

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use COREG CR safely and effectively. See full prescribing information for COREG CR.

COREG CR® (carvedilol phosphate) Extended-release Capsules
Initial U.S. Approval: 1995

RECENT MAJOR CHANGES

Drug Interactions (7) December 2008
Contraindications (4) April 2008

INDICATIONS AND USAGE

COREG CR is an alpha/beta-adrenergic blocking agent indicated for the treatment of:

- Mild to severe chronic heart failure (1.1)
- Left ventricular dysfunction following myocardial infarction in clinically stable patients (1.2)
- Hypertension (1.3)

DOSAGE AND ADMINISTRATION

Take with food. Do not crush or chew capsules. Individualize dosage and monitor during up-titration. (2)

- Heart failure: Start at 10 mg once daily and increase to 20, 40, and then 80 mg once daily over intervals of at least 2 weeks. Maintain lower doses if higher doses are not tolerated. (2.1)
- Left ventricular dysfunction following myocardial infarction: Start at 20 mg once daily and increase to 40 mg then 80 mg once daily after intervals of 3 to 10 days. A lower starting dose or slower titration may be used. (2.2)
- Hypertension: Start at 20 mg once daily and increase if needed for blood pressure control to 40 mg then 80 mg once daily over intervals of 1 to 2 weeks. (2.3)

DOSAGE FORMS AND STRENGTHS

Capsules: 10, 20, 40, 80 mg (3)

CONTRAINDICATIONS

- Bronchial asthma or related bronchospastic conditions (4)
- Second- or third-degree AV block (4)
- Sick sinus syndrome (4)
- Severe bradycardia (unless permanent pacemaker in place) (4)
- Patients in cardiogenic shock or decompensated heart failure requiring the use of IV inotropic therapy. (4)
- Severe hepatic impairment (2.4, 4)
- History of serious hypersensitivity reaction (e.g., Stevens-Johnson syndrome, anaphylactic reaction, angioedema) to carvedilol or any of the components of COREG CR. (4)

WARNINGS AND PRECAUTIONS

- Acute exacerbation of coronary artery disease upon cessation of therapy: Do not abruptly discontinue. (5.1)
- Bradycardia, hypotension, worsening heart failure/fluid retention may occur. Reduce the dose as needed. (5.2, 5.3, 5.4)
- Non-allergic bronchospasm (e.g., chronic bronchitis and emphysema): Avoid β -blockers. (4) However, if deemed necessary, use with caution and at lowest effective dose. (5.5)
- Diabetes: Monitor glucose as β -blockers may mask symptoms of hypoglycemia or worsen hyperglycemia. (5.6)

ADVERSE REACTIONS

The safety profile of COREG CR was similar to that observed for immediate-release carvedilol. Most common adverse events seen with immediate-release carvedilol. (6.1):

- Heart failure and left ventricular dysfunction following myocardial infarction ($\geq 10\%$): Dizziness, fatigue, hypotension, diarrhea, hyperglycemia, asthenia, bradycardia, weight increase
- Hypertension ($\geq 5\%$): Dizziness

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP P450 2D6 enzyme inhibitors may increase and rifampin may decrease carvedilol levels. (7.1, 7.5)
- Hypotensive agents (e.g., reserpine, MAO inhibitors, clonidine) may increase the risk of hypotension and/or severe bradycardia. (7.2)
- Cyclosporine or digoxin levels may increase. (7.3, 7.4)
- Both digitalis glycosides and β -blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. (7.4)
- Amiodarone may increase carvedilol levels resulting in further slowing of the heart rate or cardiac conduction. (7.6)
- Verapamil- or diltiazem-type calcium channel blockers may affect ECG and/or blood pressure. (7.7)
- Insulin and oral hypoglycemics action may be enhanced. (7.8)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: December 2008
CCR:IXPI

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2 **FULL PRESCRIBING INFORMATION**

3 **1 INDICATIONS AND USAGE**

4 **1.1 Heart Failure**

5 COREG CR is indicated for the treatment of mild-to-severe chronic heart failure of
6 ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitors, and
7 digitalis, to increase survival and, also, to reduce the risk of hospitalization [*see Clinical Studies*
8 (14.1)].

9 **1.2 Left Ventricular Dysfunction Following Myocardial Infarction**

10 COREG CR is indicated to reduce cardiovascular mortality in clinically stable patients
11 who have survived the acute phase of a myocardial infarction and have a left ventricular ejection
12 fraction of $\leq 40\%$ (with or without symptomatic heart failure) [*see Clinical Studies* (14.2)].

13 **1.3 Hypertension**

14 COREG CR is indicated for the management of essential hypertension [*see Clinical*
15 *Studies* (14.3, 14.4)]. It can be used alone or in combination with other antihypertensive agents,
16 especially thiazide-type diuretics [*see Drug Interactions* (7.2)].

17 **2 DOSAGE AND ADMINISTRATION**

18 COREG CR is an extended-release capsule intended for once-daily administration.
19 Patients controlled with immediate-release carvedilol tablets alone or in combination with other
20 medications may be switched to COREG CR extended-release capsules based on the total daily
21 doses shown in Table 1. Subsequent titration to higher or lower doses may be necessary as
22 clinically warranted.

23

24 **Table 1. 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

25

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

29 Alternative Administration: The capsules may be carefully opened and the beads
30 sprinkled over a spoonful of applesauce. The applesauce should not be warm because it could
31 affect the modified-release properties of this formulation. The mixture of drug and applesauce

32 should be consumed immediately in its entirety. The drug and applesauce mixture should not be
33 stored for future use. Absorption of the beads sprinkled on other foods has not been tested.

34 **2.1 Heart Failure**

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

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

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

51 The dose of COREG CR should be reduced if patients experience bradycardia (heart rate
52 <55 beats/minute).

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

56 **2.2 Left Ventricular Dysfunction Following Myocardial Infarction**

57 **DOSAGE MUST BE INDIVIDUALIZED AND MONITORED DURING**
58 **UP-TITRATION.** Treatment with COREG CR may be started as an inpatient or outpatient and
59 should be started after the patient is hemodynamically stable and fluid retention has been
60 minimized. It is recommended that COREG CR be started at 20 mg once daily and increased
61 after 3 to 10 days, based on tolerability, to 40 mg once daily, then again to the target dose of
62 80 mg once daily. A lower starting dose may be used (10 mg once daily) and/or the rate of
63 up-titration may be slowed if clinically indicated (e.g., due to low blood pressure or heart rate, or
64 fluid retention). Patients should be maintained on lower doses if higher doses are not tolerated.
65 The recommended dosing regimen need not be altered in patients who received treatment with an
66 IV or oral β -blocker during the acute phase of the myocardial infarction.

67 **2.3 Hypertension**

68 **DOSAGE MUST BE INDIVIDUALIZED.** The recommended starting dose of
69 COREG CR is 20 mg once daily. If this dose is tolerated, using standing systolic pressure
70 measured about one hour after dosing as a guide, the dose should be maintained for 7 to 14 days,
71 and then increased to 40 mg once daily if needed, based on trough blood pressure, again using

72 standing systolic pressure one hour after dosing as a guide for tolerance. This dose should also be
73 maintained for 7 to 14 days and can then be adjusted upward to 80 mg once daily if tolerated and
74 needed. Although not specifically studied, it is anticipated the full antihypertensive effect of
75 COREG CR would be seen within 7 to 14 days as had been demonstrated with
76 immediate-release carvedilol. Total daily dose should not exceed 80 mg.

77 Concomitant administration with a diuretic can be expected to produce additive effects
78 and exaggerate the orthostatic component of COREG CR action.

79 **2.4 Hepatic Impairment**

80 COREG CR should not be given to patients with severe hepatic impairment [*see*
81 *Contraindications (4)*].

82 **3 DOSAGE FORMS AND STRENGTHS**

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

- 85 • 10 mg – white and green capsule shell printed with GSK COREG CR and 10 mg
- 86 • 20 mg – white and yellow capsule shell printed with GSK COREG CR and 20 mg
- 87 • 40 mg – yellow and green capsule shell printed with GSK COREG CR and 40 mg
- 88 • 80 mg – white capsule shell printed with GSK COREG CR and 80 mg

89 **4 CONTRAINDICATIONS**

90 COREG CR is contraindicated in the following conditions:

- 91 • Bronchial asthma or related bronchospastic conditions. Deaths from status asthmaticus have
92 been reported following single doses of immediate-release carvedilol.
- 93 • Second- or third-degree AV block
- 94 • Sick sinus syndrome
- 95 • Severe bradycardia (unless a permanent pacemaker is in place)
- 96 • Patients with cardiogenic shock or who have decompensated heart failure requiring the use of
97 intravenous inotropic therapy. Such patients should first be weaned from intravenous therapy
98 before initiating COREG CR.
- 99 • Patients with severe hepatic impairment
- 100 • Patients with a history of a serious hypersensitivity reaction (e.g., Stevens-Johnson
101 syndrome, anaphylactic reaction, angioedema) to carvedilol or any of the components of
102 COREG CR

103 **5 WARNINGS AND PRECAUTIONS**

104 In clinical trials of COREG CR in patients with hypertension (338 subjects) and in
105 patients with left ventricular dysfunction following a myocardial infarction or heart failure
106 (187 subjects), the profile of adverse events observed with carvedilol phosphate was generally
107 similar to that observed with the administration of immediate-release carvedilol. Therefore, the
108 information included within this section is based on data from controlled clinical trials with
109 COREG CR as well as immediate-release carvedilol.

110 **5.1 Cessation of Therapy**

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

123 **5.2 Bradycardia**

124 In clinical trials with immediate-release carvedilol, bradycardia was reported in about 2%
125 of hypertensive patients, 9% of heart failure patients, and 6.5% of myocardial infarction patients
126 with left ventricular dysfunction. Bradycardia was reported in 0.5% of patients receiving
127 COREG CR in a study of heart failure patients and myocardial infarction patients with left
128 ventricular dysfunction. There were no reports of bradycardia in the clinical trial of COREG CR
129 in hypertension. However, if pulse rate drops below 55 beats/minute, the dosage of COREG CR
130 should be reduced.

131 **5.3 Hypotension**

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

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

148 In the CAPRICORN study of survivors of an acute myocardial infarction with left
149 ventricular dysfunction, hypotension or postural hypotension occurred in 20.2% of patients

150 receiving carvedilol compared to 12.6% of placebo patients. Syncope was reported in 3.9% and
151 1.9% of patients, respectively. These events were a cause for discontinuation of therapy in 2.5%
152 of patients receiving carvedilol, compared to 0.2% of placebo patients.

153 Starting with a low dose, administration with food, and gradual up-titration should
154 decrease the likelihood of syncope or excessive hypotension [*see Dosage and Administration*
155 (2.1, 2.2, 2.3)]. During initiation of therapy, the patient should be cautioned to avoid situations
156 such as driving or hazardous tasks, where injury could result should syncope occur.

157 **5.4 Heart Failure/Fluid Retention**

158 Worsening heart failure or fluid retention may occur during up-titration of carvedilol. If
159 such symptoms occur, diuretics should be increased and the dose of COREG CR should not be
160 advanced until clinical stability resumes [*see Dosage and Administration (2)*]. Occasionally it is
161 necessary to lower the dose of COREG CR or temporarily discontinue it. Such episodes do not
162 preclude subsequent successful titration of, or a favorable response to, COREG CR. In a
163 placebo-controlled trial of patients with severe heart failure, worsening heart failure during the
164 first 3 months was reported to a similar degree with immediate-release carvedilol and with
165 placebo. When treatment was maintained beyond 3 months, worsening heart failure was reported
166 less frequently in patients treated with carvedilol than with placebo. Worsening heart failure
167 observed during long-term therapy is more likely to be related to the patients' underlying disease
168 than to treatment with carvedilol.

169 **5.5 Nonallergic Bronchospasm**

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

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

180 **5.6 Glycemic Control in Type 2 Diabetes**

181 In general, β -blockers may mask some of the manifestations of hypoglycemia,
182 particularly tachycardia. Nonselective β -blockers may potentiate insulin-induced hypoglycemia
183 and delay recovery of serum glucose levels. Patients subject to spontaneous hypoglycemia, or
184 diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned about these
185 possibilities.

186 In heart failure patients with diabetes, carvedilol therapy may lead to worsening
187 hyperglycemia, which responds to intensification of hypoglycemic therapy. It is recommended
188 that blood glucose be monitored when dosing with COREG CR is initiated, adjusted, or

189 discontinued. Studies designed to examine the effects of carvedilol on glycemic control in
190 patients with diabetes and heart failure have not been conducted.

191 In a study designed to examine the effects of immediate-release carvedilol on glycemic
192 control in a population with mild-to-moderate hypertension and well-controlled type 2 diabetes
193 mellitus, carvedilol had no adverse effect on glycemic control, based on HbA1c measurements
194 [see *Clinical Studies (14.4)*].

195 **5.7 Peripheral Vascular Disease**

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

198 **5.8 Deterioration of Renal Function**

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

206 **5.9 Anesthesia and Major Surgery**

207 If treatment with COREG CR is to be continued perioperatively, particular care should be
208 taken when anesthetic agents which depress myocardial function, such as ether, cyclopropane,
209 and trichloroethylene, are used [see *Overdosage (10) for information on treatment of*
210 *bradycardia and hypertension*].

211 **5.10 Thyrotoxicosis**

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

215 **5.11 Pheochromocytoma**

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

220 **5.12 Prinzmetal's Variant Angina**

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

226 **5.13 Risk of Anaphylactic Reaction**

227 While taking β -blockers, patients with a history of severe anaphylactic reaction to a
228 variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or

229 therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat
230 allergic reaction.

231 **6 ADVERSE REACTIONS**

232 **6.1 Clinical Trials Experience**

233 Carvedilol has been evaluated for safety in patients with heart failure (mild, moderate,
234 and severe), in patients with left ventricular dysfunction following myocardial infarction, and in
235 hypertensive patients. The observed adverse event profile was consistent with the pharmacology
236 of the drug and the health status of the patients in the clinical trials. Adverse events reported for
237 each of these patient populations reflecting the use of either COREG CR or immediate-release
238 carvedilol are provided below. Excluded are adverse events considered too general to be
239 informative, and those not reasonably associated with the use of the drug because they were
240 associated with the condition being treated or are very common in the treated population. Rates
241 of adverse events were generally similar across demographic subsets (men and women, elderly
242 and non-elderly, blacks and non-blacks). COREG CR has been evaluated for safety in a 4-week
243 (2 weeks of immediate-release carvedilol and 2 weeks of COREG CR) clinical study (n = 187)
244 which included 157 patients with stable mild, moderate, or severe chronic heart failure and 30
245 patients with left ventricular dysfunction following acute myocardial infarction. The profile of
246 adverse events observed with COREG CR in this small, short-term study was generally similar
247 to that observed with immediate-release carvedilol. Differences in safety would not be expected
248 based on the similarity in plasma levels for COREG CR and immediate-release carvedilol.

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

251 Carvedilol has been evaluated for safety in heart failure in more than 4,500 patients
252 worldwide of whom more than 2,100 participated in placebo-controlled clinical trials.
253 Approximately 60% of the total treated population in placebo-controlled clinical trials received
254 carvedilol for at least 6 months and 30% received carvedilol for at least 12 months. In the
255 COMET trial, 1,511 patients with mild-to-moderate heart failure were treated with carvedilol for
256 up to 5.9 years (mean 4.8 years). Both in US clinical trials in mild-to-moderate heart failure that
257 compared carvedilol in daily doses up to 100 mg (n = 765) to placebo (n = 437), and in a
258 multinational clinical trial in severe heart failure (COPERNICUS) that compared carvedilol in
259 daily doses up to 50 mg (n = 1,156) with placebo (n = 1,133), discontinuation rates for adverse
260 experiences were similar in carvedilol and placebo patients. In placebo-controlled clinical trials,
261 the only cause of discontinuation >1%, and occurring more often on carvedilol was dizziness
262 (1.3% on carvedilol, 0.6% on placebo in the COPERNICUS trial).

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

268 carvedilol and placebo patients in the trials of mild-to-moderate heart failure, and 10.4 months in
269 the trial of severe heart failure patients. The adverse event profile of carvedilol observed in the
270 long-term COMET study was generally similar to that observed in the US Heart Failure Trials.
271

272 **Table 2. Adverse Events (%) Occurring More Frequently With Immediate-Release**
 273 **Carvedilol Than With Placebo in Patients With Mild-to-Moderate Heart Failure (HF)**
 274 **Enrolled in US Heart Failure Trials or in Patients With Severe Heart Failure in the**
 275 **COPERNICUS Trial (Incidence >3% in Patients Treated With Carvedilol, Regardless of**
 276 **Causality)**

	Mild-to-Moderate HF		Severe HF	
	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	—	—

277
 278 Cardiac failure and dyspnea were also reported in these studies, but the rates were equal
 279 or greater in patients who received placebo.

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

283 **Incidence >1% to ≤3%**

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

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

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

288 *Gastrointestinal:* Melena, periodontitis.

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

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

293 *Musculoskeletal:* Muscle cramps.

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

295 *Psychiatric:* Somnolence.

296 *Reproductive, male:* Impotence.

297 *Special Senses:* Blurred vision.

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

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

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

307 The most common adverse events reported with carvedilol in the CAPRICORN trial were
308 consistent with the profile of the drug in the US heart failure trials and the COPERNICUS trial.
309 The only additional adverse events reported in CAPRICORN in >3% of the patients and more
310 commonly on carvedilol were dyspnea, anemia, and lung edema. The following adverse events
311 were reported with a frequency of >1% but ≤3% and more frequently with carvedilol: Flu
312 syndrome, cerebrovascular accident, peripheral vascular disorder, hypotonia, depression,
313 gastrointestinal pain, arthritis, and gout. The overall rates of discontinuations due to adverse
314 events were similar in both groups of patients. In this database, the only cause of discontinuation
315 >1%, and occurring more often on carvedilol was hypotension (1.5% on carvedilol, 0.2% on
316 placebo).

317 **Hypertension:** COREG CR was evaluated for safety in an 8-week double-blind trial in
318 337 subjects with essential hypertension. The profile of adverse events observed with
319 COREG CR was generally similar to that observed with immediate-release carvedilol. The

320 overall rates of discontinuations due to adverse events were similar between COREG CR and
321 placebo.

322
323 **Table 3. Adverse Events (%) Occurring More Frequently With COREG CR Than With**
324 **Placebo in Patients With Hypertension (Incidence \geq 1% in Patients Treated With**
325 **Carvedilol, Regardless of Causality)**

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

326
327 The following information describes the safety experience in hypertension with
328 immediate-release carvedilol.

329 Carvedilol has been evaluated for safety in hypertension in more than 2,193 patients in
330 US clinical trials and in 2,976 patients in international clinical trials. Approximately 36% of the
331 total treated population received carvedilol for at least 6 months. In general, carvedilol was well
332 tolerated at doses up to 50 mg daily. Most adverse events reported during carvedilol therapy
333 were of mild to moderate severity. In US controlled clinical trials directly comparing carvedilol
334 monotherapy in doses up to 50 mg (n = 1,142) to placebo (n = 462), 4.9% of carvedilol patients
335 discontinued for adverse events versus 5.2% of placebo patients. Although there was no overall
336 difference in discontinuation rates, discontinuations were more common in the carvedilol group
337 for postural hypotension (1% versus 0). The overall incidence of adverse events in US
338 placebo-controlled trials was found to increase with increasing dose of carvedilol. For individual
339 adverse events this could only be distinguished for dizziness, which increased in frequency from
340 2% to 5% as total daily dose increased from 6.25 mg to 50 mg as single or divided doses.

341 Table 4 shows adverse events in US placebo-controlled clinical trials for hypertension
342 that occurred with an incidence of \geq 1% regardless of causality, and that were more frequent in
343 drug-treated patients than placebo-treated patients.

344

345 **Table 4. Adverse Events (% Occurrence) in US Placebo-Controlled Hypertension Trials**
 346 **With Immediate-Release Carvedilol (Incidence \geq 1% in Patients Treated With Carvedilol,**
 347 **Regardless of Causality)***

	Carvedilol (n = 1,142)	Placebo (n = 462)
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	—

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

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

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

Incidence $>$ 0.1% to \leq 1%

Cardiovascular: Peripheral ischemia, tachycardia.

Central and Peripheral Nervous System: Hypokinesia.

Gastrointestinal: Bilirubinemia, increased hepatic enzymes (0.2% of hypertension patients and 0.4% of heart failure patients were discontinued from therapy because of increases in hepatic enzymes) [see *Adverse Reactions (6.2)*].

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

Respiratory System: Asthma [see *Contraindications (4)*].

Reproductive, male: Decreased libido.

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

Special Senses: Tinnitus.

Urinary System: Micturition frequency increased.

Autonomic Nervous System: Dry mouth, sweating increased.

370 *Metabolic and Nutritional:* Hypokalemia, hypertriglyceridemia.

371 *Hematologic:* Anemia, leukopenia.

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

377 **6.2 Laboratory Abnormalities**

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

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

391 **6.3 Postmarketing Experience**

392 The following adverse reactions have been identified during post-approval use of
393 COREG[®] or COREG CR. Because these reactions are reported voluntarily from a population of
394 uncertain size, it is not always possible to reliably estimate their frequency or establish a causal
395 relationship to drug exposure.

396 Reports of aplastic anemia and severe skin reactions (Stevens-Johnson syndrome, toxic
397 epidermal necrolysis, and erythema multiforme) have been rare and received only when
398 carvedilol was administered concomitantly with other medications associated with such
399 reactions. Rare reports of hypersensitivity reactions (e.g., anaphylactic reaction, angioedema, and
400 urticaria) have been received for COREG and COREG CR, including cases occurring after the
401 initiation of COREG CR in patients previously treated with COREG. Urinary incontinence in
402 women (which resolved upon discontinuation of the medication) and interstitial pneumonitis
403 have been reported rarely.

404 **7 DRUG INTERACTIONS**

405 **7.1 CYP2D6 Inhibitors and Poor Metabolizers**

406 Interactions of carvedilol with potent inhibitors of CYP2D6 isoenzyme (such as
407 quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would
408 be expected to increase blood levels of the R(+) enantiomer of carvedilol [*see Clinical*

409 *Pharmacology (12.3)*]. Retrospective analysis of side effects in clinical trials showed that poor
410 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from
411 vasodilating effects of the higher concentrations of the α -blocking R(+) enantiomer.

412 **7.2 Hypotensive Agents**

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

416 Concomitant administration of clonidine with agents with β -blocking properties may
417 potentiate blood-pressure- and heart-rate-lowering effects. When concomitant treatment with
418 agents with β -blocking properties and clonidine is to be terminated, the β -blocking agent should
419 be discontinued first. Clonidine therapy can then be discontinued several days later by gradually
420 decreasing the dosage.

421 **7.3 Cyclosporine**

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

430 **7.4 Digitalis Glycosides**

431 Both digitalis glycosides and β -blockers slow atrioventricular conduction and decrease
432 heart rate. Concomitant use can increase the risk of bradycardia. Digoxin concentrations are
433 increased by about 15% when digoxin and carvedilol are administered concomitantly. Therefore,
434 increased monitoring of digoxin is recommended when initiating, adjusting, or discontinuing
435 COREG CR [*see Clinical Pharmacology (12.5)*].

436 **7.5 Inducers/Inhibitors of Hepatic Metabolism**

437 Rifampin reduced plasma concentrations of carvedilol by about 70% [*see Clinical*
438 *Pharmacology (12.5)*]. Cimetidine increased area under the curve (AUC) by about 30% but
439 caused no change in C_{\max} [*see Clinical Pharmacology (12.5)*].

440 **7.6 Amiodarone**

441 Amiodarone, and its metabolite desethyl amiodarone, inhibitors of CYP2C9 and P-
442 glycoprotein, increased concentrations of the S(-) enantiomer of carvedilol by at least 2-fold [*see*
443 *Clinical Pharmacology (12.5)*]. The concomitant administration of amiodarone or other CYP2C9
444 inhibitors such as fluconazole with COREG CR may enhance the β -blocking properties of
445 carvedilol resulting in further slowing of the heart rate or cardiac conduction. Patients should be
446 observed for signs of bradycardia or heart block, particularly when one agent is added to pre-
447 existing treatment with the other.

448 **7.7 Calcium Channel Blockers**

449 Conduction disturbance (rarely with hemodynamic compromise) has been observed when
450 carvedilol is co-administered with diltiazem. As with other agents with β -blocking properties, if
451 COREG CR is to be administered orally with calcium channel blockers of the verapamil or
452 diltiazem type, it is recommended that ECG and blood pressure be monitored.

453 **7.8 Insulin or Oral Hypoglycemics**

454 Agents with β -blocking properties may enhance the blood-sugar-reducing effect of
455 insulin and oral hypoglycemics. Therefore, in patients taking insulin or oral hypoglycemics,
456 regular monitoring of blood glucose is recommended [*see Warnings and Precautions (5.6)*].

457 **7.9 Proton Pump Inhibitors**

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

460 **8 USE IN SPECIFIC POPULATIONS**

461 **8.1 Pregnancy**

462 Pregnancy Category C. Studies performed in pregnant rats and rabbits given carvedilol
463 revealed increased post-implantation loss in rats at doses of 300 mg/kg/day (50 times the
464 maximum recommended human dose [MRHD] as mg/m^2) and in rabbits at doses of
465 75 mg/kg/day (25 times the MRHD as mg/m^2). In the rats, there was also a decrease in fetal body
466 weight at the maternally toxic dose of 300 mg/kg/day (50 times the MRHD as mg/m^2), which
467 was accompanied by an elevation in the frequency of fetuses with delayed skeletal development
468 (missing or stunted 13th rib). In rats the no-observed-effect level for developmental toxicity was
469 60 mg/kg/day (10 times the MRHD as mg/m^2); in rabbits it was 15 mg/kg/day (5 times the
470 MRHD as mg/m^2). There are no adequate and well-controlled studies in pregnant women.
471 COREG CR should be used during pregnancy only if the potential benefit justifies the potential
472 risk to the fetus.

473 **8.3 Nursing Mothers**

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

483 **8.4 Pediatric Use**

484 Effectiveness of carvedilol in patients younger than 18 years of age has not been
485 established.

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

497 **8.5 Geriatric Use**

498 The clinical studies of COREG CR in patients with hypertension, heart failure, and left
499 ventricular dysfunction following myocardial infarction did not include sufficient numbers of
500 subjects 65 years of age or older to determine whether they respond differently from younger
501 patients.

502 The following information is available for trials with immediate-release carvedilol. Of the
503 765 patients with heart failure randomized to carvedilol in US clinical trials, 31% (235) were
504 65 years of age or older, and 7.3% (56) were 75 years of age or older. Of the 1,156 patients
505 randomized to carvedilol in a long-term, placebo-controlled trial in severe heart failure, 47%
506 (547) were 65 years of age or older, and 15% (174) were 75 years of age or older. Of
507 3,025 patients receiving carvedilol in heart failure trials worldwide, 42% were 65 years of age or
508 older. Of the 975 myocardial infarction patients randomized to carvedilol in the CAPRICORN
509 trial, 48% (468) were 65 years of age or older, and 11% (111) were 75 years of age or older. Of
510 the 2,065 hypertensive patients in US clinical trials of efficacy or safety who were treated with
511 carvedilol, 21% (436) were 65 years of age or older. Of 3,722 patients receiving immediate-
512 release carvedilol in hypertension clinical trials conducted worldwide, 24% were 65 years of age
513 or older.

514 With the exception of dizziness in hypertensive patients (incidence 8.8% in the elderly
515 versus 6% in younger patients), no overall differences in the safety or effectiveness (see Figures
516 2 and 4) were observed between the older subjects and younger subjects in each of these
517 populations. Similarly, other reported clinical experience has not identified differences in
518 responses between the elderly and younger subjects, but greater sensitivity of some older
519 individuals cannot be ruled out.

520 **10 OVERDOSAGE**

521 Overdosage may cause severe hypotension, bradycardia, cardiac insufficiency,
522 cardiogenic shock, and cardiac arrest. Respiratory problems, bronchospasms, vomiting, lapses of
523 consciousness, and generalized seizures may also occur.

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

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

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

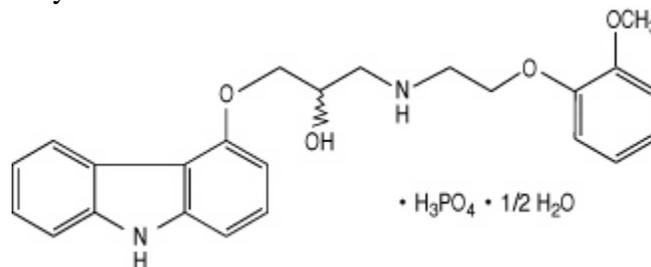
531 If peripheral vasodilation dominates, it may be necessary to administer adrenaline or
532 noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant
533 bradycardia, pacemaker therapy should be performed. For bronchospasm, β -sympathomimetics
534 (as aerosol or IV) or aminophylline IV should be given. In the event of seizures, slow IV
535 injection of diazepam or clonazepam is recommended.

536 NOTE: In the event of severe intoxication where there are symptoms of shock, treatment
537 with antidotes must be continued for a sufficiently long period of time consistent with the 7- to
538 10-hour half-life of carvedilol.

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

543 11 DESCRIPTION

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



547
548 Carvedilol phosphate is a white to almost-white solid with a molecular weight of 513.5
549 (406.5 carvedilol free base) and a molecular formula of $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_4 \cdot \text{H}_3\text{PO}_4 \cdot \frac{1}{2} \text{H}_2\text{O}$.

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

556 **12 CLINICAL PHARMACOLOGY**

557 **12.1 Mechanism of Action**

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

561 **12.2 Pharmacodynamics**

562 Heart Failure and Left Ventricular Dysfunction Following Myocardial Infarction:

563 The basis for the beneficial effects of carvedilol in patients with heart failure and in patients with
564 left ventricular dysfunction following an acute myocardial infarction is not known. The
565 concentration-response relationship for β_1 -blockade following administration of COREG CR is
566 equivalent ($\pm 20\%$) to immediate-release carvedilol tablets.

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

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

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

577 Due to the α_1 -receptor blocking activity of carvedilol, blood pressure is lowered more in
578 the standing than in the supine position, and symptoms of postural hypotension (1.8%), including
579 rare instances of syncope, can occur. Following oral administration, when postural hypotension
580 has occurred, it has been transient and is uncommon when immediate-release carvedilol is
581 administered with food at the recommended starting dose and titration increments are closely
582 followed [*see Dosage and Administration (2)*].

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

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

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

594 **12.3 Pharmacokinetics**

595 Absorption: Carvedilol is rapidly and extensively absorbed following oral administration
596 of immediate-release carvedilol tablets, with an absolute bioavailability of approximately 25% to
597 35% due to a significant degree of first-pass metabolism. COREG CR extended-release capsules
598 have approximately 85% of the bioavailability of immediate-release carvedilol tablets. For
599 corresponding dosages [*see Dosage and Administration (2)*], the exposure (AUC, C_{max}, trough
600 concentration) of carvedilol as COREG CR extended-release capsules is equivalent to those of
601 immediate-release carvedilol tablets when both are administered with food. The absorption of
602 carvedilol from COREG CR is slower and more prolonged compared to the immediate-release
603 carvedilol tablet with peak concentrations achieved approximately 5 hours after administration.
604 Plasma concentrations of carvedilol increase in a dose-proportional manner over the dosage
605 range of COREG CR 10 to 80 mg. Within-subject and between-subject variability for AUC and
606 C_{max} is similar for COREG CR and immediate-release carvedilol.

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

612 In a study with adult subjects, sprinkling the contents of the COREG CR capsule on
613 applesauce did not appear to have a significant effect on overall exposure (AUC) compared to
614 administration of the intact capsule following a standard meal but did result in a decrease in C_{max}
615 (18%).

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

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

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

632 Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of
633 R(+)-carvedilol approximately 2 to 3 times higher than S(-)-carvedilol following oral

634 administration of COREG CR in healthy subjects. Apparent clearance is 90 L/h and 213 L/h for
635 R(+)- and S(-)-carvedilol, respectively.

636 The primary P450 enzymes responsible for the metabolism of both R(+) and
637 S(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent
638 CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4' - and
639 5'-hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be
640 of primary importance in the O-methylation pathway of S(-)-carvedilol.

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

648 **12.4 Specific Populations**

649 Heart Failure: Following administration of immediate-release carvedilol tablets,
650 steady-state plasma concentrations of carvedilol and its enantiomers increased proportionally
651 over the dose range in patients with heart failure. Compared to healthy subjects, heart failure
652 patients had increased mean AUC and C_{max} values for carvedilol and its enantiomers, with up to
653 50% to 100% higher values observed in 6 patients with NYHA class IV heart failure. The mean
654 apparent terminal elimination half-life for carvedilol was similar to that observed in healthy
655 subjects.

656 For corresponding dose levels [*see Dosage and Administration (2)*], the steady-state
657 pharmacokinetics of carvedilol (AUC, C_{max} , trough concentrations) observed after administration
658 of COREG CR to chronic heart failure patients (mild, moderate, and severe) were similar to
659 those observed after administration of immediate-release carvedilol tablets.

660 Hypertension: For corresponding dose levels [*see Dosage and Administration (2)*], the
661 pharmacokinetics (AUC, C_{max} , and trough concentrations) observed with administration of
662 COREG CR were equivalent ($\pm 20\%$) to those observed with immediate-release carvedilol tablets
663 following repeat dosing in patients with essential hypertension.

664 Geriatric: Plasma levels of carvedilol average about 50% higher in the elderly compared
665 to young subjects after administration of immediate-release carvedilol.

666 Hepatic Impairment: No studies have been performed with COREG CR in patients with
667 hepatic impairment. Compared to healthy subjects, patients with severe liver impairment
668 (cirrhosis) exhibit a 4- to 7-fold increase in carvedilol levels. Carvedilol is contraindicated in
669 patients with severe liver impairment.

670 Renal Impairment: No studies have been performed with COREG CR in patients with
671 renal impairment. Although carvedilol is metabolized primarily by the liver, plasma
672 concentrations of carvedilol have been reported to be increased in patients with renal impairment
673 after dosing with immediate-release carvedilol. Based on mean AUC data, approximately 40% to

674 50% higher plasma concentrations of carvedilol were observed in hypertensive patients with
675 moderate to severe renal impairment compared to a control group of hypertensive patients with
676 normal renal function. However, the ranges of AUC values were similar for both groups.
677 Changes in mean peak plasma levels were less pronounced, approximately 12% to 26% higher in
678 patients with impaired renal function.

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

681 **12.5 Drug-Drug Interactions**

682 Since carvedilol undergoes substantial oxidative metabolism, the metabolism and
683 pharmacokinetics of carvedilol may be affected by induction or inhibition of cytochrome P450
684 enzymes.

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

687 Amiodarone: In a pharmacokinetic study conducted in 106 Japanese patients with heart
688 failure, coadministration of small loading and maintenance doses of amiodarone with carvedilol
689 resulted in at least a 2-fold increase in the steady-state trough concentrations of S(-) carvedilol
690 [see *Drug Interactions* (7.6)].

691 Cimetidine: In a pharmacokinetic study conducted in 10 healthy male subjects,
692 cimetidine (1,000 mg/day) increased the steady-state AUC of carvedilol by 30% with no change
693 in C_{max} [see *Drug Interactions* (7.5)].

694 Digoxin: Following concomitant administration of carvedilol (25 mg once daily) and
695 digoxin (0.25 mg once daily) for 14 days, steady-state AUC and trough concentrations of digoxin
696 were increased by 14% and 16%, respectively, in 12 hypertensive patients [see *Drug*
697 *Interactions* (7.5)].

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

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

704 Rifampin: In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin
705 (600 mg daily for 12 days) decreased the AUC and C_{max} of carvedilol by about 70% [see *Drug*
706 *Interactions* (7.5)].

707 Torsemide: In a study of 12 healthy subjects, combined oral administration of carvedilol
708 25 mg once daily and torsemide 5 mg once daily for 5 days did not result in any significant
709 differences in their pharmacokinetics compared with administration of the drugs alone.

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

713 **13 NONCLINICAL TOXICOLOGY**

714 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

715 In 2-year studies conducted in rats given carvedilol at doses up to 75 mg/kg/day (12 times
716 the MRHD when compared on a mg/m² basis) or in mice given up to 200 mg/kg/day (16 times
717 the MRHD on a mg/m² basis), carvedilol had no carcinogenic effect.

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

721 At doses ≥200 mg/kg/day (≥32 times the MRHD as mg/m²) carvedilol was toxic to adult
722 rats (sedation, reduced weight gain) and was associated with a reduced number of successful
723 matings, prolonged mating time, significantly fewer corpora lutea and implants per dam, and
724 complete resorption of 18% of the litters. The no-observed-effect dose level for overt toxicity
725 and impairment of fertility was 60 mg/kg/day (10 times the MRHD as mg/m²).

726 **14 CLINICAL STUDIES**

727 Support for the use of COREG CR extended-release capsules for the treatment of mild-
728 to-severe heart failure and for patients with left ventricular dysfunction following myocardial
729 infarction is based on the equivalence of pharmacokinetic and pharmacodynamic (β₁-blockade)
730 parameters between COREG CR and immediate-release carvedilol [*see Clinical Pharmacology*
731 (*12.2, 12.3*)].

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

734 **14.1 Heart Failure**

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

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

740 Four US multicenter, double-blind, placebo-controlled studies enrolled 1,094 patients
741 (696 randomized to carvedilol) with NYHA class II-III heart failure and ejection fraction ≤0.35.
742 The vast majority were on digitalis, diuretics, and an ACE inhibitor at study entry. Patients were
743 assigned to the studies based upon exercise ability. An Australia-New Zealand double-blind,
744 placebo-controlled study enrolled 415 patients (half randomized to immediate-release carvedilol)
745 with less severe heart failure. All protocols excluded patients expected to undergo cardiac
746 transplantation during the 7.5 to 15 months of double-blind follow-up. All randomized patients
747 had tolerated a 2-week course on immediate-release carvedilol 6.25 mg twice daily.

748 In each study, there was a primary end point, either progression of heart failure (1 US
749 study) or exercise tolerance (2 US studies meeting enrollment goals and the Australia-New
750 Zealand study). There were many secondary end points specified in these studies, including
751 NYHA classification, patient and physician global assessments, and cardiovascular

752 hospitalization. Other analyses not prospectively planned included the sum of deaths and total
753 cardiovascular hospitalizations. In situations where the primary end points of a trial do not show
754 a significant benefit of treatment, assignment of significance values to the other results is
755 complex, and such values need to be interpreted cautiously.

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

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

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

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

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

772 *Mortality:* Death was not a pre-specified end point in any study, but was analyzed in all
773 studies. Overall, in these 4 US trials, mortality was reduced, nominally significantly so in
774 2 studies.

775 The COMET Trial: In this double-blind trial, 3,029 patients with NYHA class II-IV
776 heart failure (left ventricular ejection fraction $\leq 35\%$) were randomized to receive either
777 carvedilol (target dose: 25 mg twice daily) or immediate-release metoprolol tartrate (target dose:
778 50 mg twice daily). The mean age of the patients was approximately 62 years, 80% were males,
779 and the mean left ventricular ejection fraction at baseline was 26%. Approximately 96% of the
780 patients had NYHA class II or III heart failure. Concomitant treatment included diuretics (99%),
781 ACE inhibitors (91%), digitalis (59%), aldosterone antagonists (11%), and "statin" lipid-
782 lowering agents (21%). The mean duration of follow-up was 4.8 years. The mean dose of
783 carvedilol was 42 mg per day.

784 The study had 2 primary end points: all-cause mortality and the composite of death plus
785 hospitalization for any reason. The results of COMET are presented in Table 5 below. All-cause
786 mortality carried most of the statistical weight and was the primary determinant of the study size.
787 All-cause mortality was 34% in the patients treated with carvedilol and was 40% in the
788 immediate-release metoprolol group ($p = 0.0017$; hazard ratio = 0.83, 95% CI 0.74–0.93). The
789 effect on mortality was primarily due to a reduction in cardiovascular death. The difference
790 between the 2 groups with respect to the composite end point was not significant ($p = 0.122$).

791 The estimated mean survival was 8.0 years with carvedilol and 6.6 years with immediate-release
792 metoprolol.

793

794 **Table 5. 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

795

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

801 **Severe Heart Failure (COPERNICUS):** In a double-blind study, 2,289 patients with
802 heart failure at rest or with minimal exertion and left ventricular ejection fraction <25% (mean
803 20%), despite digitalis (66%), diuretics (99%), and ACE inhibitors (89%) were randomized to
804 placebo or carvedilol. Carvedilol was titrated from a starting dose of 3.125 mg twice daily to the
805 maximum tolerated dose or up to 25 mg twice daily over a minimum of 6 weeks. Most subjects
806 achieved the target dose of 25 mg. The study was conducted in Eastern and Western Europe, the
807 United States, Israel, and Canada. Similar numbers of subjects per group (about 100) withdrew
808 during the titration period.

809 The primary end point of the trial was all-cause mortality, but cause-specific mortality
810 and the risk of death or hospitalization (total, cardiovascular [CV], or heart failure [HF]) were
811 also examined. The developing trial data were followed by a data monitoring committee, and
812 mortality analyses were adjusted for these multiple looks. The trial was stopped after a median
813 follow-up of 10 months because of an observed 35% reduction in mortality (from 19.7% per
814 patient year on placebo to 12.8% on carvedilol, hazard ratio 0.65, 95% CI 0.52 – 0.81,
815 p = 0.0014, adjusted) (see Figure 1). The results of COPERNICUS are shown in Table 6.

816

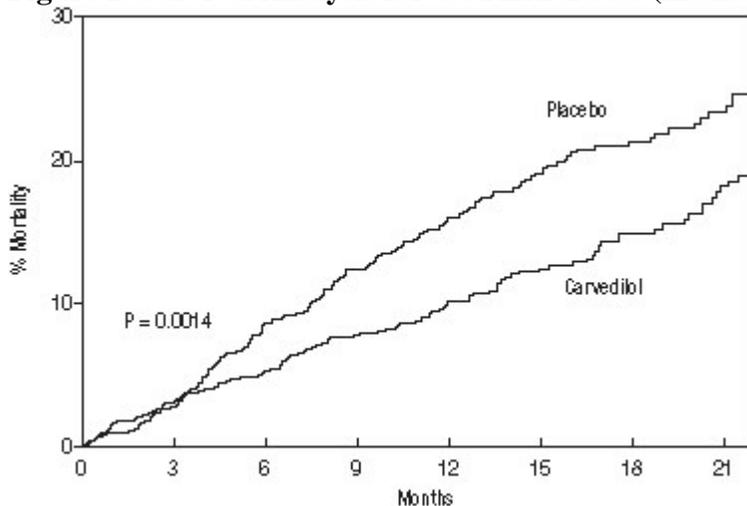
817 **Table 6. Results of COPERNICUS Trial in Patients With Severe Heart Failure**

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 + HF hospitalization	357	271	0.69 (0.59 – 0.81)	31	0.000004

818 Cardiovascular = CV; Heart failure = HF

819

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



821

822

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

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

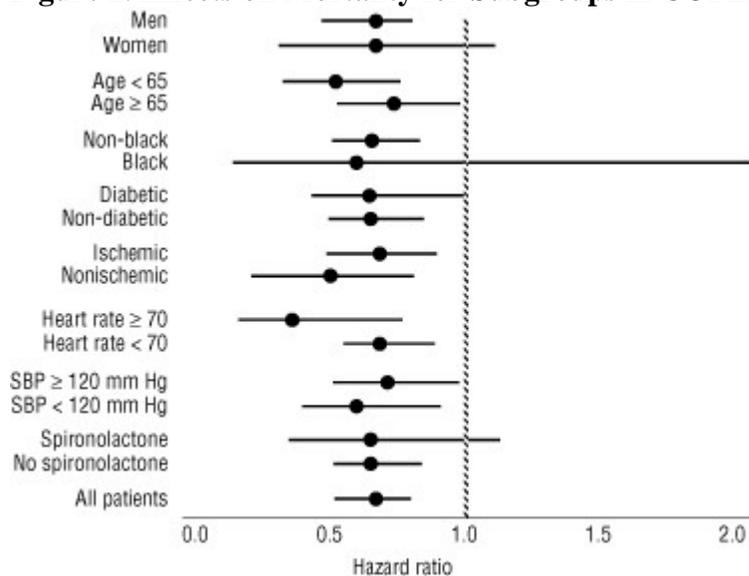
830 The protocol also specified that hospitalizations would be assessed. Fewer patients on
831 immediate-release carvedilol than on placebo were hospitalized for any reason (372 versus 432,
832 $p = 0.0029$), for cardiovascular reasons (246 versus 314, $p = 0.0003$), or for worsening heart
833 failure (198 versus 268, $p = 0.0001$).

834 Immediate-release carvedilol had a consistent and beneficial effect on all-cause mortality
835 as well as the combined end points of all-cause mortality plus hospitalization (total, CV, or for

836 heart failure) in the overall study population and in all subgroups examined, including men and
 837 women, elderly and non-elderly, blacks and non-blacks, and diabetics and non-diabetics (see
 838 Figure 2).

839

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



841

842

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

846 **14.2 Left Ventricular Dysfunction Following Myocardial Infarction**

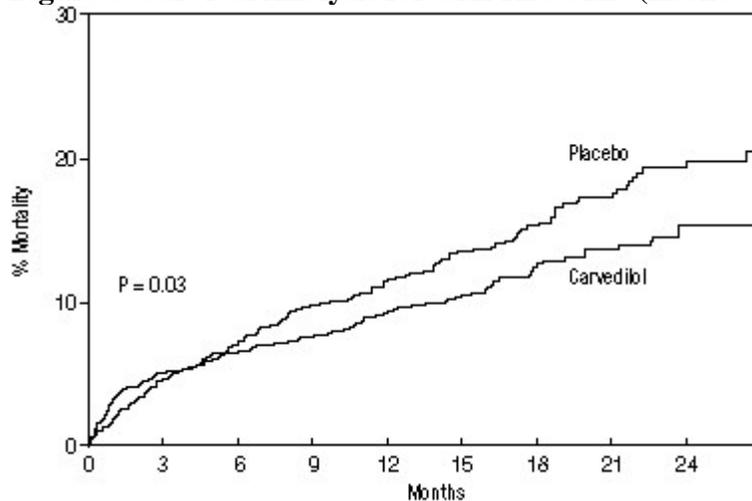
847 CAPRICORN was a double-blind study comparing carvedilol and placebo in 1,959
 848 patients with a recent myocardial infarction (within 21 days) and left ventricular ejection fraction
 849 of ≤40%, with (47%) or without symptoms of heart failure. Patients given carvedilol received
 850 6.25 mg twice daily, titrated as tolerated to 25 mg twice daily. Patients had to have a systolic
 851 blood pressure >90 mm Hg, a sitting heart rate >60 beats/minute, and no contraindication to
 852 β-blocker use. Treatment of the index infarction included aspirin (85%), IV or oral β-blockers
 853 (37%), nitrates (73%), heparin (64%), thrombolytics (40%), and acute angioplasty (12%).
 854 Background treatment included ACE inhibitors or angiotensin receptor blockers (97%),
 855 anticoagulants (20%), lipid-lowering agents (23%), and diuretics (34%). Baseline population
 856 characteristics included an average age of 63 years, 74% male, 95% Caucasian, mean blood
 857 pressure 121/74 mm Hg, 22% with diabetes, and 54% with a history of hypertension. Mean
 858 dosage achieved of carvedilol was 20 mg twice daily; mean duration of follow-up was
 859 15 months.

860 All-cause mortality was 15% in the placebo group and 12% in the carvedilol group,
 861 indicating a 23% risk reduction in patients treated with carvedilol (95% CI 2% to 40%, p = 0.03),
 862 as shown in Figure 3. The effects on mortality in various subgroups are shown in Figure 4.
 863 Nearly all deaths were cardiovascular (which were reduced by 25% by carvedilol), and most of

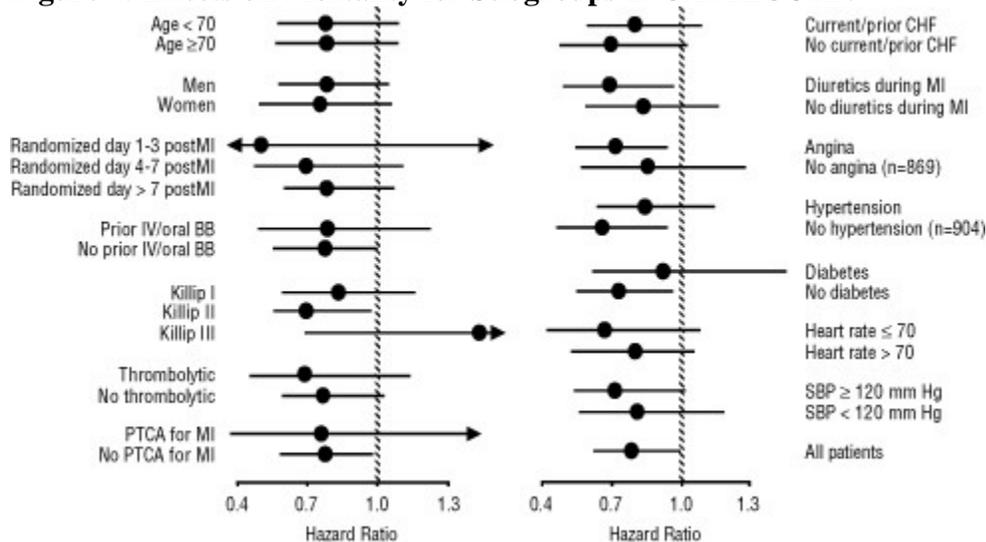
864 these deaths were sudden or related to pump failure (both types of death were reduced by
 865 carvedilol). Another study end point, total mortality and all-cause hospitalization, did not show a
 866 significant improvement.

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

871
 872 **Figure 3. Survival Analysis for CAPRICORN (intent-to-treat)**



873
 874
 875 **Figure 4. Effects on Mortality for Subgroups in CAPRICORN**



876
 877
 878 Although the clinical trials used twice-daily dosing, clinical pharmacologic and
 879 pharmacokinetic data provide a reasonable basis for concluding that once-daily dosing with
 880 COREG CR should be adequate in the treatment of left ventricular dysfunction following
 881 myocardial infarction.

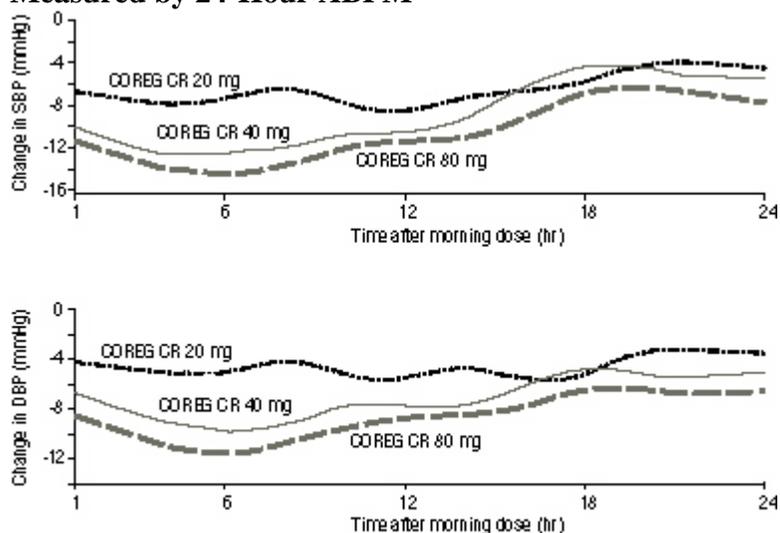
882 **14.3 Hypertension**

883 A double-blind, randomized, placebo-controlled, 8-week trial evaluated the blood
884 pressure lowering effects of COREG CR 20 mg, 40 mg, and 80 mg once daily in 338 patients
885 with essential hypertension (sitting diastolic blood pressure [DBP] ≥ 90 and ≤ 109 mm Hg). Of
886 337 evaluable patients, a total of 273 patients (81%) completed the study. Of the 64 (19%)
887 patients withdrawn from the study, 10 (3%) were due to adverse events, 10 (3%) were due to
888 lack of efficacy; the remaining 44 (13%) withdrew for other reasons. The mean age of the
889 patients was approximately 53 years, 66% were male, and the mean sitting systolic blood
890 pressure (SBP) and DBP at baseline were 150 mm Hg and 99 mm Hg, respectively. Dose
891 titration occurred at 2-week intervals.

892 Statistically significant reductions in blood pressure as measured by 24-hour ambulatory
893 blood pressure monitoring (ABPM) were observed with each dose of COREG CR compared to
894 placebo. Placebo-subtracted mean changes from baseline in mean SBP/DBP were
895 -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
896 80 mg, respectively. Placebo-subtracted mean changes from baseline in mean trough (average of
897 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
898 COREG CR 20 mg, 40 mg, and 80 mg, respectively. The placebo-corrected trough to peak
899 (3-7 hr) ratio was approximately 0.6 for COREG CR 80 mg. In this study, assessments of
900 24-hour ABPM monitoring demonstrated statistically significant blood pressure reductions with
901 COREG CR throughout the dosing period (Figure 5).

902

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



905 Lines smoothed using locally weighted regression smoothing methodology.

906

907

908 Immediate-release carvedilol was studied in 2 placebo-controlled trials that utilized
909 twice-daily dosing, at total daily doses of 12.5 to 50 mg. In these and other studies, the starting
909 dose did not exceed 12.5 mg. At 50 mg/day, COREG reduced sitting trough (12-hour) blood

910 pressure by about 9/5.5 mm Hg; at 25 mg/day the effect was about 7.5/3.5 mm Hg. Comparisons
911 of trough-to-peak blood pressure showed a trough-to-peak ratio for blood pressure response of
912 about 65%. Heart rate fell by about 7.5 beats/minute at 50 mg/day. In general, as is true for other
913 β -blockers, responses were smaller in black than non-black patients. There were no age- or
914 gender-related differences in response. The dose-related blood pressure response was
915 accompanied by a dose-related increase in adverse effects [see *Adverse Reactions (6)*].

916 **14.4 Hypertension With Type 2 Diabetes Mellitus**

917 In a double-blind study (GEMINI), carvedilol, added to an ACE inhibitor or angiotensin
918 receptor blocker, was evaluated in a population with mild-to-moderate hypertension and well-
919 controlled type 2 diabetes mellitus. The mean HbA1c at baseline was 7.2%. COREG was titrated
920 to a mean dose of 17.5 mg twice daily and maintained for 5 months. COREG had no adverse
921 effect on glycemic control, based on HbA1c measurements (mean change from baseline of
922 0.02%, 95% CI -0.06 to 0.10, p = NS) [see *Warnings and Precautions (5.6)*].

923 **16 HOW SUPPLIED/STORAGE AND HANDLING**

924 The hard gelatin capsules are available in the following strengths:

- 925 • 10 mg – white and green capsule shell printed with GSK COREG CR and 10 mg
- 926 • 20 mg – white and yellow capsule shell printed with GSK COREG CR and 20 mg
- 927 • 40 mg – yellow and green capsule shell printed with GSK COREG CR and 40 mg
- 928 • 80 mg – white capsule shell printed with GSK COREG CR and 80 mg
- 929
- 930 • 10 mg 30's: NDC 0007-3370-13
- 931 • 10 mg 90's: NDC 0007-3370-59
- 932 • 20 mg 30's: NDC 0007-3371-13
- 933 • 20 mg 90's: NDC 0007-3371-59
- 934 • 40 mg 30's: NDC 0007-3372-13
- 935 • 40 mg 90's: NDC 0007-3372-59
- 936 • 80 mg 30's: NDC 0007-3373-13
- 937 • 80 mg 90's: NDC 0007-3373-59

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

940 **17 PATIENT COUNSELING INFORMATION**

941 See FDA-Approved Patient Labeling (17.2).

942 **17.1 Patient Advice**

943 Patients taking COREG CR should be advised of the following:

- 944 • Patients should not interrupt or discontinue using COREG CR without a physician's advice.
- 945 • Patients with heart failure should consult their physician if they experience signs or
946 symptoms of worsening heart failure such as weight gain or increasing shortness of breath.

- 947 • Patients may experience a drop in blood pressure when standing, resulting in dizziness and,
948 rarely, fainting. Patients should sit or lie down when these symptoms of lowered blood
949 pressure occur.
- 950 • If experiencing dizziness or fatigue, patients should avoid driving or hazardous tasks.
- 951 • Patients should consult a physician if they experience dizziness or faintness, in case the
952 dosage should be adjusted.
- 953 • Patients should not crush or chew COREG CR capsules.
- 954 • Patients should take COREG CR with food.
- 955 • Diabetic patients should report any changes in blood sugar levels to their physician.
- 956 • Contact lens wearers may experience decreased lacrimation.

957 **17.2 FDA-Approved Patient Labeling**

958 Patient labeling is provided as a tear-off leaflet at the end of this full prescribing
959 information.

960

961 COREG CR and COREG are registered trademarks of GlaxoSmithKline.

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

963



964

965 GlaxoSmithKline

966 Research Triangle Park, NC 27709

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968

969 **PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT**

970 -----
971 **PATIENT INFORMATION LEAFLET**

972 **COREG CR[®] (Co-REG)**

973 **(carvedilol phosphate) Extended-release Capsules**

974
975 Read the Patient Information that comes with COREG CR before you start taking it and each
976 time you get a refill. There may be new information. This information does not take the place of
977 talking with your doctor about your medical condition or your treatment. If you have any
978 questions about COREG CR, ask your doctor or pharmacist.

979
980 **What is the most important information I should know about COREG CR?**

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

985
986 **What is COREG CR?**

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

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

992
993 COREG CR is not approved for use in children under 18 years of age.

994
995 **Who should not take COREG CR?**

996 Do not take COREG CR if you:

- 997 • have severe heart failure and require certain intravenous medicines that help support
998 circulation.
999 • have asthma or other breathing problems.
1000 • have a slow heartbeat or certain conditions that cause your heart to skip a beat (irregular
1001 heartbeat).
1002 • have liver problems.
1003 • are allergic to any of the ingredients in COREG CR. *See “What are the ingredients in*
1004 *COREG CR?”*

1005
1006 **What should I tell my doctor before taking COREG CR?**

1007 Tell your doctor about all of your medical conditions, including if you:

- 1008 • have asthma or other lung problems (such as bronchitis or emphysema).

- 1009 • have problems with blood flow in your feet and legs (peripheral vascular disease).
- 1010 COREG CR can make some of your symptoms worse.
- 1011 • have diabetes.
- 1012 • have thyroid problems.
- 1013 • have a condition called pheochromocytoma.
- 1014 • have had severe allergic reactions.
- 1015 • are scheduled for surgery and will be given anesthetic agents.
- 1016 • are pregnant or trying to become pregnant. It is not known if COREG CR is safe for your
- 1017 unborn baby. You and your doctor should talk about the best way to control your high blood
- 1018 pressure during pregnancy.
- 1019 • are breastfeeding. It is not known if COREG CR passes into your breast milk. You should
- 1020 not breastfeed while using COREG CR.

1021

1022 **Tell your doctor about all of the medicines you take** including prescription and non-
1023 prescription medicines, vitamins, and herbal supplements. COREG CR and certain other
1024 medicines can affect each other and cause serious side effects. COREG CR may affect the way
1025 other medicines work. Also, other medicines may affect how well COREG CR works.

1026

1027 Know the medicines you take. Keep a list of your medicines and show it to your doctor and
1028 pharmacist before you start a new medicine.

1029

1030 **How should I take COREG CR?**

- 1031 • Take COREG CR exactly as prescribed. Take COREG CR **one** time each day with food. **It is**
- 1032 **important that you take COREG CR only one time each day.** To lessen possible side
- 1033 effects, your doctor might begin with a low dose and then slowly increase the dose.
- 1034 • Swallow COREG CR capsules whole. Do not chew or crush COREG CR capsules.
- 1035 • If you have trouble swallowing COREG CR whole:
 - 1036 • The capsule may be carefully opened and the beads sprinkled over a spoonful of
 - 1037 applesauce which should be eaten right away. The applesauce should not be warm.
 - 1038 • Do not sprinkle beads on foods other than applesauce.
- 1039 • **Do not stop taking COREG CR and do not change the amount of COREG CR you take**
- 1040 **without talking to your doctor.**
- 1041 • If you miss a dose of COREG CR, take your dose as soon as you remember, unless it is time
- 1042 to take your next dose. Take your next dose at the usual time. Do not take 2 doses at the same
- 1043 time.
- 1044 • If you take too much COREG CR, call your doctor or poison control center right away.

1045

1046 **What should I avoid while taking COREG CR?**

1047 COREG CR can cause you to feel dizzy, tired, or faint. Do not drive a car, use machinery, or do
1048 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.

Rare serious allergic reactions have happened in patients who were on COREG CR. In some cases, these reactions happened in patients who had been on COREG[®] before taking COREG CR.

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

1088 not give COREG CR to other people, even if they have the same symptoms you have. It may
1089 harm them.

1090
1091 This leaflet summarizes the most important information about COREG CR. If you would like
1092 more information, talk with your doctor. You can ask your doctor or pharmacist for information
1093 about COREG CR that is written for healthcare professionals. You can also find out more about
1094 COREG CR by visiting the website www.COREGCR.com or calling 1-888-825-5249. This call
1095 is free.

1096
1097 **What are the ingredients in COREG CR?**

1098 Active ingredient: carvedilol phosphate
1099 Inactive ingredients: crospovidone, hydrogenated castor oil, hydrogenated vegetable oil,
1100 magnesium stearate, methacrylic acid copolymers, microcrystalline cellulose, and povidone
1101 COREG CR capsules come in the following strengths: 10 mg, 20 mg, 40 mg, 80 mg.

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