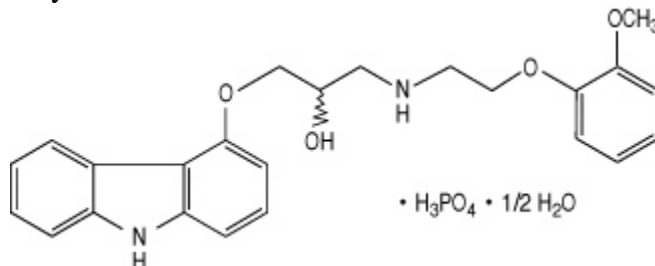


PRESCRIBING INFORMATION

COREG CRTM (carvedilol phosphate) Extended-release Capsules

DESCRIPTION

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



Carvedilol phosphate is a white to almost-white solid with a molecular weight of 513.5 (406.5 carvedilol free base) and a molecular formula of $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_4 \cdot \text{H}_3\text{PO}_4 \cdot 1/2 \text{H}_2\text{O}$.

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

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

34 **Effect of Food:** Administration of COREG CR with a high-fat meal resulted in increases
35 (~20%) in AUC and C_{max} compared to COREG CR administered with a standard meal.
36 Decreases in AUC (27%) and C_{max} (43%) were observed when COREG CR was administered in
37 the fasted state compared to administration after a standard meal. COREG CR should be taken
38 with food.

39 In a study with adult subjects, sprinkling the contents of the COREG CR capsule on
40 applesauce did not appear to have a significant effect on overall exposure (AUC) compared to
41 administration of the intact capsule following a standard meal but did result in a decrease in C_{max}
42 (18%).

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

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

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

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

63 The primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-carvedilol in
64 human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19,
65 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and 5'-hydroxylation of
66 carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be of primary
67 importance in the O-methylation pathway of S(-)-carvedilol.

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

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

75 **Heart Failure:** Following administration of immediate-release carvedilol tablets, steady-state
76 plasma concentrations of carvedilol and its enantiomers increased proportionally over the dose
77 range in patients with heart failure. Compared to healthy subjects, heart failure patients had
78 increased mean AUC and C_{max} values for carvedilol and its enantiomers, with up to 50% to
79 100% higher values observed in 6 patients with NYHA class IV heart failure. The mean apparent
80 terminal elimination half-life for carvedilol was similar to that observed in healthy subjects.

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

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

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

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

94 **Rifampin:** In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin
95 (600 mg daily for 12 days) decreased the AUC and C_{max} of carvedilol by about 70%.

96 **Cimetidine:** In a pharmacokinetic study conducted in 10 healthy male subjects, cimetidine
97 (1,000 mg/day) increased the steady-state AUC of carvedilol by 30% with no change in C_{max} .

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

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

104 **Digoxin:** Following concomitant administration of carvedilol (25 mg once daily) and digoxin
105 (0.25 mg once daily) for 14 days, steady-state AUC and trough concentrations of digoxin were
106 increased by 14% and 16%, respectively, in 12 hypertensive patients (see PRECAUTIONS,
107 Drug Interactions).

108 **Torsemide:** In a study of 12 healthy subjects, combined oral administration of carvedilol
109 25 mg once daily and torsemide 5 mg once daily for 5 days did not result in any significant
110 differences in their pharmacokinetics compared with administration of the drugs alone.

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

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

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

120 **Renal Insufficiency:** No studies have been performed with COREG CR in patients with
121 renal insufficiency. Although carvedilol is metabolized primarily by the liver, plasma
122 concentrations of carvedilol have been reported to be increased in patients with renal impairment
123 after dosing with immediate-release carvedilol. Based on mean AUC data, approximately 40% to
124 50% higher plasma concentrations of carvedilol were observed in hypertensive patients with
125 moderate to severe renal impairment compared to a control group of hypertensive patients with
126 normal renal function. However, the ranges of AUC values were similar for both groups.
127 Changes in mean peak plasma levels were less pronounced, approximately 12% to 26% higher in
128 patients with impaired renal function.

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

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

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

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

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

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

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

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

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

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

163 **CLINICAL TRIALS**

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

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

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

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

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

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

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

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

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

197 In the Australia-New Zealand study, death and total hospitalizations were reduced by about
198 25% over 18 to 24 months. In the 3 largest US studies, death and total hospitalizations were
199 reduced by 19%, 39%, and 49%, nominally statistically significant in the last 2 studies. The
200 Australia-New Zealand results were statistically borderline.

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

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

208 *Mortality:* Death was not a pre-specified end point in any study, but was analyzed in all
209 studies. Overall, in these 4 US trials, mortality was reduced, nominally significantly so in
210 2 studies.

211 **The COMET Trial:** In this double-blind trial, 3,029 patients with NYHA class II-IV heart
212 failure (left ventricular ejection fraction $\leq 35\%$) were randomized to receive either carvedilol
213 (target dose: 25 mg twice daily) or immediate-release metoprolol tartrate (target dose: 50 mg
214 twice daily). The mean age of the patients was approximately 62 years, 80% were males, and the
215 mean left ventricular ejection fraction at baseline was 26%. Approximately 96% of the patients
216 had NYHA class II or III heart failure. Concomitant treatment included diuretics (99%), ACE
217 inhibitors (91%), digitalis (59%), aldosterone antagonists (11%), and "statin" lipid-lowering
218 agents (21%). The mean duration of follow-up was 4.8 years. The mean dose of carvedilol was
219 42 mg per day.

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

229
230

Table 1. Results of COMET

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

231

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

237 ***Trials in Severe Heart Failure:*** In a double-blind study (COPERNICUS), 2,289 patients
238 with heart failure at rest or with minimal exertion and left ventricular ejection fraction <25%
239 (mean 20%), despite digitalis (66%), diuretics (99%), and ACE inhibitors (89%) were
240 randomized to placebo or carvedilol. Carvedilol was titrated from a starting dose of 3.125 mg
241 twice daily to the maximum tolerated dose or up to 25 mg twice daily over a minimum of
242 6 weeks. Most subjects achieved the target dose of 25 mg. The study was conducted in Eastern
243 and Western Europe, the United States, Israel, and Canada. Similar numbers of subjects per
244 group (about 100) withdrew during the titration period.

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

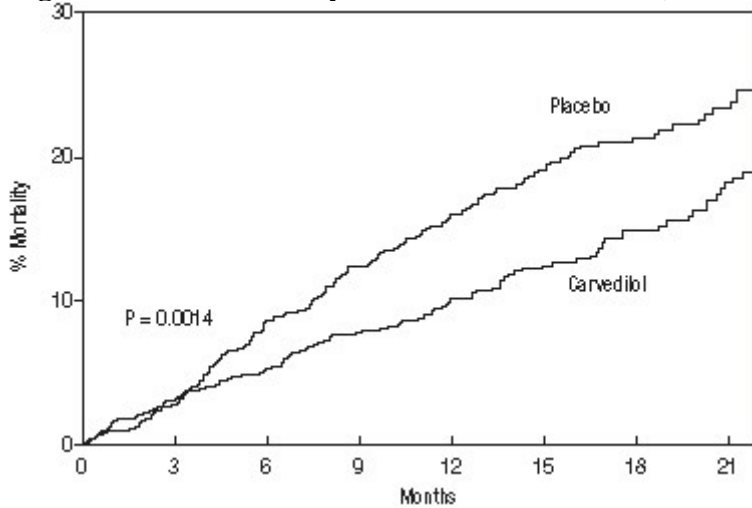
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253 **Table 2. Results of COPERNICUS**

End point	Placebo N = 1,133	Carvedilol N = 1,156	Hazard ratio (95% CI)	% Reduction	Nominal p value
Mortality	190	130	0.65 (0.52 – 0.81)	35	0.00013
Mortality + all hospitalization	507	425	0.76 (0.67 – 0.87)	24	0.00004
Mortality + CV hospitalization	395	314	0.73 (0.63 – 0.84)	27	0.00002
Mortality + CHF hospitalization	357	271	0.69 (0.59 – 0.81)	31	0.000004

254

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



256

257

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

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

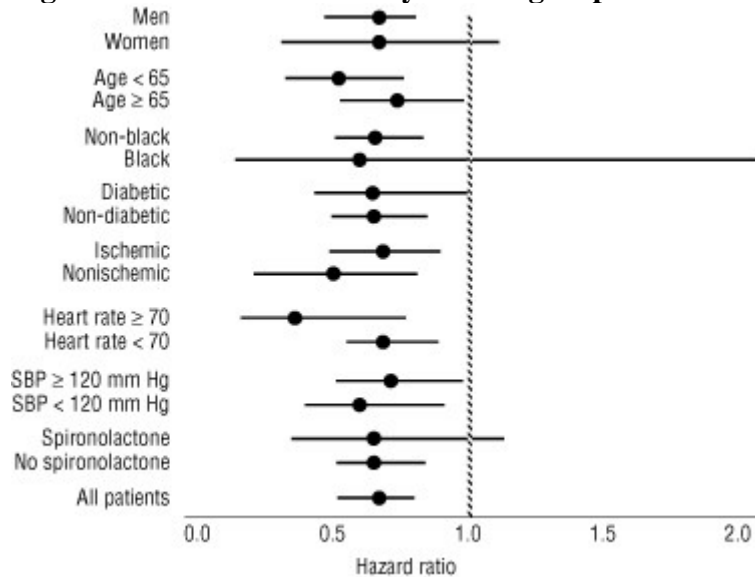
265 The protocol also specified that hospitalizations would be assessed. Fewer patients on
 266 immediate-release carvedilol than on placebo were hospitalized for any reason (372 vs. 432,
 267 $p = 0.0029$), for cardiovascular reasons (246 vs. 314, $p = 0.0003$), or for worsening heart failure
 268 (198 vs. 268, $p = 0.0001$).

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

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

274

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



276

277

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

281 **Left Ventricular Dysfunction Following Myocardial Infarction:** CAPRICORN was a
282 double-blind study comparing carvedilol and placebo in 1,959 patients with a recent myocardial
283 infarction (within 21 days) and left ventricular ejection fraction of $\leq 40\%$, with (47%) or without
284 symptoms of heart failure. Patients given carvedilol received 6.25 mg twice daily, titrated as
285 tolerated to 25 mg twice daily. Patients had to have a systolic blood pressure >90 mm Hg, a
286 sitting heart rate >60 beats/minute, and no contraindication to β -blocker use. Treatment of the
287 index infarction included aspirin (85%), IV or oral β -blockers (37%), nitrates (73%), heparin
288 (64%), thrombolytics (40%), and acute angioplasty (12%). Background treatment included ACE
289 inhibitors or angiotensin receptor blockers (97%), anticoagulants (20%), lipid-lowering agents
290 (23%), and diuretics (34%). Baseline population characteristics included an average age of
291 63 years, 74% male, 95% Caucasian, mean blood pressure 121/74 mm Hg, 22% with diabetes,
292 and 54% with a history of hypertension. Mean dosage achieved of carvedilol was 20 mg twice
293 daily; mean duration of follow-up was 15 months.

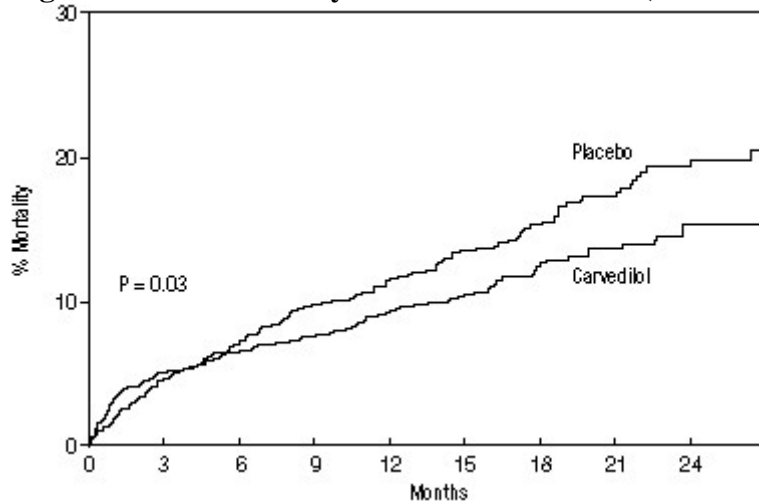
294 All-cause mortality was 15% in the placebo group and 12% in the carvedilol group, indicating
295 a 23% risk reduction in patients treated with carvedilol (95% CI 2% to 40%, $p = 0.03$), as shown
296 in Figure 3. The effects on mortality in various subgroups are shown in Figure 4. Nearly all
297 deaths were cardiovascular (which were reduced by 25% by carvedilol), and most of these deaths
298 were sudden or related to pump failure (both types of death were reduced by carvedilol). Another

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

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

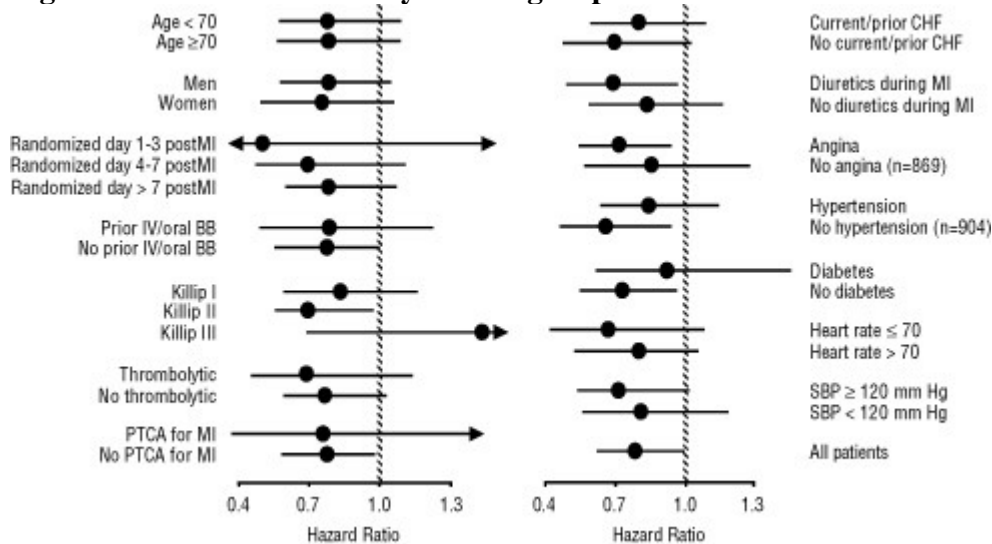
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Figure 3. Survival Analysis for CAPRICORN (intent-to-treat)



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Figure 4. Effects on Mortality for Subgroups in CAPRICORN



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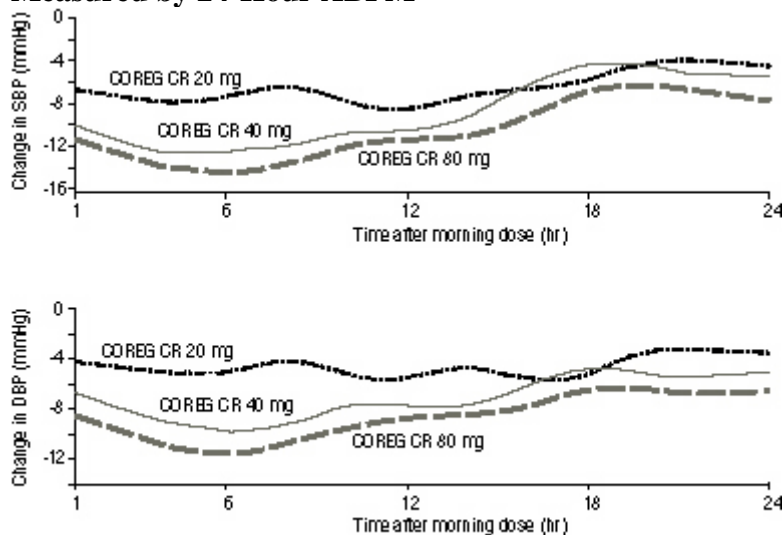
Although the clinical trials used twice-daily dosing, clinical pharmacologic and pharmacokinetic data provide a reasonable basis for concluding that once-daily dosing with COREG CR should be adequate in the treatment of left ventricular dysfunction following myocardial infarction.

316 **Hypertension:** A double-blind, randomized, placebo-controlled, 8-week trial evaluated the
 317 blood pressure lowering effects of COREG CR 20 mg, 40 mg, and 80 mg once daily in 338
 318 patients with essential hypertension (sitting diastolic blood pressure [DBP] ≥ 90 and
 319 ≤ 109 mm Hg). Of 337 evaluable patients, a total of 273 patients (81%) completed the study. Of
 320 the 64 (19%) patients withdrawn from the study, 10 (3%) were due to adverse events, 10 (3%)
 321 were due to lack of efficacy; the remaining 44 (13%) withdrew for other reasons. The mean age
 322 of the patients was approximately 53 years, 66% were male, and the mean sitting systolic blood
 323 pressure (SBP) and DBP at baseline were 150 mm Hg and 99 mm Hg, respectively. Dose
 324 titration occurred at 2-week intervals.

325 Statistically significant reductions in blood pressure as measured by 24-hour ambulatory
 326 blood pressure monitoring (ABPM) were observed with each dose of COREG CR compared to
 327 placebo. Placebo-subtracted mean changes from baseline in mean SBP/DBP were
 328 -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
 329 80 mg, respectively. Placebo-subtracted mean changes from baseline in mean trough (average of
 330 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
 331 COREG CR 20 mg, 40 mg, and 80 mg, respectively. The placebo-corrected trough to peak
 332 (3-7 hr) ratio was approximately 0.6 for COREG CR 80 mg. In this study, assessments of
 333 24-hour ABPM monitoring demonstrated statistically significant blood pressure reductions with
 334 COREG CR throughout the dosing period (Figure 5).

335

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



338

339

Lines smoothed using locally weighted regression smoothing methodology.

340 Immediate-release carvedilol was studied in 2 placebo-controlled trials that utilized
 341 twice-daily dosing, at total daily doses of 12.5 to 50 mg. In these and other studies, the starting
 342 dose did not exceed 12.5 mg. At 50 mg/day, COREG reduced sitting trough (12-hour) blood
 343 pressure by about 9/5.5 mm Hg; at 25 mg/day the effect was about 7.5/3.5 mm Hg. Comparisons

344 of trough-to-peak blood pressure showed a trough-to-peak ratio for blood pressure response of
345 about 65%. Heart rate fell by about 7.5 beats/minute at 50 mg/day. In general, as is true for other
346 β -blockers, responses were smaller in black than non-black patients. There were no age- or
347 gender-related differences in response. The dose-related blood pressure response was
348 accompanied by a dose-related increase in adverse effects (see ADVERSE REACTIONS).
349 **Hypertensive Patients with Type 2 Diabetes Mellitus (GEMINI):** In a double-blind
350 study, carvedilol, added to an ACE inhibitor or angiotensin receptor blocker, was evaluated in a
351 population with mild-to-moderate hypertension and well-controlled type 2 diabetes mellitus. The
352 mean HbA1c at baseline was 7.2%. COREG was titrated to a mean dose of 17.5 mg twice daily
353 and maintained for 5 months. COREG had no adverse effect on glycemic control, based on
354 HbA1c measurements (mean change from baseline of 0.02%, 95% CI -0.06 to 0.10, p = NS) (see
355 PRECAUTIONS, Effects on Glycemic Control in Type 2 Diabetic Patients).

356 **INDICATIONS AND USAGE**

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

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

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

368 **CONTRAINDICATIONS**

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

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

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

380 **WARNINGS**

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

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

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

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

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

410 **PRECAUTIONS**

411 **General:** In clinical trials of COREG CR in patients with hypertension (338 subjects) and in
412 patients with left ventricular dysfunction following a myocardial infarction or heart failure
413 (187 subjects), the profile of adverse events observed with carvedilol phosphate was generally
414 similar to that observed with the administration of immediate-release carvedilol. Therefore, the
415 information included within this section is based on data from controlled clinical trials with
416 COREG CR as well as immediate-release carvedilol.

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

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

424 In clinical trials of primarily mild-to-moderate heart failure with immediate-release carvedilol,
425 hypotension and postural hypotension occurred in 9.7% and syncope in 3.4% of patients
426 receiving carvedilol compared to 3.6% and 2.5% of placebo patients, respectively. The risk for
427 these events was highest during the first 30 days of dosing, corresponding to the up-titration
428 period and was a cause for discontinuation of therapy in 0.7% of carvedilol patients, compared to
429 0.4% of placebo patients. In a long-term, placebo-controlled trial in severe heart failure
430 (COPERNICUS), hypotension and postural hypotension occurred in 15.1% and syncope in 2.9%
431 of heart failure patients receiving carvedilol compared to 8.7% and 2.3% of placebo patients,
432 respectively. These events were a cause for discontinuation of therapy in 1.1% of carvedilol
433 patients, compared to 0.8% of placebo patients.

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

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

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

452 Rarely, use of carvedilol in patients with heart failure has resulted in deterioration of renal
453 function. Patients at risk appear to be those with low blood pressure (systolic blood pressure
454 <100 mm Hg), ischemic heart disease and diffuse vascular disease, and/or underlying renal
455 insufficiency. Renal function has returned to baseline when carvedilol was stopped. In patients
456 with these risk factors it is recommended that renal function be monitored during up-titration of
457 COREG CR and the drug discontinued or dosage reduced if worsening of renal function occurs.

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

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

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

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

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

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

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

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

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

- 503 • They should not interrupt or discontinue using COREG CR without a physician's advice.
- 504 • Heart failure patients should consult their physician if they experience signs or symptoms of
505 worsening heart failure such as weight gain or increasing shortness of breath.
- 506 • They may experience a drop in blood pressure when standing, resulting in dizziness and,
507 rarely, fainting. Patients should sit or lie down when these symptoms of lowered blood
508 pressure occur.
- 509 • If patients experience dizziness or fatigue, they should avoid driving or hazardous tasks.
- 510 • They should consult a physician if they experience dizziness or faintness, in case the dosage
511 should be adjusted.
- 512 • They should not crush or chew COREG CR capsules.
- 513 • They should take COREG CR with food.
- 514 • Diabetic patients should report any changes in blood sugar levels to their physician.
- 515 • Contact lens wearers may experience decreased lacrimation.

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

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

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

528 **Clonidine:** Concomitant administration of clonidine with agents with β -blocking properties
529 may potentiate blood-pressure- and heart-rate-lowering effects. When concomitant treatment
530 with agents with β -blocking properties and clonidine is to be terminated, the β -blocking agent
531 should be discontinued first. Clonidine therapy can then be discontinued several days later by
532 gradually decreasing the dosage.

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

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

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

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

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

555 **Insulin or oral hypoglycemics:** Agents with β -blocking properties may enhance the
556 blood-sugar-reducing effect of insulin and oral hypoglycemics. Therefore, in patients taking
557 insulin or oral hypoglycemics, regular monitoring of blood glucose is recommended.

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

560 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In 2-year studies conducted in
561 rats given carvedilol at doses up to 75 mg/kg/day (12 times the maximum recommended human
562 dose [MRHD] when compared on a mg/m^2 basis) or in mice given up to 200 mg/kg/day
563 (16 times the MRHD on a mg/m^2 basis), carvedilol had no carcinogenic effect.

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

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

572 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Studies performed in pregnant rats
573 and rabbits given carvedilol revealed increased post-implantation loss in rats at doses of
574 300 mg/kg/day (50 times the MRHD as mg/m^2) and in rabbits at doses of 75 mg/kg/day
575 (25 times the MRHD as mg/m^2). In the rats, there was also a decrease in fetal body weight at the
576 maternally toxic dose of 300 mg/kg/day (50 times the MRHD as mg/m^2), which was

577 accompanied by an elevation in the frequency of fetuses with delayed skeletal development
578 (missing or stunted 13th rib). In rats the no-observed-effect level for developmental toxicity was
579 60 mg/kg/day (10 times the MRHD as mg/m²); in rabbits it was 15 mg/kg/day (5 times the
580 MRHD as mg/m²). There are no adequate and well-controlled studies in pregnant women.
581 COREG CR should be used during pregnancy only if the potential benefit justifies the potential
582 risk to the fetus.

583 **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Studies in rats
584 have shown that carvedilol and/or its metabolites (as well as other β -blockers) cross the placental
585 barrier and are excreted in breast milk. There was increased mortality at one week post partum in
586 neonates from rats treated with 60 mg/kg/day (10 times the MRHD as mg/m²) and above during
587 the last trimester through day 22 of lactation. Because many drugs are excreted in human milk
588 and because of the potential for serious adverse reactions in nursing infants from β -blockers,
589 especially bradycardia, a decision should be made whether to discontinue nursing or to
590 discontinue the drug, taking into account the importance of the drug to the mother. The effects of
591 other α - and β -blocking agents have included perinatal and neonatal distress.

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

594 In a double-blind trial, 161 children (mean age 6 years, range 2 months to 17 years; 45% less
595 than 2 years old) with chronic heart failure [NYHA class II-IV, left ventricular ejection fraction
596 <40% for children with a systemic left ventricle (LV), and moderate-severe ventricular
597 dysfunction qualitatively by echo for those with a systemic ventricle that was not an LV] who
598 were receiving standard background treatment were randomized to placebo or to 2 dose levels of
599 carvedilol. These dose levels produced placebo-corrected heart rate reduction of 4-6 heart beats
600 per minute, indicative of β -blockade activity. Exposure appeared to be lower in pediatric subjects
601 than adults. After 8 months of follow-up, there was no significant effect of treatment on clinical
602 outcomes. Adverse reactions in this trial that occurred in greater than 10% of patients treated
603 with immediate-release carvedilol and at twice the rate of placebo-treated patients included chest
604 pain (17% versus 6%), dizziness (13% versus 2%), and dyspnea (11% versus 0%).

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

609 The following information is available for trials with immediate-release carvedilol. Of the
610 765 patients with heart failure randomized to carvedilol in US clinical trials, 31% (235) were
611 65 years of age or older, and 7.3% (56) were 75 years of age or older. Of the 1,156 patients
612 randomized to carvedilol in a long-term, placebo-controlled trial in severe heart failure, 47%
613 (547) were 65 years of age or older, and 15% (174) were 75 years of age or older. Of
614 3,025 patients receiving carvedilol in heart failure trials worldwide, 42% were 65 years of age or
615 older. Of the 975 myocardial infarction patients randomized to carvedilol in the CAPRICORN
616 trial, 48% (468) were 65 years of age or older, and 11% (111) were 75 years of age or older. Of

617 the 2,065 hypertensive patients in US clinical trials of efficacy or safety who were treated with
618 carvedilol, 21% (436) were 65 years of age or older. Of 3,722 patients receiving immediate-
619 release carvedilol in hypertension clinical trials conducted worldwide, 24% were 65 years of age
620 or older.

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

627 **ADVERSE REACTIONS**

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

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

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

656 experiences were similar in carvedilol and placebo patients. In placebo-controlled clinical trials,
657 the only cause of discontinuation >1%, and occurring more often on carvedilol was dizziness
658 (1.3% on carvedilol, 0.6% on placebo in the COPERNICUS trial).

659 Table 3 shows adverse events reported in patients with mild-to-moderate heart failure enrolled
660 in US placebo-controlled clinical trials, and with severe heart failure enrolled in the
661 COPERNICUS trial. Shown are adverse events that occurred more frequently in drug-treated
662 patients than placebo-treated patients with an incidence of >3% in patients treated with
663 carvedilol regardless of causality. Median study medication exposure was 6.3 months for both
664 carvedilol and placebo patients in the trials of mild-to-moderate heart failure, and 10.4 months in
665 the trial of severe heart failure patients. The adverse event profile of carvedilol observed in the
666 long-term COMET study was generally similar to that observed in the US Heart Failure Trials.
667

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

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

673
674 Cardiac failure and dyspnea were also reported in these studies, but the rates were equal or
675 greater in patients who received placebo.

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

679 **Incidence >1% to ≤3%**

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

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

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

684 **Gastrointestinal:** Melena, periodontitis.

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

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

689 **Musculoskeletal:** Muscle cramps.

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

691 **Psychiatric:** Somnolence.

692 **Reproductive, male:** Impotence.

693 **Special Senses:** Blurred vision.

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

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

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

703 The most common adverse events reported with carvedilol in the CAPRICORN trial were
704 consistent with the profile of the drug in the US heart failure trials and the COPERNICUS trial.
705 The only additional adverse events reported in CAPRICORN in >3% of the patients and more
706 commonly on carvedilol were dyspnea, anemia, and lung edema. The following adverse events
707 were reported with a frequency of >1% but ≤3% and more frequently with carvedilol: Flu
708 syndrome, cerebrovascular accident, peripheral vascular disorder, hypotonia, depression,
709 gastrointestinal pain, arthritis, and gout. The overall rates of discontinuations due to adverse
710 events were similar in both groups of patients. In this database, the only cause of discontinuation
711 >1%, and occurring more often on carvedilol was hypotension (1.5% on carvedilol, 0.2% on
712 placebo).

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

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

717
718 **Table 4. Adverse Events (% Occurrence) Occurring More Frequently With COREG CR**
719 **Than With Placebo in Patients With Hypertension (Incidence \geq 1% in Patients Treated**
720 **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

721
722 The following information describes the safety experience in hypertension with immediate-
723 release carvedilol.

724 Carvedilol has been evaluated for safety in hypertension in more than 2,193 patients in US
725 clinical trials and in 2,976 patients in international clinical trials. Approximately 36% of the total
726 treated population received carvedilol for at least 6 months. In general, carvedilol was well
727 tolerated at doses up to 50 mg daily. Most adverse events reported during carvedilol therapy
728 were of mild to moderate severity. In US controlled clinical trials directly comparing carvedilol
729 monotherapy in doses up to 50 mg (n = 1,142) to placebo (n = 462), 4.9% of carvedilol patients
730 discontinued for adverse events vs. 5.2% of placebo patients. Although there was no overall
731 difference in discontinuation rates, discontinuations were more common in the carvedilol group
732 for postural hypotension (1% vs. 0). The overall incidence of adverse events in US
733 placebo-controlled trials was found to increase with increasing dose of carvedilol. For individual
734 adverse events this could only be distinguished for dizziness, which increased in frequency from
735 2% to 5% as total daily dose increased from 6.25 mg to 50 mg as single or divided doses.

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

739

740 **Table 5. Adverse Events (% Occurrence) in US Placebo-Controlled Hypertension Trials**
 741 **With Immediate-Release Carvedilol (Incidence \geq 1% in Patients Treated With Carvedilol,**
 742 **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

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

744
 745 Dyspnea and fatigue were also reported in these studies, but the rates were equal or greater in
 746 patients who received placebo.

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

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

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

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

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

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

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

759 **Reproductive:** Male: Decreased libido.

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

762 **Special Senses:** Tinnitus.

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

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

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

766 **Hematologic:** Anemia, leukopenia.

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

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

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

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

790 **OVERDOSAGE**

791 The acute oral LD50 doses in male and female mice and male and female rats are over
792 8,000 mg/kg. Overdosage may cause severe hypotension, bradycardia, cardiac insufficiency,
793 cardiogenic shock, and cardiac arrest. Respiratory problems, bronchospasms, vomiting, lapses of
794 consciousness, and generalized seizures may also occur.

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

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

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

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

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

807 NOTE: In the event of severe intoxication where there are symptoms of shock, treatment with
808 antidotes must be continued for a sufficiently long period of time consistent with the 7- to
809 10-hour half-life of carvedilol.

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

814 **DOSAGE AND ADMINISTRATION**

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

820

821 **Table 6. Dosing Conversion**

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

822

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

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

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

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

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

847 The dose of COREG CR should be reduced if patients experience bradycardia (heart rate
848 <55 beats/minute).

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

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

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

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

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

876 **HOW SUPPLIED**

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

- 879 10 mg – white and green capsule shell printed with GSK COREG CR and 10 mg
- 880 20 mg – white and yellow capsule shell printed with GSK COREG CR and 20 mg
- 881 40 mg – yellow and green capsule shell printed with GSK COREG CR and 40 mg
- 882 80 mg – white capsule shell printed with GSK COREG CR and 80 mg
- 883
- 884 10 mg 30's: NDC 0007-3370-13
- 885 10 mg 90's: NDC 0007-3370-59
- 886 20 mg 30's: NDC 0007-3371-13
- 887 20 mg 90's: NDC 0007-3371-59
- 888 40 mg 30's: NDC 0007-3372-13
- 889 40 mg 90's: NDC 0007-3372-59
- 890 80 mg 30's: NDC 0007-3373-13
- 891 80 mg 90's: NDC 0007-3373-59

892 **STORAGE**

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

895

896 COREG CR is a trademark of GlaxoSmithKline.

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

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900 GlaxoSmithKline

901 Research Triangle Park, NC 27709

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PATIENT INFORMATION LEAFLET
COREG CR™ (Co-REG)
(carvedilol phosphate) Extended-release Capsules

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

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

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

What is COREG CR?

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

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

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

Who should not take COREG CR?

Do not take COREG CR if you:

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

What should I tell my doctor before taking COREG CR?

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

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

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

956

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

961

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

964

965 **How should I take COREG CR?**

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

980

981 **What should I avoid while taking COREG CR?**

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

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What are possible side effects of COREG CR?

Serious side effects of COREG CR include:

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

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

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

How should I store COREG CR?

Store COREG CR at less than 86°F (30°C).
Safely throw away COREG CR that is out of date or no longer needed.

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

General information about COREG CR

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

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

1024 about COREG CR that is written for healthcare professionals. You can also find out more about
1025 COREG CR by visiting the website www.COREGCR.com or calling 1-888-825-5249. This call
1026 is free.

1027

1028 **What are the ingredients in COREG CR?**

1029 Active ingredient: carvedilol phosphate

1030 Inactive ingredients: crospovidone, hydrogenated castor oil, hydrogenated vegetable oil,
1031 magnesium stearate, methacrylic acid copolymers, microcrystalline cellulose, and povidone

1032 COREG CR capsules come in the following strengths: 10 mg, 20 mg, 40 mg, 80 mg.

1033

1034 COREG CR is a trademark of GlaxoSmithKline.

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