolized by conjugation via  
42 glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile  
43 into the feces. Demethylation and hydroxylation at the phenol ring produce three active  
44 metabolites with  $\beta$ -receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl  
45 metabolite is approximately 13 times more potent than carvedilol for  $\beta$ -blockade.

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

49 Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of  
50 R(+)-carvedilol approximately 2 to 3 times higher than S(-)-carvedilol following oral  
51 administration in healthy subjects. The mean apparent terminal elimination half-lives for  
52 R(+)-carvedilol range from 5 to 9 hours compared with 7 to 11 hours for the S(-)-enantiomer.

53 The primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-carvedilol in  
54 human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19,  
55 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and 5'-hydroxylation of  
56 carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be of primary  
57 importance in the O-methylation pathway of S(-)-carvedilol.

58 Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of  
59 debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma  
60 concentrations of R(+)-carvedilol compared to extensive metabolizers. In contrast, plasma levels  
61 of S(-)-carvedilol are increased only about 20% to 25% in poor metabolizers, indicating this  
62 enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol. The  
63 pharmacokinetics of carvedilol do not appear to be different in poor metabolizers of  
64 S-mephenytoin (patients deficient in cytochrome P450 2C19).

65 Carvedilol is more than 98% bound to plasma proteins, primarily with albumin. The  
66 plasma-protein binding is independent of concentration over the therapeutic range. Carvedilol is  
67 a basic, lipophilic compound with a steady-state volume of distribution of approximately 115 L,  
68 indicating substantial distribution into extravascular tissues. Plasma clearance ranges from 500 to  
69 700 mL/min.

70 **Congestive Heart Failure:** Steady-state plasma concentrations of carvedilol and its  
71 enantiomers increased proportionally over the 6.25 to 50 mg dose range in patients with  
72 congestive heart failure. Compared to healthy subjects, congestive heart failure patients had  
73 increased mean AUC and  $C_{max}$  values for carvedilol and its enantiomers, with up to 50% to

74 100% higher values observed in 6 patients with NYHA class IV heart failure. The mean apparent  
75 terminal elimination half-life for carvedilol was similar to that observed in healthy subjects.

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

79 **Rifampin:** In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin  
80 (600 mg daily for 12 days) decreased the AUC and  $C_{max}$  of carvedilol by about 70%.

81 **Cimetidine:** In a pharmacokinetic study conducted in 10 healthy male subjects,  
82 cimetidine (1000 mg/day) increased the steady-state AUC of carvedilol by 30% with no change  
83 in  $C_{max}$ .

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

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

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

93 **Torsemide:** In a study of 12 healthy subjects, combined oral administration of carvedilol  
94 25 mg once daily and torsemide 5 mg once daily for 5 days did not result in any significant  
95 differences in their pharmacokinetics compared with administration of the drugs alone.

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

99 **Special Populations: Elderly:** Plasma levels of carvedilol average about 50% higher in the  
100 elderly compared to young subjects.

101 **Hepatic Impairment:** Compared to healthy subjects, patients with cirrhotic liver disease  
102 exhibit significantly higher concentrations of carvedilol (approximately 4- to 7-fold) following  
103 single-dose therapy (see WARNINGS, Hepatic Injury).

104 **Renal Insufficiency:** Although carvedilol is metabolized primarily by the liver, plasma  
105 concentrations of carvedilol have been reported to be increased in patients with renal  
106 impairment. Based on mean AUC data, approximately 40% to 50% higher plasma concentrations  
107 of carvedilol were observed in hypertensive patients with moderate to severe renal impairment  
108 compared to a control group of hypertensive patients with normal renal function. However, the  
109 ranges of AUC values were similar for both groups. Changes in mean peak plasma levels were  
110 less pronounced, approximately 12% to 26% higher in patients with impaired renal function.

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

113 **Pharmacodynamics: Congestive Heart Failure:** The basis for the beneficial effects of  
114 COREG in congestive heart failure is not established.

115 Two placebo-controlled studies compared the acute hemodynamic effects of COREG to  
116 baseline measurements in 59 and 49 patients with NYHA class II-IV heart failure receiving  
117 diuretics, ACE inhibitors, and digitalis. There were significant reductions in systemic blood  
118 pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and heart rate. Initial  
119 effects on cardiac output, stroke volume index, and systemic vascular resistance were small and  
120 variable.

121 These studies measured hemodynamic effects again at 12 to 14 weeks. COREG significantly  
122 reduced systemic blood pressure, pulmonary artery pressure, right atrial pressure, systemic  
123 vascular resistance, and heart rate, while stroke volume index was increased.

124 Among 839 patients with NYHA class II-III heart failure treated for 26 to 52 weeks in 4 US  
125 placebo-controlled trials, average left ventricular ejection fraction (EF) measured by radionuclide  
126 ventriculography increased by 9 EF units (%) in COREG patients and by 2 EF units in placebo  
127 patients at a target dose of 25-50 mg twice daily. The effects of carvedilol on ejection fraction  
128 were related to dose. Doses of 6.25 mg twice daily, 12.5 mg twice daily, and 25 mg twice daily  
129 were associated with placebo-corrected increases in EF of 5 EF units, 6 EF units, and 8 EF units,  
130 respectively; each of these effects were nominally statistically significant.

131 **Left Ventricular Dysfunction Following Myocardial Infarction:** The basis for the  
132 beneficial effects of COREG in patients with left ventricular dysfunction following an acute  
133 myocardial infarction is not established.

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

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

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

144 Due to the  $\alpha_1$ -receptor blocking activity of carvedilol, blood pressure is lowered more in the  
145 standing than in the supine position, and symptoms of postural hypotension (1.8%), including  
146 rare instances of syncope, can occur. Following oral administration, when postural hypotension  
147 has occurred, it has been transient and is uncommon when COREG is administered with food at  
148 the recommended starting dose and titration increments are closely followed (see DOSAGE  
149 AND ADMINISTRATION).

150 In hypertensive patients with normal renal function, therapeutic doses of COREG decreased  
151 renal vascular resistance with no change in glomerular filtration rate or renal plasma flow.

152 Changes in excretion of sodium, potassium, uric acid, and phosphorus in hypertensive patients  
153 with normal renal function were similar after COREG and placebo.

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

157 **CLINICAL TRIALS**

158 **Congestive Heart Failure:** A total of 3,946 patients with mild to severe heart failure were  
159 evaluated in placebo-controlled studies of carvedilol.

160 In the largest study (COPERNICUS), 2,289 patients with heart failure at rest or with minimal  
161 exertion and left ventricular ejection fraction <25% (mean 20%), despite digitalis (66%),  
162 diuretics (99%), and ACE inhibitors (89%) were randomized to placebo or carvedilol. Carvedilol  
163 was titrated from a starting dose of 3.125 mg twice daily to the maximum tolerated dose or up to  
164 25 mg twice daily over a minimum of 6 weeks. Most subjects achieved the target dose of 25 mg.  
165 The study was conducted in Eastern and Western Europe, the United States, Israel, and Canada.  
166 Similar numbers of subjects per group (about 100) withdrew during the titration period.

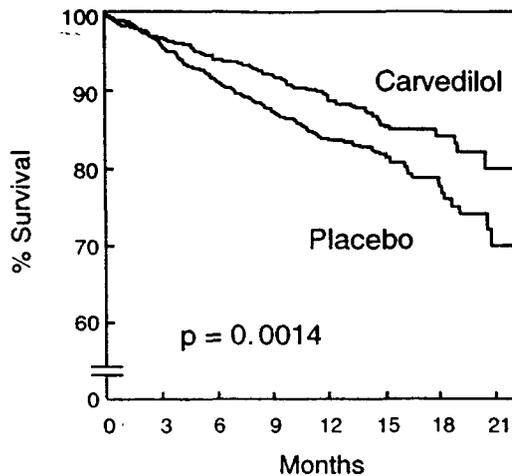
167 The primary end point of the trial was all-cause mortality, but cause-specific mortality and the  
168 risk of death or hospitalization (total, cardiovascular [CV], or congestive heart failure [CHF])  
169 were also examined. The developing trial data were followed by a data monitoring committee,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

174 **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

175

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



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

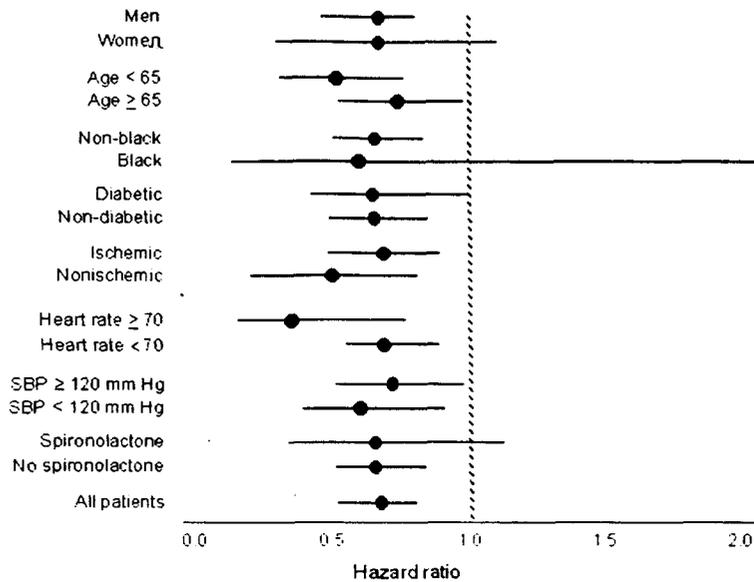
181 Patients' global assessments, in which carvedilol-treated patients were compared to placebo,  
182 were based on pre-specified, periodic patient self-assessments regarding whether clinical status  
183 post-treatment showed ~~gradations of improvement, worsening or no change~~ remained the same  
84 compared to baseline. Patients treated with carvedilol showed significant improvements in global  
185 assessments compared with those treated with placebo in COPERNICUS.

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

190 COREG had a consistent and beneficial effect on all-cause mortality as well as the combined  
191 end points of all-cause mortality plus hospitalization (total, CV, or for heart failure) in the overall  
192 study population and in all subgroups examined, including men and women, elderly and  
193 non-elderly, blacks and non-blacks, and diabetics and non-diabetics (see Figure 2).

194

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



196  
197

198 Carvedilol was also studied in five other multicenter, placebo-controlled studies.

199 Four US multicenter, double-blind, placebo-controlled studies enrolled 1,094 patients  
200 (696 randomized to carvedilol) with NYHA class II-III heart failure and ejection fraction <0.35.  
201 The vast majority were on digitalis, diuretics, and an ACE inhibitor at study entry. Patients were  
202 assigned to the studies based upon exercise ability. An Australia-New Zealand double-blind,  
203 placebo-controlled study enrolled 415 patients (half randomized to carvedilol) with less severe  
204 heart failure. All protocols excluded patients expected to undergo cardiac transplantation during  
205 the 7.5 to 15 months of double-blind follow-up. All randomized patients had tolerated a 2-week  
206 course on carvedilol 6.25 mg twice daily.

207 In each study, there was a primary end point, either progression of heart failure (one US  
208 study) or exercise tolerance (two US studies meeting enrollment goals and the Australia-New  
209 Zealand study). There were many secondary end points specified in these studies, including  
210 NYHA classification, patient and physician global assessments, and cardiovascular  
211 hospitalization. Death was not a specified end point in any study, but it was analyzed in all  
212 studies. Other analyses not prospectively planned included the sum of deaths and total  
213 cardiovascular hospitalizations. In situations where the primary end points of a trial do not show  
214 a significant benefit of treatment, assignment of significance values to the other results is  
215 complex, and such values need to be interpreted cautiously.

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

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

221 In the Australia-New Zealand study, death and total hospitalizations were reduced by about  
222 25% over 18 to 24 months. In the three largest US studies, death and total hospitalizations were  
223 reduced by 19%, 39%, and 49%, nominally statistically significant in the last two studies. The  
224 Australia-New Zealand results were statistically borderline.

225 *Functional Measures:* None of the multicenter studies had NYHA classification as a primary  
226 end point, but all such studies had it as a secondary end point. There was at least a trend toward  
227 improvement in NYHA class in all studies. Exercise tolerance was the primary end point in  
228 3 studies; in none was a statistically significant effect found.

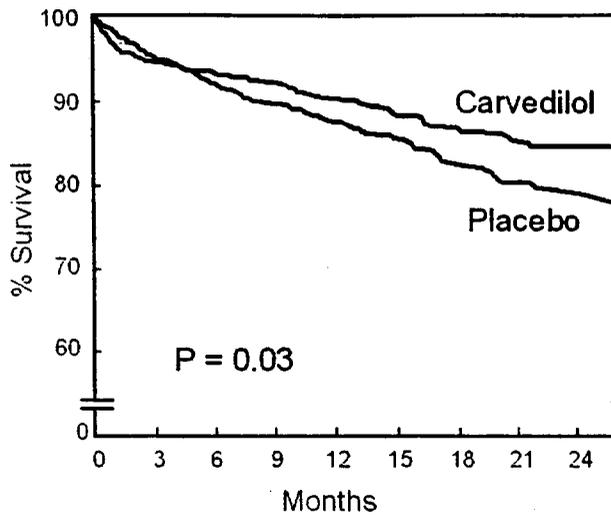
229 *Subjective Measures:* Quality of life, as measured with a standard questionnaire (a primary  
230 end point in one study), was unaffected by carvedilol. However, patients' and investigators'  
231 global assessments showed significant improvement in most studies.

232 *Mortality:* Overall, in these four US trials, mortality was reduced, nominally significantly so  
233 in 2 studies.

234 **Left Ventricular Dysfunction Following Myocardial Infarction:** CAPRICORN was a  
235 double-blind study comparing carvedilol and placebo in 1,959 patients with a recent myocardial  
236 infarction (within 21 days) and left ventricular ejection fraction of  $\leq 40\%$ , with (47%) or without  
237 symptoms of heart failure. Patients given carvedilol received 6.25 mg twice daily, titrated as  
238 tolerated to 25 mg twice daily. Patients had to have a systolic blood pressure  $>90$  mm Hg, a  
239 sitting heart rate  $>60$  beats/minute, and no contraindication to  $\beta$ -blocker use. Treatment of the  
240 index infarction included aspirin (85%), IV or oral  $\beta$ -blockers (37%), nitrates (73%), heparin  
241 (64%), thrombolytics (40%), and acute angioplasty (12%). Background treatment included ACE  
242 inhibitors or angiotensin receptor blockers (97%), anticoagulants (20%), lipid-lowering agents  
243 (23%), and diuretics (34%). Baseline population characteristics included an average age of  
244 63 years, 74% male, 95% Caucasian, mean blood pressure 121/74 mm Hg, 22% with diabetes,  
245 and 54% with a history of hypertension. Mean dosages achieved of carvedilol were ~~22 mg~~  
246 ~~twice daily for placebo and 20 mg twice daily for carvedilol~~; mean duration of follow-up was  
247 15 months.

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

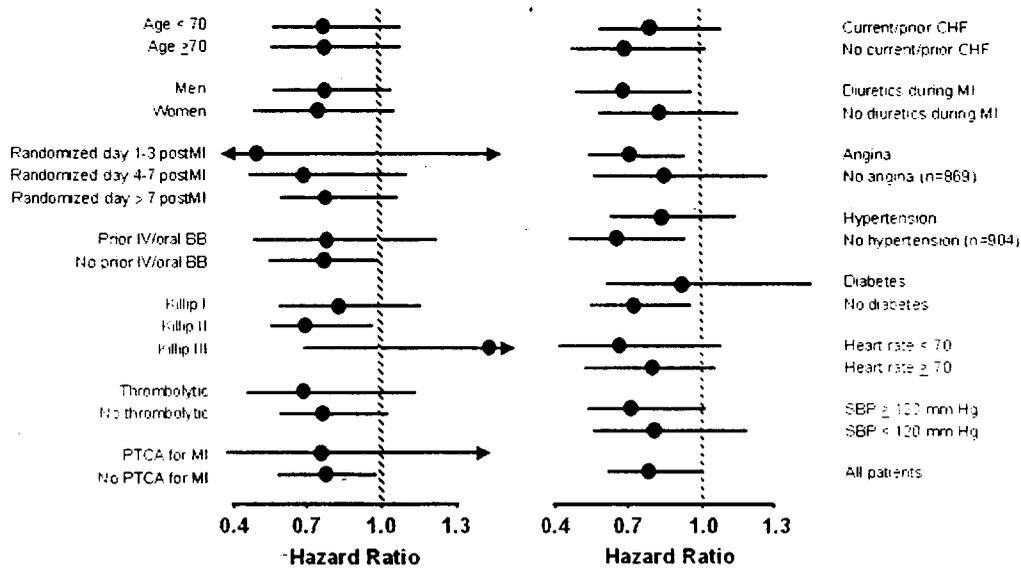
255 **Figure 3. Survival Analysis for CAPRICORN (intent-to-treat)**



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



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261 **Hypertension:** COREG was studied in two placebo-controlled trials that utilized twice-daily  
 262 dosing, at total daily doses of 12.5 to 50 mg. In these and other studies, the starting dose did not  
 263 exceed 12.5 mg. At 50 mg/day, COREG reduced sitting trough (12-hour) blood pressure by  
 264 about 9/5.5 mm Hg; at 25 mg/day the effect was about 7.5/3.5 mm Hg. Comparisons of trough to  
 265 peak blood pressure showed a trough to peak ratio for blood pressure response of about 65%.  
 266 Heart rate fell by about 7.5 beats/minute at 50 mg/day. In general, as is true for other β-blockers,  
 267 responses were smaller in black than non-black patients. There were no age- or gender-related  
 :68 differences in response.

269 The peak antihypertensive effect occurred 1 to 2 hours after a dose. The dose-related blood  
270 pressure response was accompanied by a dose-related increase in adverse effects (see ADVERSE  
271 REACTIONS).

## 272 INDICATIONS AND USAGE

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

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

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

## 284 CONTRAINDICATIONS

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

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

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

## 293 WARNINGS

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

307 ~~Discontinuation of Treatment: Since COREG has  $\beta$ -blocking activity, it should not be~~  
308 ~~discontinued abruptly particularly in patients with ischemic heart disease. Instead, it~~  
309 ~~should be discontinued over 1 to 2 weeks, whenever possible.~~

310 **Hepatic Injury:** Mild hepatocellular injury, confirmed by rechallenge, has occurred rarely with  
311 COREG therapy in the treatment of hypertension. In controlled studies of hypertensive patients,  
312 the incidence of liver function abnormalities reported as adverse experiences was 1.1% (13 of  
313 1,142 patients) in patients receiving COREG and 0.9% (4 of 462 patients) in those receiving  
314 placebo. One patient receiving carvedilol in a placebo-controlled trial withdrew for abnormal  
315 hepatic function.

316 In controlled studies of primarily mild-to-moderate congestive heart failure, the incidence of  
317 liver function abnormalities reported as adverse experiences was 5.0% (38 of 765 patients) in  
318 patients receiving COREG and 4.6% (20 of 437 patients) in those receiving placebo. Three  
319 patients receiving COREG (0.4%) and two patients receiving placebo (0.5%) in  
320 placebo-controlled trials withdrew for abnormal hepatic function. Similarly, in a long-term,  
321 placebo-controlled trial in severe heart failure, there was no difference in the incidence of liver  
322 function abnormalities reported as adverse experiences between patients receiving COREG and  
323 those receiving placebo. No patients receiving COREG and one patient receiving placebo  
324 (0.09%) withdrew for hepatitis. In addition, patients treated with COREG had lower values for  
325 hepatic transaminases than patients treated with placebo, possibly because COREG-induced  
326 improvements in cardiac function led to less hepatic congestion and/or improved hepatic blood  
327 flow.

328 In the CAPRICORN study of survivors of an acute myocardial infarction with left ventricular  
329 dysfunction the incidence of liver function abnormalities reported as adverse experiences was  
330 2.0% (19 of 969 patients) in patients receiving COREG and 1.5% (15 of 980 patients) in those  
331 receiving placebo. Of the patients who received carvedilol in the CAPRICORN trial, one patient  
332 (0.1%) withdrew from the study due to cholestatic jaundice.

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

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

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

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

347 **Diabetes and Hypoglycemia:** In general,  $\beta$ -blockers may mask some of the manifestations  
348 of hypoglycemia, particularly tachycardia. Nonselective  $\beta$ -blockers may potentiate  
349 insulin-induced hypoglycemia and delay recovery of serum glucose levels. Patients subject to  
350 spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents,  
351 should be cautioned about these possibilities. In congestive heart failure patients, there is a risk  
352 of worsening hyperglycemia (see PRECAUTIONS).

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

### 356 PRECAUTIONS

357 **General:** In clinical trials, COREG caused bradycardia in about 2% of hypertensive patients,  
358 9% of congestive heart failure patients, and 6.5% of myocardial infarction patients with left  
359 ventricular dysfunction. If pulse rate drops below 55 beats/minute, the dosage should be reduced.

360 In clinical trials of primarily mild-to-moderate heart failure, hypotension and postural  
361 hypotension occurred in 9.7% and syncope in 3.4% of patients receiving COREG compared to  
362 3.6% and 2.5% of placebo patients, respectively. The risk for these events was highest during the  
363 first 30 days of dosing, corresponding to the up-titration period and was a cause for  
364 discontinuation of therapy in 0.7% of COREG patients, compared to 0.4% of placebo patients. In  
365 a long-term, placebo-controlled trial in severe heart failure (COPERNICUS), hypotension and  
366 postural hypotension occurred in 15.1% and syncope in 2.9% of heart failure patients receiving  
367 COREG compared to 8.7% and 2.3% of placebo patients, respectively. These events were a  
368 cause for discontinuation of therapy in 1.1% of COREG patients, compared to 0.8% of placebo  
369 patients.

370 Postural hypotension occurred in 1.8% and syncope in 0.1% of hypertensive patients,  
371 primarily following the initial dose or at the time of dose increase and was a cause for  
372 discontinuation of therapy in 1% of patients.

373 In the CAPRICORN study of survivors of an acute myocardial infarction, hypotension or  
374 postural hypotension occurred in 20.2% of patients receiving COREG compared to 12.6% of  
375 placebo patients. Syncope was reported in 3.9% and 1.9% of patients, respectively. These events  
376 were a cause for discontinuation of therapy in 2.5% of patients receiving COREG, compared to  
377 0.2% of placebo patients.

378 To decrease the likelihood of syncope or excessive hypotension, treatment should be initiated  
379 with 3.125 mg twice daily for congestive heart failure patients, and at 6.25 mg twice daily for  
380 hypertensive patients and survivors of an acute myocardial infarction with left ventricular  
381 dysfunction. Dosage should then be increased slowly, according to recommendations in the  
382 DOSAGE AND ADMINISTRATION section, and the drug should be taken with food. During  
383 initiation of therapy, the patient should be cautioned to avoid situations such as driving or  
384 hazardous tasks, where injury could result should syncope occur.

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

392 Worsening heart failure or fluid retention may occur during up-titration of carvedilol. If such  
393 symptoms occur, diuretics should be increased and the carvedilol dose should not be advanced  
394 until clinical stability resumes (see DOSAGE AND ADMINISTRATION). Occasionally it is  
395 necessary to lower the carvedilol dose or temporarily discontinue it. Such episodes do not  
396 preclude subsequent successful titration of, or a favorable response to, carvedilol. In a  
397 placebo-controlled trial of patients with severe heart failure, worsening heart failure during the  
398 first 3 months was reported to a similar degree with carvedilol and with placebo. When treatment  
399 was maintained beyond 3 months, worsening heart failure was reported less frequently in  
400 patients treated with carvedilol than with placebo. Worsening heart failure observed during  
401 long-term therapy is more likely to be related to the patients' underlying disease than to  
402 treatment with carvedilol.

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

407 Agents with non-selective  $\beta$ -blocking activity may provoke chest pain in patients with  
408 Prinzmetal's variant angina. There has been no clinical experience with carvedilol in these  
409 patients although the  $\alpha$ -blocking activity may prevent such symptoms. However, caution should  
410 be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant  
411 angina.

412 In congestive heart failure patients with diabetes, carvedilol therapy may lead to worsening  
413 hyperglycemia, which responds to intensification of hypoglycemic therapy. It is recommended  
414 that blood glucose be monitored when carvedilol dosing is initiated, adjusted, or discontinued.

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

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

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

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

- 430 • they should not interrupt or discontinue using COREG without a physician's advice.
- 431 • congestive heart failure patients should consult their physician if they experience signs or  
432 symptoms of worsening heart failure such as weight gain or increasing shortness of breath.
- 433 • they may experience a drop in blood pressure when standing, resulting in dizziness and,  
434 rarely, fainting. Patients should sit or lie down when these symptoms of lowered blood  
435 pressure occur.
- 436 • if patients experience dizziness or fatigue, they should avoid driving or hazardous tasks.
- 437 • they should consult a physician if they experience dizziness or faintness, in case the dosage  
438 should be adjusted.
- 439 • they should take COREG with food.
- 440 • diabetic patients should report any changes in blood sugar levels to their physician.
- 441 • contact lens wearers may experience decreased lacrimation.

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

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

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

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

459 **Cyclosporine:** Modest increases in mean trough cyclosporine concentrations were observed  
460 following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic  
461 vascular rejection. In about 30% of patients, the dose of cyclosporine had to be reduced in order  
462 to maintain cyclosporine concentrations within the therapeutic range, while in the remainder no  
463 adjustment was needed. On the average for the group, the dose of cyclosporine was reduced

464 about 20% in these patients. Due to wide interindividual variability in the dose adjustment  
465 required, it is recommended that cyclosporine concentrations be monitored closely after initiation  
466 of carvedilol therapy and that the dose of cyclosporine be adjusted as appropriate.

467 **Digoxin:** Digoxin concentrations are increased by about 15% when digoxin and carvedilol  
468 are administered concomitantly. Both digoxin and COREG slow AV conduction. Therefore,  
469 increased monitoring of digoxin is recommended when initiating, adjusting, or discontinuing  
470 COREG.

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

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

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

482 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In 2-year studies conducted in  
483 rats given carvedilol at doses up to 75 mg/kg/day (12 times the maximum recommended human  
484 dose [MRHD] when compared on a  $mg/m^2$  basis) or in mice given up to 200 mg/kg/day  
485 (16 times the MRHD on a  $mg/m^2$  basis), carvedilol had no carcinogenic effect.

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

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

494 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Studies performed in pregnant  
495 rats and rabbits given carvedilol revealed increased post-implantation loss in rats at doses of  
496 300 mg/kg/day (50 times the MRHD as  $mg/m^2$ ) and in rabbits at doses of 75 mg/kg/day  
497 (25 times the MRHD as  $mg/m^2$ ). In the rats, there was also a decrease in fetal body weight at the  
498 maternally toxic dose of 300 mg/kg/day (50 times the MRHD as  $mg/m^2$ ), which was  
499 accompanied by an elevation in the frequency of fetuses with delayed skeletal development  
500 (missing or stunted 13th rib). In rats the no-observed-effect level for developmental toxicity was  
501 60 mg/kg/day (10 times the MRHD as  $mg/m^2$ ); in rabbits it was 15 mg/kg/day (5 times the  
502 MRHD as  $mg/m^2$ ). There are no adequate and well-controlled studies in pregnant women.

503 COREG should be used during pregnancy only if the potential benefit justifies the potential risk  
504 to the fetus.

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

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

516 **Geriatric Use:** Of the 765 patients with congestive heart failure randomized to COREG in US  
517 clinical trials, 31% (235) were 65 years of age or older. Of the 1,156 patients randomized to  
518 COREG in a long-term, placebo-controlled trial in severe heart failure, 47% (547) were 65 years  
519 of age or older. Of 3,025 patients receiving COREG in congestive heart failure trials worldwide,  
520 42% were 65 years of age or older. There were no notable differences in efficacy or the  
521 incidence of adverse events between older and younger patients.

522 Of the 975 myocardial infarction patients randomized to COREG in the CAPRICORN trial,  
523 48% (468) were 65 years of age or older, and 11% (111) were 75 years of age or older. There  
524 were no notable differences in efficacy or the incidence of adverse events between older and  
525 younger patients.

526 Of the 2,065 hypertensive patients in US clinical trials of efficacy or safety who were treated  
527 with COREG, 21% (436) were 65 years of age or older. Of 3,722 patients receiving COREG in  
528 hypertension clinical trials conducted worldwide, 24% were 65 years of age or older. There were  
529 no notable differences in efficacy or the incidence of adverse events between older and younger  
530 patients. With the exception of dizziness (incidence 8.8% in the elderly vs. 6% in younger  
531 patients), there were no events for which the incidence in the elderly exceeded that in the  
532 younger population by greater than 2.0%.

533 Similar results were observed in a postmarketing surveillance study of 3,328 COREG  
534 patients, of whom approximately 20% were 65 years of age or older.

## 535 **ADVERSE REACTIONS**

536 **Congestive Heart Failure:** COREG has been evaluated for safety in congestive heart failure  
537 in more than 3,000 patients worldwide of whom more than 2,100 participated in  
538 placebo-controlled clinical trials. Approximately 60% of the total treated population received  
539 COREG for at least 6 months and 30% received COREG for at least 12 months. The adverse  
540 experience profile of COREG in patients with congestive heart failure was consistent with the  
41 pharmacology of the drug and the health status of the patients. Both in US clinical trials in

542 mild-to-moderate heart failure that compared COREG in daily doses up to 100 mg (n = 765) to  
543 placebo (n = 437), and in a multinational clinical trial in severe heart failure (COPERNICUS) that  
544 compared COREG in daily doses up to 50 mg (n = 1,156) with placebo (n = 1,133),  
545 discontinuation rates for adverse experiences were similar in carvedilol and placebo patients. In  
546 these databases, the only cause of discontinuation >1%, and occurring more often on carvedilol  
547 was dizziness (1.3% on carvedilol, 0.6% on placebo in the COPERNICUS trial).

548 Table 2 shows adverse events reported in patients with mild-to-moderate heart failure enrolled  
549 in US placebo-controlled clinical trials, and with severe heart failure enrolled in the  
550 COPERNICUS trial. Shown are adverse events that occurred more frequently in drug-treated  
551 patients than placebo-treated patients with an incidence of >3% in patients treated with  
552 carvedilol regardless of causality. Median study medication exposure was 6.3 months for both  
553 carvedilol and placebo patients in the trials of mild-to-moderate heart failure, and 10.4 months in  
554 the trial of severe heart failure patients.

555 **Table 2. Adverse Events (% Occurrence) Occurring More Frequently with COREG Than**  
556 **With Placebo in Patients With Mild-to-Moderate Heart Failure Enrolled in US Heart**  
557 **Failure Trials or in Patients With Severe Heart Failure in the COPERNICUS Trial**  
558 **(Incidence >3% in Patients Treated with Carvedilol, Regardless of Causality)**

	Mild-to-Moderate HF		Severe Heart Failure	
	COREG (n = 765)	Placebo (n = 437)	COREG (n = 1,156)	Placebo (n = 1,133)
Body as a Whole				
Asthenia	7	7	11	9
Fatigue	24	22	-	-
Pain	9	8	1	1
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

	Mild-to-Moderate HF		Severe Heart Failure	
	COREG	Placebo	COREG	Placebo
	(n = 765)	(n = 437)	(n = 1,156)	(n = 1,133)
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				
Sinusitis	5	4	2	1
Bronchitis	5	4	5	5
Upper respiratory Infection	18	18	14	13
Cough Increased	8	9	5	4
Rales	4	4	4	2
Vision				
Vision abnormal	5	2	-	-

559

560 In addition to the events in Table 2, in these trials chest pain, injury, cardiac failure,  
561 abdominal pain, gout, insomnia, depression, anemia, viral infection, dyspnea, and rales were also  
562 reported, but rates were equal or greater in placebo-treated patients. Rates of adverse events  
563 were generally similar across demographic subsets (men and women, elderly and non-elderly,  
564 blacks and non-blacks).

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

568

569

**Incidence >1% to ≤3%**

570 **Body as a Whole:** Allergy, malaise, hypovolemia, hypovolemia, fever, leg edema, infection,  
571 back pain.

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

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

575 **Gastrointestinal:** Melena, periodontitis.

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

577 **Metabolic and Nutritional:** Hyperuricemia, hypoglycemia, hyponatremia, increased alkaline  
578 phosphatase, glycosuria, hypovolemia, diabetes mellitus, GGT increased, weight loss,  
579 hyperkalemia, creatinine increased.

580 **Musculoskeletal:** Muscle cramps.

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

582 **Psychiatric:** Somnolence.

583 **Resistance Mechanism:** Infection.

584 **Reproductive, male:** Impotence.

585 **Special Senses:** Blurred vision.

586 **Urinary System:** Renal insufficiency, albuminuria, hematuria.

587 ~~—Rates of adverse events were generally similar across demographic subsets (men and women,~~  
588 ~~elderly and non-elderly, blacks and non-blacks).~~

589 **Postmarketing Experience:** The following adverse reaction has been reported in  
590 postmarketing experience: reports of aplastic anemia have been rare and received only when  
591 carvedilol was administered concomitantly with other medications associated with the event.

592 **Left Ventricular Dysfunction Following Myocardial Infarction:** COREG has been  
593 evaluated for safety in survivors of an acute myocardial infarction with left ventricular  
594 dysfunction in the CAPRICORN trial which involved 969 patients who received COREG and  
595 980 who received placebo. Approximately 75% of the patients received COREG for at least  
596 6 months and 53% received COREG for at least 12 months. Patients were treated for an average  
597 of 12.9 months and 12.8 months with COREG and placebo, respectively.

598 The most common adverse events reported with COREG in the CAPRICORN trial were  
599 consistent with the profile of the drug in the US heart failure trials and the COPERNICUS trial,  
600 as well as the health status of the patients. The only additional adverse events reported in  
601 CAPRICORN in >3% of the patients and more commonly on carvedilol were dyspnea, anemia,  
602 and lung edema. Hypertension and myocardial infarction were also reported, but rates were equal  
603 or greater in placebo-treated patients. The following adverse events were reported with a  
604 frequency of >1% but ≤3% and more frequently with COREG: flu syndrome, cerebrovascular  
605 accident, peripheral vascular disorder, hypotonia, depression, gastrointestinal pain, arthritis, gout  
606 and urinary tract infection. The overall rates of discontinuations due to adverse events were  
607 similar in both groups of patients. In this database, the only cause of discontinuation >1%, and  
608 occurring more often on carvedilol was hypotension (1.5% on carvedilol, 0.2% on placebo).

609 **Hypertension:** COREG has been evaluated for safety in hypertension in more than  
610 2,193 patients in US clinical trials and in 2,976 patients in international clinical trials.  
611 Approximately 36% of the total treated population received COREG for at least 6 months. In  
612 general, COREG was well tolerated at doses up to 50 mg daily. Most adverse events reported  
613 during COREG therapy were of mild to moderate severity. In US controlled clinical trials  
614 directly comparing COREG monotherapy in doses up to 50 mg (n = 1,142) to placebo (n = 462),  
615 4.9% of COREG patients discontinued for adverse events vs. 5.2% of placebo patients. Although  
616 there was no overall difference in discontinuation rates, discontinuations were more common in  
617 the carvedilol group for postural hypotension (1% vs. 0). The overall incidence of adverse events  
618 in US placebo-controlled trials was found to increase with increasing dose of COREG. For  
619 individual adverse events this could only be distinguished for dizziness, which increased in  
620 frequency from 2% to 5% as total daily dose increased from 6.25 mg to 50 mg.

622 Table 3 shows adverse events in US placebo-controlled clinical trials for hypertension that  
 623 occurred with an incidence of >1% regardless of causality, and that were more frequent in  
 624 drug-treated patients than placebo-treated patients.

625 **Table 3. Adverse Events in US Placebo-Controlled Hypertension Trials Incidence ≥1%,**  
 626 **Regardless of Causality**

	Adverse Reactions	
	COREG (n = 1,142) % occurrence	Placebo (n = 462) % occurrence
Cardiovascular		
Bradycardia	2	—
Postural hypotension	2	—
Peripheral Edema	1	—
Central Nervous System		
Dizziness	6	5
Insomnia	2	1
Gastrointestinal		
Diarrhea	2	1
Hematologic		
Thrombocytopenia	1	—
Metabolic		
Hypertriglyceridemia	1	—
Resistance Mechanism		
Viral infection	2	1
Respiratory		
Pharyngitis	2	1
Urinary/Renal		
Urinary tract infection	2	1

627  
 628 In addition to the events in Table 3, abdominal pain, back pain, chest pain, dependent edema,  
 629 dyspepsia, dyspnea, fatigue, headache, injury, nausea, pain, rhinitis, sinusitis, somnolence, and  
 630 upper respiratory tract infection were also reported, but rates were equal or greater in  
 631 placebo-treated patients. Rates of adverse events were generally similar across demographic  
 632 subsets (men and women, elderly and non-elderly, blacks and non-blacks).

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

636 **Incidence >0.1% to ≤1%**

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

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

639 **Gastrointestinal:** Bilirubinemia, increased hepatic enzymes (0.2% of hypertension patients  
 640 and 0.4% of congestive heart failure patients were discontinued from therapy because of  
 641 increases in hepatic enzymes; see WARNINGS, Hepatic Injury).

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

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

645 **Reproductive:** Male: decreased libido.

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

648 **Special Senses:** Tinnitus.

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

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

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

652 **Hematologic:** Anemia, leukopenia.

653 ~~Rates of adverse events were generally similar across demographic subsets (men and women,~~  
654 ~~elderly and non-elderly, blacks and non-blacks).~~

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

660 Other adverse events occurred sporadically in single patients and cannot be distinguished  
661 from concurrent disease states or medications.

662 COREG therapy has not been associated with clinically significant changes in routine  
663 laboratory tests in hypertensive patients. No clinically relevant changes were noted in serum  
664 potassium, fasting serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric  
665 acid, blood urea nitrogen, or creatinine.

## 666 OVERDOSAGE

667 The acute oral LD50 doses in male and female mice and male and female rats are over  
668 8000 mg/kg. Overdosage may cause severe hypotension, bradycardia, cardiac insufficiency,  
669 cardiogenic shock, and cardiac arrest. Respiratory problems, bronchospasms, vomiting, lapses of  
670 consciousness, and generalized seizures may also occur.

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

674 *for excessive bradycardia:* atropine, 2 mg IV.

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

678 If peripheral vasodilation dominates, it may be necessary to administer adrenaline or  
679 noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant  
680 bradycardia, pacemaker therapy should be performed. For bronchospasm,  $\beta$ -sympathomimetics

681 (as aerosol or IV) or aminophylline IV should be given. In the event of seizures, slow IV  
682 injection of diazepam or clonazepam is recommended.

683 NOTE: In the event of severe intoxication where there are symptoms of shock, treatment with  
684 antidotes must be continued for a sufficiently long period of time consistent with the 7- to  
685 10-hour half-life of carvedilol.

686 Cases of overdosage with COREG alone or in combination with other drugs have been  
687 reported. Quantities ingested in some cases exceeded 1,000 milligrams. Symptoms experienced  
688 included low blood pressure and heart rate. Standard supportive treatment was provided and  
689 individuals recovered.

## 690 **DOSAGE AND ADMINISTRATION**

691 **Congestive Heart Failure: DOSAGE MUST BE INDIVIDUALIZED AND CLOSELY**  
692 **MONITORED BY A PHYSICIAN DURING UP-TITRATION.** Prior to initiation of COREG, it  
693 is recommended that fluid retention be minimized. The recommended starting dose of COREG is  
694 3.125 mg, twice daily for two weeks. Patients who tolerate a dose of 3.125 mg twice daily may  
695 have their dose increased to 6.25, 12.5, and 25 mg twice daily over successive intervals of at  
696 least two weeks. Patients should be maintained on lower doses if higher doses are not tolerated.  
697 A maximum dose of 50 mg twice daily has been administered to patients with mild-to-moderate  
698 heart failure weighing over 85 kg (187 lbs).

699 Patients should be advised that initiation of treatment and (to a lesser extent) dosage increases  
700 may be associated with transient symptoms of dizziness or lightheadedness (and rarely syncope)  
701 within the first hour after dosing. Thus during these periods they should avoid situations such as  
702 driving or hazardous tasks, where symptoms could result in injury. In addition, COREG should  
703 be taken with food to slow the rate of absorption. Vasodilatory symptoms often do not require  
704 treatment, but it may be useful to separate the time of dosing of COREG from that of the ACE  
705 inhibitor or to reduce temporarily the dose of the ACE inhibitor. The dose of COREG should not  
706 be increased until symptoms of worsening heart failure or vasodilation have been stabilized.

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

709 The dose of COREG should be reduced if patients experience bradycardia (heart rate  
710 <55 beats/minute).

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

714 **Left Ventricular Dysfunction Following Myocardial Infarction: DOSAGE MUST BE**  
715 **INDIVIDUALIZED AND MONITORED DURING UP-TITRATION.** Treatment with COREG  
716 may be started as an inpatient or outpatient and should be started after the patient is  
717 hemodynamically stable and fluid retention has been minimized. It is recommended that COREG  
718 be started at 6.25 mg twice daily and increased after 3 to 10 days, based on tolerability to  
719 12.5 mg twice daily, then again to the target dose of 25 mg twice daily. A lower starting dose

720 may be used (3.125 mg twice daily) and/or, the rate of up-titration may be slowed if clinically  
721 indicated (e.g., due to low blood pressure or heart rate, or fluid retention). Patients should be  
722 maintained on lower doses if higher doses are not tolerated. The recommended dosing regimen  
723 need not be altered in patients who received treatment with an IV or oral  $\beta$ -blocker during the  
724 acute phase of the myocardial infarction.

725 **Hypertension: DOSAGE MUST BE INDIVIDUALIZED.** The recommended starting dose of  
726 COREG is 6.25 mg twice daily. If this dose is tolerated, using standing systolic pressure  
727 measured about 1 hour after dosing as a guide, the dose should be maintained for 7 to 14 days,  
728 and then increased to 12.5 mg twice daily if needed, based on trough blood pressure, again using  
729 standing systolic pressure one hour after dosing as a guide for tolerance. This dose should also be  
730 maintained for 7 to 14 days and can then be adjusted upward to 25 mg twice daily if tolerated  
731 and needed. The full antihypertensive effect of COREG is seen within 7 to 14 days. Total daily  
732 dose should not exceed 50 mg. COREG should be taken with food to slow the rate of absorption  
733 and reduce the incidence of orthostatic effects.

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

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

### 738 HOW SUPPLIED

739 **Tablets:** White, oval, film-coated tablets: 3.125 mg—engraved with 39 and SB, in bottles of 100;  
740 6.25 mg—engraved with 4140 and SB, in bottles of 100; 12.5 mg—engraved with 4141 and SB, in  
741 bottles of 100; 25 mg—engraved with 4142 and SB, in bottles of 100. The 6.25 mg, 12.5 mg, and  
742 25 mg tablets are TILTAB tablets.

743 Store below 30°C (86°F). Protect from moisture. Dispense in a tight, light-resistant container.  
744

745 3.125 mg 100's: NDC 0007-4139-20

746 6.25 mg 100's: NDC 0007-4140-20

747 12.5 mg 100's: NDC 0007-4141-20

748 25 mg 100's: NDC 0007-4142-20  
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750 COREG and TILTAB are registered trademarks of GlaxoSmithKline.  
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759 GlaxoSmithKline

760 Research Triangle Park, NC 27709

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**Confidential**



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**Coreg®**

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(carvedilol)

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**SKF-105517**

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**Item 2A.2 Highlighted Prescribing Information**

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18 SB Document Number: SKF-105517/RSD-101W47/1

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25 pages redacted from this section of  
the approval package consisted of draft labeling