

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 for oral use
Initial U.S. Approval: 1995

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)
- Elderly patients (>65 years of age): When switching from higher doses of immediate-release carvedilol to COREG CR, a lower starting dose should be considered to reduce the risk of hypotension and syncope. (2.5)

DOSAGE FORMS AND STRENGTHS

Capsules: 10 mg, 20 mg, 40 mg, 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: XX/XXXX

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1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

3 1.1 Heart Failure

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

7 1.2 Left Ventricular Dysfunction following Myocardial Infarction

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

12 1.3 Hypertension

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

16 2 DOSAGE AND ADMINISTRATION

17 COREG CR is an extended-release capsule intended for once-daily administration. Patients
18 controlled with immediate-release carvedilol tablets alone or in combination with other
19 medications may be switched to COREG CR extended-release capsules based on the total daily
20 doses shown in Table 1.

21
22 **Table 1. Dosing Conversion**

Daily Dose of Immediate-Release Carvedilol Tablets	Daily Dose of COREG CR Capsules ^a
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
^a When switching from carvedilol 12.5 mg or 25 mg twice daily, a starting dose of COREG CR 20 mg or 40 mg once daily, respectively, may be warranted for elderly patients or those at increased risk of hypotension, dizziness, or syncope. Subsequent titration to higher doses should, as appropriate, be made after an interval of at least 2 weeks.	

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

27 Alternative Administration

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

33 **2.1 Heart Failure**

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

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

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

50 The dose of COREG CR should be reduced if patients experience bradycardia (heart rate less
51 than 55 beats per minute).

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

55 **2.2 Left Ventricular Dysfunction following Myocardial Infarction**

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

64 regimen need not be altered in patients who received treatment with an IV or oral β -blocker
65 during the acute phase of the myocardial infarction.

66 **2.3 Hypertension**

67 DOSAGE MUST BE INDIVIDUALIZED. The recommended starting dose of COREG CR is
68 20 mg once daily. If this dose is tolerated, using standing systolic pressure measured about
69 1 hour after dosing as a guide, the dose should be maintained for 7 to 14 days, and then increased
70 to 40 mg once daily if needed, based on trough blood pressure, again using standing systolic
71 pressure 1 hour after dosing as a guide for tolerance. This dose should also be maintained for 7 to
72 14 days and can then be adjusted upward to 80 mg once daily if tolerated and needed. Although
73 not specifically studied, it is anticipated the full antihypertensive effect of COREG CR would be
74 seen within 7 to 14 days as had been demonstrated with immediate-release carvedilol. Total daily
75 dose should not exceed 80 mg.

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

78 **2.4 Hepatic Impairment**

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

81 **2.5 Geriatric Use**

82 When switching elderly patients (aged 65 years or older) who are taking the higher doses of
83 immediate-release carvedilol tablets (25 mg twice daily) to COREG CR, a lower starting dose
84 (40 mg) of COREG CR is recommended to minimize the potential for dizziness, syncope, or
85 hypotension [*see Dosage and Administration (2)*]. Patients who have switched and who tolerate
86 COREG CR should, as appropriate, have their dose increased after an interval of at least 2 weeks
87 [*see Use in Specific Populations (8.5)*].

88 **3 DOSAGE FORMS AND STRENGTHS**

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

- 91 • 10 mg – white and green capsule shell printed with “GSK COREG CR” and “10 mg”
- 92 • 20 mg – white and yellow capsule shell printed with “GSK COREG CR” and “20 mg”
- 93 • 40 mg – yellow and green capsule shell printed with “GSK COREG CR” and “40 mg”
- 94 • 80 mg – white capsule shell printed with “GSK COREG CR” and “80 mg”

95 **4 CONTRAINDICATIONS**

96 COREG CR is contraindicated in the following conditions:

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

109 **5 WARNINGS AND PRECAUTIONS**

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

116 **5.1 Cessation of Therapy**

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

129 **5.2 Bradycardia**

130 In clinical trials with immediate-release carvedilol, bradycardia was reported in about 2% of
131 hypertensive subjects, 9% of heart failure subjects, and 6.5% of myocardial infarction subjects
132 with left ventricular dysfunction. Bradycardia was reported in 0.5% of subjects receiving

133 COREG CR in a trial of heart failure subjects and myocardial infarction subjects with left
134 ventricular dysfunction. There were no reports of bradycardia in the clinical trial of COREG CR
135 in hypertension. However, if pulse rate drops below 55 beats per minute, the dosage of
136 COREG CR should be reduced.

137 **5.3 Hypotension**

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

148 In a trial comparing subjects with heart failure switched to COREG CR or maintained on
149 immediate-release carvedilol, there was a 2-fold increase in the combined incidence of
150 hypotension, syncope, or dizziness in elderly subjects (older than 65 years) switched from the
151 highest dose of carvedilol (25 mg twice daily) to COREG CR 80 mg once daily [*see Dosage and*
152 *Administration (2), Use in Specific Populations (8.5)*].

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

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

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

168 **5.4 Heart Failure/Fluid Retention**

169 Worsening heart failure or fluid retention may occur during up-titration of carvedilol. If such
170 symptoms occur, diuretics should be increased and the dose of COREG CR should not be

171 advanced until clinical stability resumes [*see Dosage and Administration (2)*]. Occasionally it is
172 necessary to lower the dose of COREG CR or temporarily discontinue it. Such episodes do not
173 preclude subsequent successful titration of, or a favorable response to, COREG CR. In a
174 placebo-controlled trial of subjects with severe heart failure, worsening heart failure during the
175 first 3 months was reported to a similar degree with immediate-release carvedilol and with
176 placebo. When treatment was maintained beyond 3 months, worsening heart failure was reported
177 less frequently in subjects treated with carvedilol than with placebo. Worsening heart failure
178 observed during long-term therapy is more likely to be related to the patients' underlying disease
179 than to treatment with carvedilol.

180 **5.5 Non-allergic Bronchospasm**

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

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

191 **5.6 Glycemic Control in Type 2 Diabetes**

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

197 In heart failure patients with diabetes, carvedilol therapy may lead to worsening hyperglycemia,
198 which responds to intensification of hypoglycemic therapy. It is recommended that blood
199 glucose be monitored when dosing with COREG CR is initiated, adjusted, or discontinued. Trials
200 designed to examine the effects of carvedilol on glycemic control in patients with diabetes and
201 heart failure have not been conducted.

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

206 **5.7 Peripheral Vascular Disease**

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

209 **5.8 Deterioration of Renal Function**

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

216 **5.9 Major Surgery**

217 Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major
218 surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may
219 augment the risks of general anesthesia and surgical procedures.

220 **5.10 Thyrotoxicosis**

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

224 **5.11 Pheochromocytoma**

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

229 **5.12 Prinzmetal's Variant Angina**

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

235 **5.13 Risk of Anaphylactic Reaction**

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

240 **5.14 Intraoperative Floppy Iris Syndrome**

241 Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in some
242 patients treated with alpha-1 blockers (COREG CR is an alpha/beta blocker). This variant of
243 small pupil syndrome is characterized by the combination of a flaccid iris that billows in
244 response to intraoperative irrigation currents, progressive intraoperative miosis despite
245 preoperative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the
246 phacoemulsification incisions. The patient's ophthalmologist should be prepared for possible
247 modifications to the surgical technique, such as utilization of iris hooks, iris dilator rings, or
248 viscoelastic substances. There does not appear to be a benefit of stopping alpha-1 blocker
249 therapy prior to cataract surgery.

250 **6 ADVERSE REACTIONS**

251 **6.1 Clinical Trials Experience**

252 Carvedilol has been evaluated for safety in subjects with heart failure (mild, moderate, and
253 severe), in subjects with left ventricular dysfunction following myocardial infarction, and in
254 hypertensive subjects. The observed adverse event profile was consistent with the pharmacology
255 of the drug and the health status of the subjects in the clinical trials. Adverse events reported for
256 each of these populations reflecting the use of either COREG CR or immediate-release
257 carvedilol are provided below. Excluded are adverse events considered too general to be
258 informative, and those not reasonably associated with the use of the drug because they were
259 associated with the condition being treated or are very common in the treated population. Rates
260 of adverse events were generally similar across demographic subsets (men and women, elderly
261 and non-elderly, blacks and non-blacks). COREG CR has been evaluated for safety in a 4-week
262 (2 weeks of immediate-release carvedilol and 2 weeks of COREG CR) clinical trial (n = 187)
263 which included 157 subjects with stable mild, moderate, or severe chronic heart failure and 30
264 subjects with left ventricular dysfunction following acute myocardial infarction. The profile of
265 adverse events observed with COREG CR in this small, short-term trial was generally similar to
266 that observed with immediate-release carvedilol. Differences in safety would not be expected
267 based on the similarity in plasma levels for COREG CR and immediate-release carvedilol.

268 Heart Failure

269 The following information describes the safety experience in heart failure with immediate-
270 release carvedilol.

271 Carvedilol has been evaluated for safety in heart failure in more than 4,500 subjects worldwide
272 of whom more than 2,100 participated in placebo-controlled clinical trials. Approximately 60%
273 of the total treated population in placebo-controlled clinical trials received carvedilol for at least
274 6 months and 30% received carvedilol for at least 12 months. In the COMET trial, 1,511 subjects
275 with mild-to-moderate heart failure were treated with carvedilol for up to 5.9 years (mean:
276 4.8 years). Both in US clinical trials in mild-to-moderate heart failure that compared carvedilol in
277 daily doses up to 100 mg (n = 765) with placebo (n = 437), and in a multinational clinical trial in

278 severe heart failure (COPERNICUS) that compared carvedilol in daily doses up to 50 mg
279 (n = 1,156) with placebo (n = 1,133), discontinuation rates for adverse experiences were similar
280 in carvedilol and placebo subjects. In placebo-controlled clinical trials, the only cause of
281 discontinuation greater than 1%, and occurring more often on carvedilol was dizziness (1.3% on
282 carvedilol, 0.6% on placebo in the COPERNICUS trial).

283 Table 2 shows adverse events reported in subjects with mild-to-moderate heart failure enrolled in
284 US placebo-controlled clinical trials, and with severe heart failure enrolled in the COPERNICUS
285 trial. Shown are adverse events that occurred more frequently in drug-treated subjects than
286 placebo-treated subjects with an incidence of greater than 3% in subjects treated with carvedilol
287 regardless of causality. Median trial medication exposure was 6.3 months for both carvedilol and
288 placebo subjects in the trials of mild-to-moderate heart failure, and 10.4 months in the trial of
289 subjects with severe heart failure. The adverse event profile of carvedilol observed in the long-
290 term COMET trial was generally similar to that observed in the US Heart Failure Trials.

291

292 **Table 2. Adverse Events (%) Occurring More Frequently with Immediate-Release**
 293 **Carvedilol than with Placebo in Subjects with Mild-to-Moderate Heart Failure (HF)**
 294 **Enrolled in US Heart Failure Trials or in Subjects with Severe Heart Failure in the**
 295 **COPERNICUS Trial (Incidence >3% in Subjects Treated with Carvedilol, Regardless of**
 296 **Causality)**

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

297
 298 Cardiac failure and dyspnea were also reported in these trials, but the rates were equal or greater
 299 in subjects who received placebo.

300 The following adverse events were reported with a frequency of greater than 1% but less than or
301 equal to 3% and more frequently with carvedilol in either the US placebo-controlled trials in
302 subjects with mild-to-moderate heart failure, or in subjects with severe heart failure in the
303 COPERNICUS trial.

304 **Incidence greater than 1% to less than or equal to 3%**

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

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

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

309 *Gastrointestinal:* Melena, periodontitis.

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

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

314 *Musculoskeletal:* Muscle cramps.

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

316 *Psychiatric:* Somnolence.

317 *Reproductive, male:* Impotence.

318 *Special Senses:* Blurred vision.

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

320 Left Ventricular Dysfunction following Myocardial Infarction

321 The following information describes the safety experience in left ventricular dysfunction
322 following acute myocardial infarction with immediate-release carvedilol.

323 Carvedilol has been evaluated for safety in survivors of an acute myocardial infarction with left
324 ventricular dysfunction in the CAPRICORN trial which involved 969 subjects who received
325 carvedilol and 980 who received placebo. Approximately 75% of the subjects received carvedilol
326 for at least 6 months and 53% received carvedilol for at least 12 months. Subjects were treated
327 for an average of 12.9 months and 12.8 months with carvedilol and placebo, respectively.

328 The most common adverse events reported with carvedilol in the CAPRICORN trial were
329 consistent with the profile of the drug in the US heart failure trials and the COPERNICUS trial.

330 The only additional adverse events reported in CAPRICORN in greater than 3% of the subjects
331 and more commonly on carvedilol were dyspnea, anemia, and lung edema. The following
332 adverse events were reported with a frequency of greater than 1% but less than or equal to 3%
333 and more frequently with carvedilol: flu syndrome, cerebrovascular accident, peripheral vascular

334 disorder, hypotonia, depression, gastrointestinal pain, arthritis, and gout. The overall rates of
 335 discontinuations due to adverse events were similar in both groups of subjects. In this database,
 336 the only cause of discontinuation greater than 1%, and occurring more often on carvedilol was
 337 hypotension (1.5% on carvedilol, 0.2% on placebo).

338 Hypertension

339 COREG CR was evaluated for safety in an 8-week double-blind trial in 337 subjects with
 340 essential hypertension. The profile of adverse events observed with COREG CR was generally
 341 similar to that observed with immediate-release carvedilol. The overall rates of discontinuations
 342 due to adverse events were similar between COREG CR and placebo.

343

344 **Table 3. Adverse Events (%) Occurring More Frequently with COREG CR than with**
 345 **Placebo in Subjects with Hypertension (Incidence ≥1% in Subjects Treated with**
 346 **Carvedilol, Regardless of Causality)**

Adverse Event	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

347

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

350 Carvedilol has been evaluated for safety in hypertension in more than 2,193 subjects in US
 351 clinical trials and in 2,976 subjects in international clinical trials. Approximately 36% of the total
 352 treated population received carvedilol for at least 6 months. In general, carvedilol was well
 353 tolerated at doses up to 50 mg daily. Most adverse events reported during carvedilol therapy
 354 were of mild to moderate severity. In US controlled clinical trials directly comparing carvedilol
 355 monotherapy in doses up to 50 mg (n = 1,142) with placebo (n = 462), 4.9% of carvedilol
 356 subjects discontinued for adverse events versus 5.2% of placebo subjects. Although there was no
 357 overall difference in discontinuation rates, discontinuations were more common in the carvedilol
 358 group for postural hypotension (1% versus 0). The overall incidence of adverse events in US
 359 placebo-controlled trials was found to increase with increasing dose of carvedilol. For individual
 360 adverse events this could only be distinguished for dizziness, which increased in frequency from
 361 2% to 5% as total daily dose increased from 6.25 mg to 50 mg as single or divided doses.

362 Table 4 shows adverse events in US placebo-controlled clinical trials for hypertension that
 363 occurred with an incidence of greater than or equal to 1% regardless of causality, and that were
 364 more frequent in drug-treated subjects than placebo-treated subjects.

365
 366 **Table 4. Adverse Events (% Occurrence) in US Placebo-Controlled Hypertension Trials**
 367 **with Immediate-Release Carvedilol (Incidence ≥1% in Subjects Treated with Carvedilol,**
 368 **Regardless of Causality)***

Adverse Event	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	—

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

370
 371 Dyspnea and fatigue were also reported in these trials, but the rates were equal or greater in
 372 subjects who received placebo.

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

376 **Incidence greater than 0.1% to less than or equal to 1%**

377 *Cardiovascular:* Peripheral ischemia, tachycardia.

378 *Central and Peripheral Nervous System:* Hypokinesia.

379 *Gastrointestinal:* Bilirubinemia, increased hepatic enzymes (0.2% of hypertension patients and
 380 0.4% of heart failure patients were discontinued from therapy because of increases in hepatic
 381 enzymes) [see Adverse Reactions (6.2)].

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

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

385 *Reproductive, male:* Decreased libido.
386 *Skin and Appendages:* Pruritus, rash erythematous, rash maculopapular, rash psoriaform,
387 photosensitivity reaction.
388 *Special Senses:* Tinnitus.
389 *Urinary System:* Micturition frequency increased.
390 *Autonomic Nervous System:* Dry mouth, sweating increased.
391 *Metabolic and Nutritional:* Hypokalemia, hypertriglyceridemia.
392 *Hematologic:* Anemia, leukopenia.

393 The following events were reported in less than or equal to 0.1% of subjects and are potentially
394 important: complete AV block, bundle branch block, myocardial ischemia, cerebrovascular
395 disorder, convulsions, migraine, neuralgia, paresis, anaphylactoid reaction, alopecia, exfoliative
396 dermatitis, amnesia, GI hemorrhage, bronchospasm, pulmonary edema, decreased hearing,
397 respiratory alkalosis, increased BUN, decreased HDL, pancytopenia, and atypical lymphocytes.

398 **6.2 Laboratory Abnormalities**

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

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

412 **6.3 Postmarketing Experience**

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

417 Blood and Lymphatic System Disorders Aplastic anemia.

418 Immune System Disorders

419 Hypersensitivity (e.g., anaphylactic reactions, angioedema, urticaria).

420 Renal and Urinary Disorders

421 Urinary incontinence.

422 Respiratory, Thoracic and Mediastinal Disorders

423 Interstitial pneumonitis.

424 Skin and Subcutaneous Tissue Disorders

425 Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme.

426 **7 DRUG INTERACTIONS**

427 **7.1 CYP2D6 Inhibitors and Poor Metabolizers**

428 Interactions of carvedilol with potent inhibitors of CYP2D6 isoenzyme (such as quinidine,
429 fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would be
430 expected to increase blood levels of the R(+) enantiomer of carvedilol [*see Clinical*
431 *Pharmacology (12.3)*]. Retrospective analysis of side effects in clinical trials showed that poor
432 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from
433 vasodilating effects of the higher concentrations of the α -blocking R(+) enantiomer.

434 **7.2 Hypotensive Agents**

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

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

443 **7.3 Cyclosporine**

444 Modest increases in mean trough cyclosporine concentrations were observed following initiation
445 of carvedilol treatment in 21 renal transplant subjects suffering from chronic vascular rejection.
446 In about 30% of subjects, the dose of cyclosporine had to be reduced in order to maintain
447 cyclosporine concentrations within the therapeutic range, while in the remainder no adjustment
448 was needed. On the average for the group, the dose of cyclosporine was reduced about 20% in
449 these subjects. Due to wide interindividual variability in the dose adjustment required, it is
450 recommended that cyclosporine concentrations be monitored closely after initiation of carvedilol
451 therapy and that the dose of cyclosporine be adjusted as appropriate.

452 **7.4 Digitalis Glycosides**

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

458 **7.5 Inducers/Inhibitors of Hepatic Metabolism**

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

462 **7.6 Amiodarone**

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

470 **7.7 Calcium Channel Blockers**

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

475 **7.8 Insulin or Oral Hypoglycemics**

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

479 **7.9 Proton Pump Inhibitors**

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

482 **7.10 Anesthesia**

483 If treatment with COREG CR is to be continued perioperatively, particular care should be taken
484 when anesthetic agents that depress myocardial function, such as ether, cyclopropane, and
485 trichloroethylene, are used [see *Overdosage (10)*].

486 **8 USE IN SPECIFIC POPULATIONS**

487 **8.1 Pregnancy**

488 Pregnancy Category C. Studies performed in pregnant rats and rabbits given carvedilol revealed
489 increased post-implantation loss in rats at doses of 300 mg per kg per day (50 times the
490 maximum recommended human dose [MRHD] as mg per m²) and in rabbits at doses of 75 mg
491 per kg per day (25 times the MRHD as mg per m²). In the rats, there was also a decrease in fetal
492 body weight at the maternally toxic dose of 300 mg per kg per day (50 times the MRHD as mg
493 per m²), which was accompanied by an elevation in the frequency of fetuses with delayed
494 skeletal development (missing or stunted 13th rib). In rats the no-observed-effect level for
495 developmental toxicity was 60 mg per kg per day (10 times the MRHD as mg per m²); in rabbits
496 it was 15 mg per kg per day (5 times the MRHD as mg per m²). There are no adequate and
497 well-controlled studies in pregnant women. COREG CR should be used during pregnancy only if
498 the potential benefit justifies the potential risk to the fetus.

499 **8.3 Nursing Mothers**

500 It is not known whether this drug is excreted in human milk. Studies in rats have shown that
501 carvedilol and/or its metabolites (as well as other β -blockers) cross the placental barrier and are
502 excreted in breast milk. There was increased mortality at 1 week post partum in neonates from
503 rats treated with 60 mg per kg per day (10 times the MRHD as mg per m²) and above during the
504 last trimester through day 22 of lactation. Because many drugs are excreted in human milk and
505 because of the potential for serious adverse reactions in nursing infants from β -blockers,
506 especially bradycardia, a decision should be made whether to discontinue nursing or to
507 discontinue the drug, taking into account the importance of the drug to the mother. The effects of
508 other α - and β -blocking agents have included perinatal and neonatal distress.

509 **8.4 Pediatric Use**

510 Effectiveness of carvedilol in patients younger than 18 years has not been established.
511 In a double-blind trial, 161 children (mean age: 6 years; range: 2 months to 17 years; 45%
512 younger than 2 years) with chronic heart failure [NYHA class II-IV, left ventricular ejection
513 fraction less than 40% for children with a systemic left ventricle (LV), and moderate-severe
514 ventricular dysfunction qualitatively by echo for those with a systemic ventricle that was not an
515 LV] who were receiving standard background treatment were randomized to placebo or to 2 dose
516 levels of carvedilol. These dose levels produced placebo-corrected heart rate reduction of 4 to 6
517 heart beats per minute, indicative of β -blockade activity. Exposure appeared to be lower in
518 pediatric subjects than adults. After 8 months of follow-up, there was no significant effect of
519 treatment on clinical outcomes. Adverse reactions in this trial that occurred in greater than 10%
520 of subjects treated with immediate-release carvedilol and at twice the rate of placebo-treated
521 subjects included chest pain (17% versus 6%), dizziness (13% versus 2%), and dyspnea (11%
522 versus 0%).

523 **8.5 Geriatric Use**

524 The initial clinical trials of COREG CR in subjects with hypertension, heart failure, and left
525 ventricular dysfunction following myocardial infarction did not include sufficient numbers of
526 subjects aged 65 years or older to determine whether they respond differently from younger
527 patients.

528 A randomized trial (n = 405) comparing subjects with mild to severe heart failure switched to
529 COREG CR or maintained on immediate-release carvedilol included 220 subjects who were
530 aged 65 years or older. In this elderly subgroup, the combined incidence of dizziness,
531 hypotension, or syncope was 24% (18/75) in subjects switched from the highest dose of
532 immediate-release carvedilol (25 mg twice daily) to the highest dose of COREG CR (80 mg once
533 daily) compared with 11% (4/36) in subjects maintained on immediate-release carvedilol (25 mg
534 twice daily). When switching from the higher doses of immediate-release carvedilol to COREG
535 CR, a lower starting dose is recommended for elderly patients [*see Dosage and Administration*
536 (2.5)].

537 The following information is available for trials with immediate-release carvedilol. Of the
538 765 subjects with heart failure randomized to carvedilol in US clinical trials, 31% (235) were
539 aged 65 years or older, and 7.3% (56) were aged 75 years or older. Of the 1,156 subjects
540 randomized to carvedilol in a long-term, placebo-controlled trial in severe heart failure, 47%
541 (547) were aged 65 years or older, and 15% (174) were aged 75 years or older. Of 3,025 subjects
542 receiving carvedilol in heart failure trials worldwide, 42% were aged 65 years or older. Of the
543 975 subjects with myocardial infarction randomized to carvedilol in the CAPRICORN trial, 48%
544 (468) were aged 65 years or older, and 11% (111) were aged 75 years or older. Of the 2,065
545 hypertensive subjects in US clinical trials of efficacy or safety who were treated with carvedilol,
546 21% (436) were aged 65 years or older. Of 3,722 subjects receiving immediate-release carvedilol
547 in hypertension clinical trials conducted worldwide, 24% were aged 65 years or older.

548 With the exception of dizziness in hypertensive subjects (incidence 8.8% in the elderly versus
549 6% in younger subjects), no overall differences in the safety or effectiveness (see Figures 2 and
550 4) were observed between the older subjects and younger subjects in each of these populations.
551 Similarly, other reported clinical experience has not identified differences in responses between
552 the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled
553 out.

554 **10 OVERDOSAGE**

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

558 The patient should be placed in a supine position and, where necessary, kept under observation
559 and treated under intensive-care conditions. The following agents may be administered:

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

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

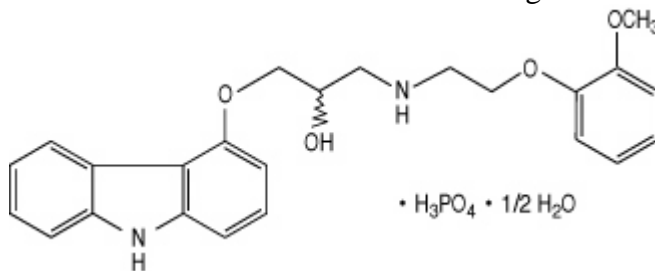
564 If peripheral vasodilation dominates, it may be necessary to administer adrenaline or
565 noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant
566 bradycardia, pacemaker therapy should be performed. For bronchospasm, β -sympathomimetics
567 (as aerosol or IV)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

569 NOTE: In the event of severe intoxication where there are symptoms of shock, treatment with
570 antidotes must be continued for a sufficiently long period of time consistent with the 7- to
571 10-hour half-life of carvedilol.

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

576 11 DESCRIPTION

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



580

581 Carvedilol phosphate is a white-to-almost white solid with a molecular weight of 513.5 (406.5
582 carvedilol free base) and a molecular formula of C₂₄H₂₆N₂O₄•H₃PO₄•1/2 H₂O.

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

589 12 CLINICAL PHARMACOLOGY

590 12.1 Mechanism of Action

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

594 12.2 Pharmacodynamics

595 Heart Failure and Left Ventricular Dysfunction following Myocardial Infarction

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

600 Hypertension

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

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

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

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

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

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

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

628 **12.3 Pharmacokinetics**

629 Absorption

630 Carvedilol is rapidly and extensively absorbed following oral administration of immediate-
631 release carvedilol tablets, with an absolute bioavailability of approximately 25% to 35% due to a
632 significant degree of first-pass metabolism. COREG CR extended-release capsules have
633 approximately 85% of the bioavailability of immediate-release carvedilol tablets. For
634 corresponding dosages [*see Dosage and Administration (2)*], the exposure (AUC, C_{\max} , trough
635 concentration) of carvedilol as COREG CR extended-release capsules is equivalent to those of
636 immediate-release carvedilol tablets when both are administered with food. The absorption of
637 carvedilol from COREG CR is slower and more prolonged compared with the immediate-release
638 carvedilol tablet with peak concentrations achieved approximately 5 hours after administration.
639 Plasma concentrations of carvedilol increase in a dose-proportional manner over the dosage
640 range of COREG CR 10 to 80 mg. Within-subject and between-subject variability for AUC and
641 C_{\max} is similar for COREG CR and immediate-release carvedilol.

642 *Effect of Food:* Administration of COREG CR with a high-fat meal resulted in increases
643 (~20%) in AUC and C_{\max} compared with COREG CR administered with a standard meal.
644 Decreases in AUC (27%) and C_{\max} (43%) were observed when COREG CR was administered in
645 the fasted state compared with administration after a standard meal. COREG CR should be taken
646 with food.

647 In a trial with adult subjects, sprinkling the contents of the COREG CR capsule on applesauce
648 did not appear to have a significant effect on overall exposure (AUC) compared with
649 administration of the intact capsule following a standard meal, but did result in a decrease in C_{\max}
650 (18%).

651 Distribution

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

656 Metabolism and Excretion

657 Carvedilol is extensively metabolized. Following oral administration of radiolabelled carvedilol
658 to healthy volunteers, carvedilol accounted for only about 7% of the total radioactivity in plasma
659 as measured by AUC. Less than 2% of the dose was excreted unchanged in the urine. Carvedilol
660 is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative
661 metabolites are further metabolized by conjugation via glucuronidation and sulfation. The

662 metabolites of carvedilol are excreted primarily via the bile into the feces. Demethylation and
663 hydroxylation at the phenol ring produce 3 active metabolites with β -receptor blocking activity.
664 Based on preclinical studies, the 4'-hydroxyphenyl metabolite is approximately 13 times more
665 potent than carvedilol for β -blockade.

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

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

673 The primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-carvedilol in
674 human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19,
675 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and 5'-hydroxylation of
676 carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be of primary
677 importance in the O-methylation pathway of S(-)-carvedilol.

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

685 **12.4 Specific Populations**

686 Heart Failure

687 Following administration of immediate-release carvedilol tablets, steady-state plasma
688 concentrations of carvedilol and its enantiomers increased proportionally over the dose range in
689 subjects with heart failure. Compared with healthy subjects, subjects with heart failure had
690 increased mean AUC and C_{\max} values for carvedilol and its enantiomers, with up to 50% to
691 100% higher values observed in 6 subjects with NYHA class IV heart failure. The mean apparent
692 terminal elimination half-life for carvedilol was similar to that observed in healthy subjects.

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

697 Hypertension

698 For corresponding dose levels [see *Dosage and Administration (2)*], the pharmacokinetics
699 (AUC, C_{max}, and trough concentrations) observed with administration of COREG CR were
700 equivalent (±20%) to those observed with immediate-release carvedilol tablets following repeat
701 dosing in subjects with essential hypertension.

702 Geriatric

703 Plasma levels of carvedilol average about 50% higher in the elderly compared with young
704 subjects after administration of immediate-release carvedilol.

705 Hepatic Impairment

706 No trials have been performed with COREG CR in subjects with hepatic impairment. Compared
707 with healthy subjects, subjects with severe liver impairment (cirrhosis) exhibit a 4- to 7-fold
708 increase in carvedilol levels. Carvedilol is contraindicated in patients with severe liver
709 impairment.

710 Renal Impairment

711 No trials have been performed with COREG CR in subjects with renal impairment. Although
712 carvedilol is metabolized primarily by the liver, plasma concentrations of carvedilol have been
713 reported to be increased in patients with renal impairment after dosing with immediate-release
714 carvedilol. Based on mean AUC data, approximately 40% to 50% higher plasma concentrations
715 of carvedilol were observed in hypertensive subjects with moderate to severe renal impairment
716 compared with a control group of hypertensive subjects with normal renal function. However,
717 the ranges of AUC values were similar for both groups. Changes in mean peak plasma levels
718 were less pronounced, approximately 12% to 26% higher in subjects with impaired renal
719 function.

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

722 **12.5 Drug-Drug Interactions**

723 Since carvedilol undergoes substantial oxidative metabolism, the metabolism and
724 pharmacokinetics of carvedilol may be affected by induction or inhibition of cytochrome P450
725 enzymes.

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

727 Amiodarone

728 In a pharmacokinetic trial conducted in 106 Japanese subjects with heart failure,
729 coadministration of small loading and maintenance doses of amiodarone with carvedilol resulted
730 in at least a 2-fold increase in the steady-state trough concentrations of S(-)-carvedilol [see *Drug*
731 *Interactions (7.6)*].

732 Cimetidine

733 In a pharmacokinetic trial conducted in 10 healthy male subjects, cimetidine (1,000 mg per day)
734 increased the steady-state AUC of carvedilol by 30% with no change in C_{max} [see *Drug*
735 *Interactions (7.5)*].

736 Digoxin

737 Following concomitant administration of carvedilol (25 mg once daily) and digoxin (0.25 mg
738 once daily) for 14 days, steady-state AUC and trough concentrations of digoxin were increased
739 by 14% and 16%, respectively, in 12 hypertensive subjects [see *Drug Interactions (7.4)*].

740 Glyburide

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

744 Hydrochlorothiazide

745 A single oral dose of carvedilol 25 mg did not alter the pharmacokinetics of a single oral dose of
746 hydrochlorothiazide 25 mg in 12 subjects with hypertension. Likewise, hydrochlorothiazide had
747 no effect on the pharmacokinetics of carvedilol.

748 Rifampin

749 In a pharmacokinetic trial conducted in 8 healthy male subjects, rifampin (600 mg daily for
750 12 days) decreased the AUC and C_{max} of carvedilol by about 70% [see *Drug Interactions (7.5)*].

751 Torsemide

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

755 Warfarin

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

759 **13 NONCLINICAL TOXICOLOGY**

760 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

761 In 2-year studies conducted in rats given carvedilol at doses up to 75 mg per kg per day (12 times
762 the MRHD when compared on a mg per m^2 basis) or in mice given up to 200 mg per kg per day
763 (16 times the MRHD on a mg per m^2 basis), carvedilol had no carcinogenic effect.

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

767 At doses greater than or equal to 200 mg per kg per day (greater than or equal to 32 times the
768 MRHD as mg per m²) carvedilol was toxic to adult rats (sedation, reduced weight gain) and was
769 associated with a reduced number of successful matings, prolonged mating time, significantly
770 fewer corpora lutea and implants per dam, and complete resorption of 18% of the litters. The
771 no-observed-effect dose level for overt toxicity and impairment of fertility was 60 mg per kg per
772 day (10 times the MRHD as mg per m²).

773 **14 CLINICAL STUDIES**

774 Support for the use of COREG CR extended-release capsules for the treatment of mild-to-severe
775 heart failure and for patients with left ventricular dysfunction following myocardial infarction is
776 based on the equivalence of pharmacokinetic and pharmacodynamic (β_1 -blockade) parameters
777 between COREG CR and immediate-release carvedilol [*see Clinical Pharmacology (12.2,*
778 *12.3)*].

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

781 **14.1 Heart Failure**

782 A total of 6,975 subjects with mild-to-severe heart failure were evaluated in placebo-controlled
783 and active-controlled trials of immediate-release carvedilol.

784 Mild-to-Moderate Heart Failure

785 Carvedilol was studied in 5 multicenter, placebo-controlled trials, and in 1 active-controlled trial
786 (COMET trial) involving subjects with mild-to-moderate heart failure.

787 Four US multicenter, double-blind, placebo-controlled trials enrolled 1,094 subjects (696
788 randomized to carvedilol) with NYHA class II-III heart failure and ejection fraction less than or
789 equal to 0.35. The vast majority were on digitalis, diuretics, and an ACE inhibitor at trial entry.
790 Subjects were assigned to the trials based upon exercise ability. An Australia-New Zealand
791 double-blind, placebo-controlled trial enrolled 415 subjects (half randomized to
792 immediate-release carvedilol) with less severe heart failure. All protocols excluded subjects
793 expected to undergo cardiac transplantation during the 7.5 to 15 months of double-blind
794 follow-up. All randomized subjects had tolerated a 2-week course on immediate-release
795 carvedilol 6.25 mg twice daily.

796 In each trial, there was a primary end point, either progression of heart failure (1 US trial) or
797 exercise tolerance (2 US trials meeting enrollment goals and the Australia-New Zealand trial).
798 There were many secondary end points specified in these trials, including NYHA classification,
799 patient and physician global assessments, and cardiovascular hospitalization. Other analyses not
800 prospectively planned included the sum of deaths and total cardiovascular hospitalizations. In
801 situations where the primary end points of a trial do not show a significant benefit of treatment,
802 assignment of significance values to the other results is complex, and such values need to be
803 interpreted cautiously.

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

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

809 In the Australia-New Zealand trial, death and total hospitalizations were reduced by about 25%
810 over 18 to 24 months. In the 3 largest US trials, death and total hospitalizations were reduced by
811 19%, 39%, and 49%, nominally statistically significant in the last 2 trials. The Australia-New
812 Zealand results were statistically borderline.

813 **Functional Measures:** None of the multicenter trials had NYHA classification as a primary end
814 point, but all such trials had it as a secondary end point. There was at least a trend toward
815 improvement in NYHA class in all trials. Exercise tolerance was the primary end point in
816 3 trials; in none was a statistically significant effect found.

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

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

822 The COMET Trial

823 In this double-blind trial, 3,029 subjects with NYHA class II-IV heart failure (left ventricular
824 ejection fraction less than or equal to 35%) were randomized to receive either carvedilol (target
825 dose: 25 mg twice daily) or immediate-release metoprolol tartrate (target dose: 50 mg twice
826 daily). The mean age of the subjects was approximately 62 years, 80% were males, and the mean
827 left ventricular ejection fraction at baseline was 26%. Approximately 96% of the subjects had
828 NYHA class II or III heart failure. Concomitant treatment included diuretics (99%), ACE
829 inhibitors (91%), digitalis (59%), aldosterone antagonists (11%), and "statin" lipid-lowering
830 agents (21%). The mean duration of follow-up was 4.8 years. The mean dose of carvedilol was
831 42 mg per day.

832 The trial had 2 primary end points: all-cause mortality and the composite of death plus
833 hospitalization for any reason. The results of COMET are presented in Table 5 below. All-cause
834 mortality carried most of the statistical weight and was the primary determinant of the trial size.
835 All-cause mortality was 34% in the subjects treated with carvedilol and was 40% in the
836 immediate-release metoprolol group ($P = 0.0017$; hazard ratio = 0.83, 95% CI: 0.74 to 0.93). The
837 effect on mortality was primarily due to a reduction in cardiovascular death. The difference
838 between the 2 groups with respect to the composite end point was not significant ($P = 0.122$).
839 The estimated mean survival was 8.0 years with carvedilol and 6.6 years with immediate-release
840 metoprolol.

841

842 **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

843

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

849 **Severe Heart Failure (COPERNICUS)**

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

857 The primary end point of the trial was all-cause mortality, but cause-specific mortality and the
 858 risk of death or hospitalization (total, cardiovascular [CV], or heart failure [HF]) were also
 859 examined. The developing trial data were followed by a data monitoring committee, and
 860 mortality analyses were adjusted for these multiple looks. The trial was stopped after a median
 861 follow-up of 10 months because of an observed 35% reduction in mortality (from 19.7% per
 862 patient-year on placebo to 12.8% on carvedilol, hazard ratio 0.65, 95% CI: 0.52 to 0.81,
 863 $P = 0.0014$, adjusted) (see Figure 1). The results of COPERNICUS are shown in Table 6.

864

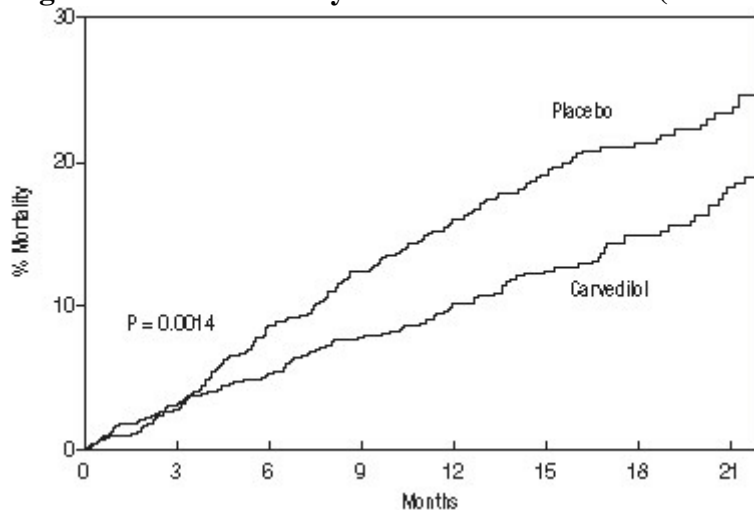
865 **Table 6. Results of COPERNICUS Trial in Subjects with Severe Heart Failure**

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

866 Cardiovascular = CV; Heart failure = HF.

867

868 **Figure 1. Survival Analysis for COPERNICUS (Intent-to-Treat)**



869

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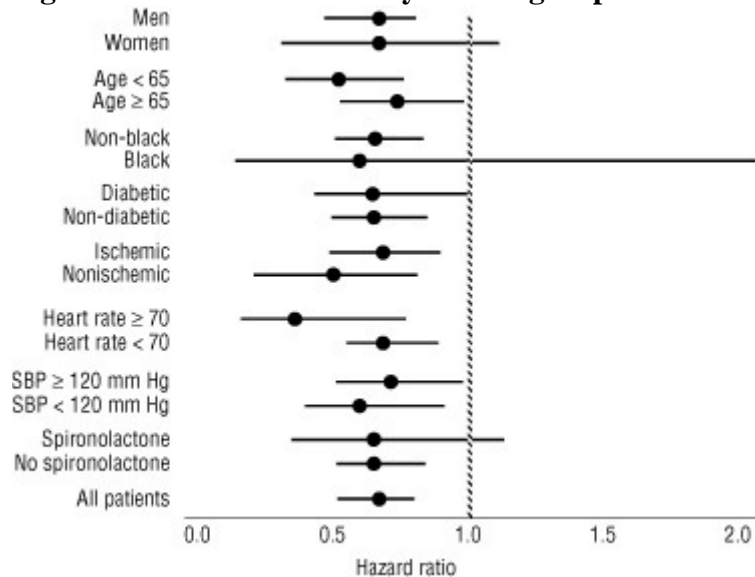
871 The effect on mortality was principally the result of a reduction in the rate of sudden death
872 among subjects without worsening heart failure.

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

878 The protocol also specified that hospitalizations would be assessed. Fewer subjects on
879 immediate-release carvedilol than on placebo were hospitalized for any reason (372 versus 432,
880 $P = 0.0029$), for cardiovascular reasons (246 versus 314, $P = 0.0003$), or for worsening heart
881 failure (198 versus 268, $P = 0.0001$).

882 Immediate-release carvedilol had a consistent and beneficial effect on all-cause mortality as well
 883 as the combined end points of all-cause mortality plus hospitalization (total, CV, or for heart
 884 failure) in the overall trial population and in all subgroups examined, including men and women,
 885 elderly and non-elderly, blacks and non-blacks, and diabetics and non-diabetics (see Figure 2).
 886

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



888
889

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

893 **14.2 Left Ventricular Dysfunction following Myocardial Infarction**

894 CAPRICORN was a double-blind trial comparing carvedilol and placebo in 1,959 subjects with a
 895 recent myocardial infarction (within 21 days) and left ventricular ejection fraction of less than or
 896 equal to 40%, with (47%) or without symptoms of heart failure. Subjects given carvedilol
 897 received 6.25 mg twice daily, titrated as tolerated to 25 mg twice daily. Subjects had to have a
 898 systolic blood pressure greater than 90 mm Hg, a sitting heart rate greater than 60 beats per
 899 minute, and no contraindication to β -blocker use. Treatment of the index infarction included
 900 aspirin (85%), IV or oral β -blockers (37%), nitrates (73%), heparin (64%), thrombolytics (40%),
 901 and acute angioplasty (12%). Background treatment included ACE inhibitors or angiotensin
 902 receptor blockers (97%), anticoagulants (20%), lipid-lowering agents (23%), and diuretics
 903 (34%). Baseline population characteristics included an average age of 63 years, 74% male, 95%
 904 Caucasian, mean blood pressure 121/74 mm Hg, 22% with diabetes, and 54% with a history of
 905 hypertension. Mean dosage achieved of carvedilol was 20 mg twice daily; mean duration of
 906 follow-up was 15 months.

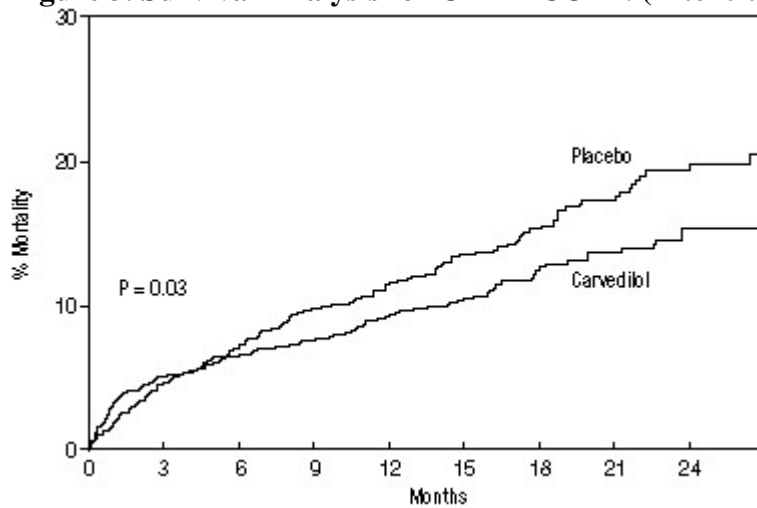
907 All-cause mortality was 15% in the placebo group and 12% in the carvedilol group, indicating a
 908 23% risk reduction in subjects treated with carvedilol (95% CI: 2% to 40%, $P = 0.03$), as shown

909 in Figure 3. The effects on mortality in various subgroups are shown in Figure 4. Nearly all
 910 deaths were cardiovascular (which were reduced by 25% by carvedilol), and most of these deaths
 911 were sudden or related to pump failure (both types of death were reduced by carvedilol). Another
 912 trial end point, total mortality and all-cause hospitalization, did not show a significant
 913 improvement.

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

918

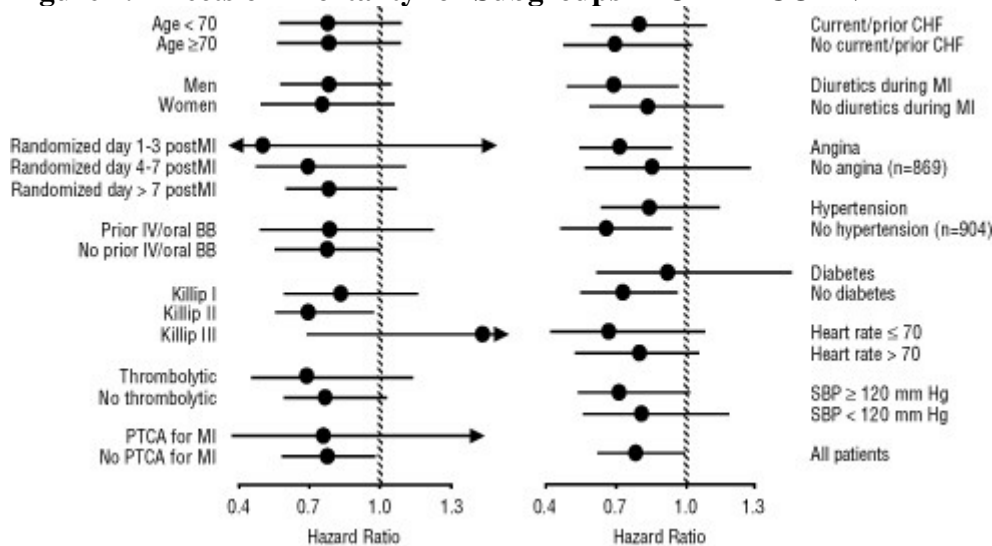
919 **Figure 3. Survival Analysis for CAPRICORN (Intent-to-Treat)**



920

921

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



923

924

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

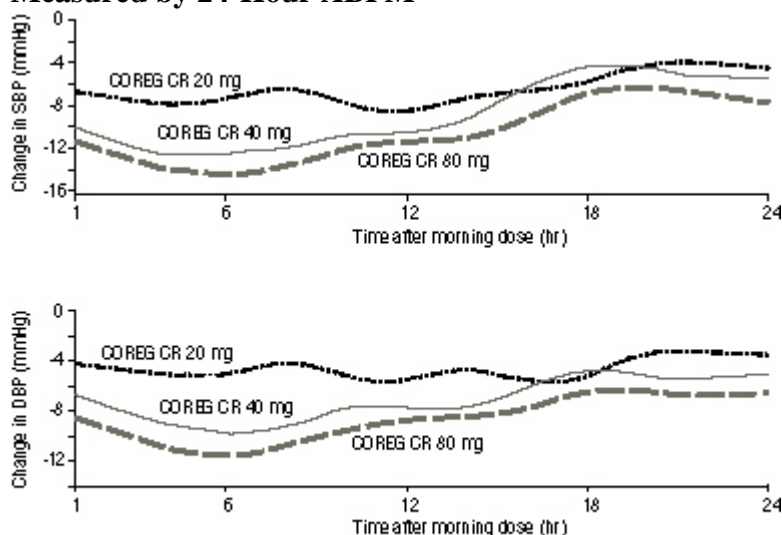
928 14.3 Hypertension

929 A double-blind, randomized, placebo-controlled, 8-week trial evaluated the blood pressure-
930 lowering effects of COREG CR 20 mg, 40 mg, and 80 mg once daily in 338 subjects with
931 essential hypertension (sitting diastolic blood pressure [DBP] greater than or equal to 90 and less
932 than or equal to 109 mm Hg). Of 337 evaluable subjects, a total of 273 subjects (81%) completed
933 the trial. Of the 64 (19%) subjects withdrawn from the trial, 10 (3%) were due to adverse events,
934 10 (3%) were due to lack of efficacy; the remaining 44 (13%) withdrew for other reasons. The
935 mean age of the subjects was approximately 53 years, 66% were male, and the mean sitting
936 systolic blood pressure (SBP) and DBP at baseline were 150 mm Hg and 99 mm Hg,
937 respectively. Dose titration occurred at 2-week intervals.

938 Statistically significant reductions in blood pressure as measured by 24-hour ambulatory blood
939 pressure monitoring (ABPM) were observed with each dose of COREG CR compared with
940 placebo. Placebo-subtracted mean changes from baseline in mean SBP/DBP were
941 -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
942 80 mg, respectively. Placebo-subtracted mean changes from baseline in mean trough (average of
943 hours 20 to 24) SBP/DBP were -3.3/-2.8 mm Hg, -4.9/-5.2 mm Hg, and -8.4/-7.4 mm Hg for
944 COREG CR 20 mg, 40 mg, and 80 mg, respectively. The placebo-corrected trough to peak (3 to
945 7 h) ratio was approximately 0.6 for COREG CR 80 mg. In this trial, assessments of 24-hour
946 ABPM monitoring demonstrated statistically significant blood pressure reductions with
947 COREG CR throughout the dosing period (Figure 5).

948

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



951

Lines smoothed using locally weighted regression smoothing methodology.

952

953 Immediate-release carvedilol was studied in 2 placebo-controlled trials that utilized twice-daily
954 dosing, at total daily doses of 12.5 to 50 mg. In these and other trials, the starting dose did not
955 exceed 12.5 mg. At 50 mg per day, COREG reduced sitting trough (12-hour) blood pressure by
956 about 9/5.5 mm Hg; at 25 mg per day the effect was about 7.5/3.5 mm Hg. Comparisons of
957 trough-to-peak blood pressure showed a trough-to-peak ratio for blood pressure response of
958 about 65%. Heart rate fell by about 7.5 beats per minute at 50 mg per day. In general, as is true
959 for other β -blockers, responses were smaller in black than non-black subjects. There were no
960 age- or gender-related differences in response. The dose-related blood pressure response was
961 accompanied by a dose-related increase in adverse effects [see *Adverse Reactions (6)*].

962 **14.4 Hypertension with Type 2 Diabetes Mellitus**

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

969 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

- 971 • 10 mg – white and green capsule shell printed with “GSK COREG CR” and “10 mg”
- 972 • 20 mg – white and yellow capsule shell printed with “GSK COREG CR” and “20 mg”
- 973 • 40 mg – yellow and green capsule shell printed with “GSK COREG CR” and “40 mg”
- 974 • 80 mg – white capsule shell printed with “GSK COREG CR” and “80 mg”

975

- 976 • 10 mg bottles of 30: NDC 0007-3370-13
- 977 • 20 mg bottles of 30: NDC 0007-3371-13
- 978 • 40 mg bottles of 30: NDC 0007-3372-13
- 979 • 80 mg bottles of 30: NDC 0007-3373-13

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

982 **17 PATIENT COUNSELING INFORMATION**

983 *Advise the patient to read the FDA-approved patient labeling (Patient Information).*

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

- 985 • Patients should not interrupt or discontinue using COREG CR without a physician’s advice.
- 986 • Patients with heart failure should consult their physician if they experience signs or
- 987 symptoms of worsening heart failure such as weight gain or increasing shortness of breath.
- 988 • Patients may experience a drop in blood pressure when standing, resulting in dizziness and,
- 989 rarely, fainting. Patients should sit or lie down when these symptoms of lowered blood
- 990 pressure occur.
- 991 • If experiencing dizziness or fatigue, patients should avoid driving or hazardous tasks.
- 992 • Patients should consult a physician if they experience dizziness or faintness, in case the
- 993 dosage should be adjusted.
- 994 • Patients should not crush or chew COREG CR capsules.
- 995 • Patients should take COREG CR with food.
- 996 • Diabetic patients should report any changes in blood sugar levels to their physician.
- 997 • Contact lens wearers may experience decreased lacrimation.
- 998

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 1001 companies. The maker of this brand is not affiliated with and does not endorse the GSK group of
 1002 companies or its products.

1003
 1004



1005
 1006 GlaxoSmithKline
 1007 Research Triangle Park, NC 27709

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1010
 1011
 1012 CCR:XXPI

1013 **PHARMACIST—DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT**

1014 -----
1015 **PATIENT INFORMATION**

1016 **COREG CR® (Co-REG)**

1017 **(carvedilol phosphate)**

1018 **Extended-release Capsules**

1019
1020 Read the Patient Information that comes with COREG CR before you start taking it
1021 and each time you get a refill. There may be new information. This information
1022 does not take the place of talking with your doctor about your medical condition or
1023 your treatment. If you have any questions about COREG CR, ask your doctor or
1024 pharmacist.

1025
1026 **What is the most important information I should know about COREG CR?**

1027 **It is important for you to take your medicine every day as directed by your**
1028 **doctor. If you stop taking COREG CR suddenly, you could have chest pain**
1029 **and a heart attack. If your doctor decides that you should stop taking**
1030 **COREG CR, your doctor may slowly lower your dose over time before**
1031 **stopping it completely.**

1032
1033 **What is COREG CR?**

1034 COREG CR is a prescription medicine that belongs to a group of medicines called
1035 "beta-blockers". COREG CR is used, often with other medicines, for the following
1036 conditions:

- 1037 • to treat patients with certain types of heart failure
1038 • to treat patients who had a heart attack that worsened how well the heart
1039 pumps
1040 • to treat patients with high blood pressure (hypertension)

1041
1042 COREG CR is not approved for use in children under 18 years of age.

1043
1044 **Who should not take COREG CR?**

1045 Do not take COREG CR if you:

- 1046 • have severe heart failure and require certain intravenous medicines that help
1047 support circulation.
1048 • have asthma or other breathing problems.
1049 • have a slow heartbeat or certain conditions that cause your heart to skip a beat
1050 (irregular heartbeat).
1051 • have liver problems.
1052 • are allergic to any of the ingredients in COREG CR. See **"What are the**
1053 **ingredients in COREG CR?"**

1054

1055 **What should I tell my doctor before taking COREG CR?**

1056 Tell your doctor about all of your medical conditions, including if you:

- 1057 • have asthma or other lung problems (such as bronchitis or emphysema).
- 1058 • have problems with blood flow in your feet and legs (peripheral vascular
- 1059 disease). COREG CR can make some of your symptoms worse.
- 1060 • have diabetes.
- 1061 • have thyroid problems.
- 1062 • have a condition called pheochromocytoma.
- 1063 • have had severe allergic reactions.
- 1064 • are scheduled for surgery and will be given anesthetic agents.
- 1065 • are scheduled for cataract surgery and have taken or are currently taking
- 1066 COREG CR.
- 1067 • are pregnant or trying to become pregnant. It is not known if COREG CR is safe
- 1068 for your unborn baby. You and your doctor should talk about the best way to
- 1069 control your high blood pressure during pregnancy.
- 1070 • are breastfeeding. It is not known if COREG CR passes into your breast milk.
- 1071 You should not breastfeed while using COREG CR.

1072

1073 **Tell your doctor about all of the medicines you take** including prescription and
1074 non-prescription medicines, vitamins, and herbal supplements. COREG CR and
1075 certain other medicines can affect each other and cause serious side effects.
1076 COREG CR may affect the way other medicines work. Also, other medicines may
1077 affect how well COREG CR works.

1078

1079 Know the medicines you take. Keep a list of your medicines and show it to your
1080 doctor and pharmacist before you start a new medicine.

1081

1082 **How should I take COREG CR?**

- 1083 • Take COREG CR exactly as prescribed. Take COREG CR **one** time each day with
- 1084 food. **It is important that you take COREG CR only one time each day.** To
- 1085 lessen possible side effects, your doctor might begin with a low dose and then
- 1086 slowly increase the dose.
- 1087 • Swallow COREG CR capsules whole. Do not chew or crush COREG CR capsules.
- 1088 • If you have trouble swallowing COREG CR whole:
 - 1089 • The capsule may be carefully opened and the beads sprinkled over a spoonful
 - 1090 of applesauce which should be eaten right away. The applesauce should not
 - 1091 be warm.
 - 1092 • Do not sprinkle beads on foods other than applesauce.
- 1093 • **Do not stop taking COREG CR and do not change the amount of**
- 1094 **COREG CR you take without talking to your doctor.**

- 1095 • If you miss a dose of COREG CR, take your dose as soon as you remember,
1096 unless it is time to take your next dose. Take your next dose at the usual time.
1097 Do not take 2 doses at the same time.
- 1098 • If you take too much COREG CR, call your doctor or poison control center right
1099 away.

1100

1101 **What should I avoid while taking COREG CR?**

1102 COREG CR can cause you to feel dizzy, tired, or faint. Do not drive a car, use
1103 machinery, or do anything that needs you to be alert if you have these symptoms.

1104

1105 **What are possible side effects of COREG CR?**

1106 Serious side effects of COREG CR include:

- 1107 • **chest pain and heart attack if you suddenly stop taking COREG CR.** See
1108 **“What is the most important information I should know about COREG
1109 CR?”**
- 1110 • **slow heart beat.**
- 1111 • **low blood pressure (which may cause dizziness or fainting when you
1112 stand up).** If these happen, sit or lie down, and tell your doctor right away.
- 1113 • **worsening heart failure.** Tell your doctor right away if you have signs and
1114 symptoms that your heart failure may be worse, such as weight gain or
1115 increased shortness of breath.
- 1116 • **changes in your blood sugar. If you have diabetes, tell your doctor if
1117 you have any changes in your blood sugar levels.**
- 1118 • masking (hiding) the symptoms of low blood sugar, especially a fast heartbeat.
- 1119 • **new or worsening symptoms of peripheral vascular disease.**
- 1120 • leg pain that happens when you walk, but goes away when you rest
- 1121 • no feeling (numbness) in your legs or feet while you are resting
- 1122 • cold legs or feet
- 1123 • masking the symptoms of hyperthyroidism (overactive thyroid), such as a fast
1124 heartbeat.
- 1125 • **worsening of severe allergic reactions.** Medicines to treat a severe allergic
1126 reaction may not work as well while you are taking COREG CR.
- 1127 • **rare but serious allergic reactions** (including hives or swelling of the face,
1128 lips, tongue, and/or throat that may cause difficulty in breathing or swallowing)
1129 have happened in patients who were on COREG or COREG CR. These reactions
1130 can be life-threatening. In some cases, these reactions happened in patients
1131 who had been on COREG before taking COREG CR.

1132

1133 Common side effects of COREG CR include shortness of breath, weight gain,
1134 diarrhea, and tiredness. If you wear contact lenses, you may have fewer tears or
1135 dry eyes that can become bothersome.

1136
1137 Call your doctor if you have any side effects that bother you or don't go away.

1138
1139 Call your doctor for medical advice about side effects. You may report side effects
1140 to FDA at 1-800-FDA-1088.

1141
1142 **How should I store COREG CR?**

1143 Store COREG CR at less than 86°F (30°C).
1144 Safely throw away COREG CR that is out of date or no longer needed.

1145 **Keep COREG CR and all medicines out of the reach of children.**

1146
1147 **General information about COREG CR**

1148 Medicines are sometimes prescribed for conditions other than those described in
1149 patient information leaflets. Do not use COREG CR for a condition for which it was
1150 not prescribed. Do not give COREG CR to other people, even if they have the same
1151 symptoms you have. It may harm them.

1152
1153 This leaflet summarizes the most important information about COREG CR. If you
1154 would like more information, talk with your doctor. You can ask your doctor or
1155 pharmacist for information about COREG CR that is written for healthcare
1156 professionals. You can also find out more about COREG CR by visiting the website
1157 www.COREGCR.com or calling 1-888-825-5249. This call is free.

1158
1159 **What are the ingredients in COREG CR?**

1160 Active ingredient: carvedilol phosphate
1161 Inactive ingredients: crospovidone, hydrogenated castor oil, hydrogenated
1162 vegetable oil, magnesium stearate, methacrylic acid copolymers, microcrystalline
1163 cellulose, and povidone
1164 COREG CR capsules come in the following strengths: 10 mg, 20 mg, 40 mg, 80 mg.

1165
1166 **What is high blood pressure (hypertension)?**

1167 Blood pressure is the force of blood in your blood vessels when your heart beats
1168 and when your heart rests. You have high blood pressure when the force is too
1169 much. High blood pressure makes the heart work harder to pump blood through the
1170 body and causes damage to blood vessels. COREG CR can help your blood vessels
1171 relax so your blood pressure is lower. Medicines that lower blood pressure may
1172 lower your chance of having a stroke or heart attack.

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