

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

-----**RECENT MAJOR CHANGES**-----

Warnings and Precautions, Major Surgery (5.9)	October 2010
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-----**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, 20, 40, 80 mg (3)

-----**CONTRAINDICATIONS**-----

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

-----**WARNINGS AND PRECAUTIONS**-----

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

-----**ADVERSE REACTIONS**-----

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

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

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

-----**DRUG INTERACTIONS**-----

- CYP P450 2D6 enzyme inhibitors may increase and rifampin may decrease carvedilol levels. (7.1, 7.5)
- Hypotensive agents (e.g., reserpine, MAO inhibitors, clonidine) may increase the risk of hypotension and/or severe bradycardia. (7.2)
- Cyclosporine or digoxin levels may increase. (7.3, 7.4)
- Both digitalis glycosides and β -blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. (7.4)

- Amiodarone may increase carvedilol levels resulting in further slowing of the heart rate or cardiac conduction. (7.6)
- Verapamil- or diltiazem-type calcium channel blockers may affect ECG and/or blood pressure. (7.7)
- Insulin and oral hypoglycemics action may be enhanced. (7.8)

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

Revised: November 2010
CCR:11PI

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68 **1 INDICATIONS AND USAGE**

69 **1.1 Heart Failure**

70 COREG CR is indicated for the treatment of mild-to-severe chronic heart failure of
71 ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitors, and
72 digitalis, to increase survival and, also, to reduce the risk of hospitalization [see *Clinical Studies*
73 (14.1)].

74 **1.2 Left Ventricular Dysfunction Following Myocardial Infarction**

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

78 **1.3 Hypertension**

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

82 **2 DOSAGE AND ADMINISTRATION**

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

87

88 **Table 1. Dosing Conversion**

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

* 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.

89

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

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

98 **2.1 Heart Failure**

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

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

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

115 The dose of COREG CR should be reduced if patients experience bradycardia (heart rate
116 <55 beats/minute).

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

120 **2.2 Left Ventricular Dysfunction Following Myocardial Infarction**

121 DOSAGE MUST BE INDIVIDUALIZED AND MONITORED DURING
122 UP-TITRATION. Treatment with COREG CR may be started as an inpatient or outpatient and
123 should be started after the patient is hemodynamically stable and fluid retention has been
124 minimized. It is recommended that COREG CR be started at 20 mg once daily and increased
125 after 3 to 10 days, based on tolerability, to 40 mg once daily, then again to the target dose of
126 80 mg once daily. A lower starting dose may be used (10 mg once daily) and/or the rate of
127 up-titration may be slowed if clinically indicated (e.g., due to low blood pressure or heart rate, or
128 fluid retention). Patients should be maintained on lower doses if higher doses are not tolerated.
129 The recommended dosing regimen need not be altered in patients who received treatment with an
130 IV or oral β -blocker during the acute phase of the myocardial infarction.

131 **2.3 Hypertension**

132 DOSAGE MUST BE INDIVIDUALIZED. The recommended starting dose of
133 COREG CR is 20 mg once daily. If this dose is tolerated, using standing systolic pressure
134 measured about one hour after dosing as a guide, the dose should be maintained for 7 to 14 days,
135 and then increased to 40 mg once daily if needed, based on trough blood pressure, again using
136 standing systolic pressure one hour after dosing as a guide for tolerance. This dose should also be
137 maintained for 7 to 14 days and can then be adjusted upward to 80 mg once daily if tolerated and
138 needed. Although not specifically studied, it is anticipated the full antihypertensive effect of

139 COREG CR would be seen within 7 to 14 days as had been demonstrated with
140 immediate-release carvedilol. Total daily dose should not exceed 80 mg.

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

143 **2.4 Hepatic Impairment**

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

146 **2.5 Geriatric Use**

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

153 **3 DOSAGE FORMS AND STRENGTHS**

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

- 156 • 10 mg – white and green capsule shell printed with GSK COREG CR and 10 mg
- 157 • 20 mg – white and yellow capsule shell printed with GSK COREG CR and 20 mg
- 158 • 40 mg – yellow and green capsule shell printed with GSK COREG CR and 40 mg
- 159 • 80 mg – white capsule shell printed with GSK COREG CR and 80 mg

160 **4 CONTRAINDICATIONS**

161 COREG CR is contraindicated in the following conditions:

- 162 • Bronchial asthma or related bronchospastic conditions. Deaths from status asthmaticus have
163 been reported following single doses of immediate-release carvedilol.
- 164 • Second- or third-degree AV block
- 165 • Sick sinus syndrome
- 166 • Severe bradycardia (unless a permanent pacemaker is in place)
- 167 • Patients with cardiogenic shock or who have decompensated heart failure requiring the use of
168 intravenous inotropic therapy. Such patients should first be weaned from intravenous therapy
169 before initiating COREG CR.
- 170 • Patients with severe hepatic impairment
- 171 • Patients with a history of a serious hypersensitivity reaction (e.g., Stevens-Johnson
172 syndrome, anaphylactic reaction, angioedema) to carvedilol or any of the components of
173 COREG CR.

174 **5 WARNINGS AND PRECAUTIONS**

175 In clinical trials of COREG CR in patients with hypertension (338 subjects) and in
176 patients with left ventricular dysfunction following a myocardial infarction or heart failure
177 (187 subjects), the profile of adverse events observed with carvedilol phosphate was generally

178 similar to that observed with the administration of immediate-release carvedilol. Therefore, the
179 information included within this section is based on data from controlled clinical trials with
180 COREG CR as well as immediate-release carvedilol.

181 **5.1 Cessation of Therapy**

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

194 **5.2 Bradycardia**

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

202 **5.3 Hypotension**

203 In clinical trials of primarily mild-to-moderate heart failure with immediate-release
204 carvedilol, hypotension and postural hypotension occurred in 9.7% and syncope in 3.4% of
205 patients receiving carvedilol compared to 3.6% and 2.5% of placebo patients, respectively. The
206 risk for these events was highest during the first 30 days of dosing, corresponding to the
207 up-titration period and was a cause for discontinuation of therapy in 0.7% of carvedilol patients,
208 compared to 0.4% of placebo patients. In a long-term, placebo-controlled trial in severe heart
209 failure (COPERNICUS), hypotension and postural hypotension occurred in 15.1% and syncope
210 in 2.9% of heart failure patients receiving carvedilol compared to 8.7% and 2.3% of placebo
211 patients, respectively. These events were a cause for discontinuation of therapy in 1.1% of
212 carvedilol patients, compared to 0.8% of placebo patients.

213 In a trial comparing heart failure patients switched to COREG CR or maintained on
214 immediate-release carvedilol, there was a 2-fold increase in the combined incidence of
215 hypotension, syncope or dizziness in elderly patients (> 65 years) switched from the highest dose
216 of carvedilol (25 mg twice daily) to COREG CR 80 mg once daily [*see Dosage and*
217 *Administration (2), Use in Specific Populations (8.5)].*

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

224 In the CAPRICORN study of survivors of an acute myocardial infarction with left
225 ventricular dysfunction, hypotension or postural hypotension occurred in 20.2% of patients
226 receiving carvedilol compared to 12.6% of placebo patients. Syncope was reported in 3.9% and
227 1.9% of patients, respectively. These events were a cause for discontinuation of therapy in 2.5%
228 of patients receiving carvedilol, compared to 0.2% of placebo patients.

229 Starting with a low dose, administration with food, and gradual up-titration should
230 decrease the likelihood of syncope or excessive hypotension [*see Dosage and Administration*
231 (2.1, 2.2, 2.3)]. During initiation of therapy, the patient should be cautioned to avoid situations
232 such as driving or hazardous tasks, where injury could result should syncope occur.

233 **5.4 Heart Failure/Fluid Retention**

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

245 **5.5 Nonallergic Bronchospasm**

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

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

256 **5.6 Glycemic Control in Type 2 Diabetes**

257 In general, β -blockers may mask some of the manifestations of hypoglycemia,
258 particularly tachycardia. Nonselective β -blockers may potentiate insulin-induced hypoglycemia

259 and delay recovery of serum glucose levels. Patients subject to spontaneous hypoglycemia, or
260 diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned about these
261 possibilities.

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

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

271 **5.7 Peripheral Vascular Disease**

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

274 **5.8 Deterioration of Renal Function**

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

282 **5.9 Major Surgery**

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

286 5.10 Thyrotoxicosis

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

290 **5.11 Pheochromocytoma**

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

295 **5.12 Prinzmetal's Variant Angina**

296 Agents with non-selective β -blocking activity may provoke chest pain in patients with
297 Prinzmetal's variant angina. There has been no clinical experience with carvedilol in these
298 patients although the α -blocking activity may prevent such symptoms. However, caution should

299 be taken in the administration of COREG CR to patients suspected of having Prinzmetal's
300 variant angina.

301 **5.13 Risk of Anaphylactic Reaction**

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

306 **6 ADVERSE REACTIONS**

307 **6.1 Clinical Trials Experience**

308 Carvedilol has been evaluated for safety in patients with heart failure (mild, moderate,
309 and severe), in patients with left ventricular dysfunction following myocardial infarction, and in
310 hypertensive patients. The observed adverse event profile was consistent with the pharmacology
311 of the drug and the health status of the patients in the clinical trials. Adverse events reported for
312 each of these patient populations reflecting the use of either COREG CR or immediate-release
313 carvedilol are provided below. Excluded are adverse events considered too general to be
314 informative, and those not reasonably associated with the use of the drug because they were
315 associated with the condition being treated or are very common in the treated population. Rates
316 of adverse events were generally similar across demographic subsets (men and women, elderly
317 and non-elderly, blacks and non-blacks). COREG CR has been evaluated for safety in a 4-week
318 (2 weeks of immediate-release carvedilol and 2 weeks of COREG CR) clinical study (n = 187)
319 which included 157 patients with stable mild, moderate, or severe chronic heart failure and 30
320 patients with left ventricular dysfunction following acute myocardial infarction. The profile of
321 adverse events observed with COREG CR in this small, short-term study was generally similar
322 to that observed with immediate-release carvedilol. Differences in safety would not be expected
323 based on the similarity in plasma levels for COREG CR and immediate-release carvedilol.

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

326 Carvedilol has been evaluated for safety in heart failure in more than 4,500 patients
327 worldwide of whom more than 2,100 participated in placebo-controlled clinical trials.
328 Approximately 60% of the total treated population in placebo-controlled clinical trials received
329 carvedilol for at least 6 months and 30% received carvedilol for at least 12 months. In the
330 COMET trial, 1,511 patients with mild-to-moderate heart failure were treated with carvedilol for
331 up to 5.9 years (mean 4.8 years). Both in US clinical trials in mild-to-moderate heart failure that
332 compared carvedilol in daily doses up to 100 mg (n = 765) to placebo (n = 437), and in a
333 multinational clinical trial in severe heart failure (COPERNICUS) that compared carvedilol in
334 daily doses up to 50 mg (n = 1,156) with placebo (n = 1,133), discontinuation rates for adverse
335 experiences were similar in carvedilol and placebo patients. In placebo-controlled clinical trials,
336 the only cause of discontinuation >1%, and occurring more often on carvedilol was dizziness
337 (1.3% on carvedilol, 0.6% on placebo in the COPERNICUS trial).

338 Table 2 shows adverse events reported in patients with mild-to-moderate heart failure
339 enrolled in US placebo-controlled clinical trials, and with severe heart failure enrolled in the
340 COPERNICUS trial. Shown are adverse events that occurred more frequently in drug-treated
341 patients than placebo-treated patients with an incidence of >3% in patients treated with
342 carvedilol regardless of causality. Median study medication exposure was 6.3 months for both
343 carvedilol and placebo patients in the trials of mild-to-moderate heart failure, and 10.4 months in
344 the trial of severe heart failure patients. The adverse event profile of carvedilol observed in the
345 long-term COMET study was generally similar to that observed in the US Heart Failure Trials.
346

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

	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	—	—

352
 353 Cardiac failure and dyspnea were also reported in these studies, but the rates were equal
 354 or greater in patients who received placebo.

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

358 **Incidence >1% to ≤3%**

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

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

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

363 *Gastrointestinal:* Melena, periodontitis.

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

365 *Metabolic and Nutritional:* Hyperuricemia, hypoglycemia, hyponatremia, increased
366 alkaline phosphatase, glycosuria, hypervolemia, diabetes mellitus, GGT increased, weight loss,
367 hyperkalemia, creatinine increased.

368 *Musculoskeletal:* Muscle cramps.

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

370 *Psychiatric:* Somnolence.

371 *Reproductive, male:* Impotence.

372 *Special Senses:* Blurred vision.

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

374 Left Ventricular Dysfunction Following Myocardial Infarction: The following
375 information describes the safety experience in left ventricular dysfunction following acute
376 myocardial infarction with immediate-release carvedilol.

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

382 The most common adverse events reported with carvedilol in the CAPRICORN trial were
383 consistent with the profile of the drug in the US heart failure trials and the COPERNICUS trial.
384 The only additional adverse events reported in CAPRICORN in >3% of the patients and more
385 commonly on carvedilol were dyspnea, anemia, and lung edema. The following adverse events
386 were reported with a frequency of >1% but ≤3% and more frequently with carvedilol: Flu
387 syndrome, cerebrovascular accident, peripheral vascular disorder, hypotonia, depression,
388 gastrointestinal pain, arthritis, and gout. The overall rates of discontinuations due to adverse
389 events were similar in both groups of patients. In this database, the only cause of discontinuation
390 >1%, and occurring more often on carvedilol was hypotension (1.5% on carvedilol, 0.2% on
391 placebo).

392 Hypertension: COREG CR was evaluated for safety in an 8-week double-blind trial in
393 337 subjects with essential hypertension. The profile of adverse events observed with
394 COREG CR was generally similar to that observed with immediate-release carvedilol. The

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

397

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

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

401

402 The following information describes the safety experience in hypertension with
403 immediate-release carvedilol.

404

405 Carvedilol has been evaluated for safety in hypertension in more than 2,193 patients in
406 US clinical trials and in 2,976 patients in international clinical trials. Approximately 36% of the
407 total treated population received carvedilol for at least 6 months. In general, carvedilol was well
408 tolerated at doses up to 50 mg daily. Most adverse events reported during carvedilol therapy
409 were of mild to moderate severity. In US controlled clinical trials directly comparing carvedilol
410 monotherapy in doses up to 50 mg (n = 1,142) to placebo (n = 462), 4.9% of carvedilol patients
411 discontinued for adverse events versus 5.2% of placebo patients. Although there was no overall
412 difference in discontinuation rates, discontinuations were more common in the carvedilol group
413 for postural hypotension (1% versus 0). The overall incidence of adverse events in US
414 placebo-controlled trials was found to increase with increasing dose of carvedilol. For individual
415 adverse events this could only be distinguished for dizziness, which increased in frequency from
416 2% to 5% as total daily dose increased from 6.25 mg to 50 mg as single or divided doses.

416

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

419

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

	Carvedilol (n = 1,142)	Placebo (n = 462)
Cardiovascular		
Bradycardia	2	—
Postural hypotension	2	—
Peripheral edema	1	—
Central Nervous System		
Dizziness	6	5
Insomnia	2	1
Gastrointestinal		
Diarrhea	2	1
Hematologic		
Thrombocytopenia	1	—
Metabolic		
Hypertriglyceridemia	1	—

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

424

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

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

430

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

431

Cardiovascular: Peripheral ischemia, tachycardia.

432

Central and Peripheral Nervous System: Hypokinesia.

433

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

436

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

438

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

439

Reproductive, male: Decreased libido.

440

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

442

Special Senses: Tinnitus.

443

Urinary System: Micturition frequency increased.

444

Autonomic Nervous System: Dry mouth, sweating increased.

445

Metabolic and Nutritional: Hypokalemia, hypertriglyceridemia.

446 *Hematologic:* Anemia, leukopenia.

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

452 **6.2 Laboratory Abnormalities**

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

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

466 **6.3 Postmarketing Experience**

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

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

479 **7 DRUG INTERACTIONS**

480 **7.1 CYP2D6 Inhibitors and Poor Metabolizers**

481 Interactions of carvedilol with potent inhibitors of CYP2D6 isoenzyme (such as
482 quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would
483 be expected to increase blood levels of the R(+) enantiomer of carvedilol [*see Clinical*
484 *Pharmacology (12.3)*]. Retrospective analysis of side effects in clinical trials showed that poor

485 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from
486 vasodilating effects of the higher concentrations of the α -blocking R(+) enantiomer.

487 **7.2 Hypotensive Agents**

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

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

496 **7.3 Cyclosporine**

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

505 **7.4 Digitalis Glycosides**

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

511 **7.5 Inducers/Inhibitors of Hepatic Metabolism**

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

515 **7.6 Amiodarone**

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

523 **7.7 Calcium Channel Blockers**

524 Conduction disturbance (rarely with hemodynamic compromise) has been observed when
525 carvedilol is co-administered with diltiazem. As with other agents with β -blocking properties, if

526 COREG CR is to be administered orally with calcium channel blockers of the verapamil or
527 diltiazem type, it is recommended that ECG and blood pressure be monitored.

528 **7.8 Insulin or Oral Hypoglycemics**

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

532 **7.9 Proton Pump Inhibitors**

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

535 **7.10 Anesthesia**

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

539 **8 USE IN SPECIFIC POPULATIONS**

540 **8.1 Pregnancy**

541 Pregnancy Category C. Studies performed in pregnant rats and rabbits given carvedilol
542 revealed increased post-implantation loss in rats at doses of 300 mg/kg/day (50 times the
543 maximum recommended human dose [MRHD] as mg/m^2) and in rabbits at doses of
544 75 mg/kg/day (25 times the MRHD as mg/m^2). In the rats, there was also a decrease in fetal body
545 weight at the maternally toxic dose of 300 mg/kg/day (50 times the MRHD as mg/m^2), which
546 was accompanied by an elevation in the frequency of fetuses with delayed skeletal development
547 (missing or stunted 13th rib). In rats the no-observed-effect level for developmental toxicity was
548 60 mg/kg/day (10 times the MRHD as mg/m^2); in rabbits it was 15 mg/kg/day (5 times the
549 MRHD as mg/m^2). There are no adequate and well-controlled studies in pregnant women.
550 COREG CR should be used during pregnancy only if the potential benefit justifies the potential
551 risk to the fetus.

552 **8.3 Nursing Mothers**

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

562 **8.4 Pediatric Use**

563 Effectiveness of carvedilol in patients younger than 18 years of age has not been
564 established.

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

576 **8.5 Geriatric Use**

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

581 A randomized study (n = 405) comparing mild to severe heart failure patients switched to
582 COREG CR or maintained on immediate-release carvedilol included 220 patients who were 65
583 years of age or older. In this elderly subgroup, the combined incidence of dizziness, hypotension,
584 or syncope was 24% (18/75) in patients switched from the highest dose of immediate-release
585 carvedilol (25 mg twice daily) to the highest dose of COREG CR (80 mg once daily) compared
586 to 11% (4/36) in patients maintained on immediate-release carvedilol (25 mg twice daily). When
587 switching from the higher doses of immediate-release carvedilol to COREG CR, a lower starting
588 dose is recommended for elderly patients [*see Dosage and Administration (2.5)*].

589 The following information is available for trials with immediate-release carvedilol. Of the
590 765 patients with heart failure randomized to carvedilol in US clinical trials, 31% (235) were
591 65 years of age or older, and 7.3% (56) were 75 years of age or older. Of the 1,156 patients
592 randomized to carvedilol in a long-term, placebo-controlled trial in severe heart failure, 47%
593 (547) were 65 years of age or older, and 15% (174) were 75 years of age or older. Of
594 3,025 patients receiving carvedilol in heart failure trials worldwide, 42% were 65 years of age or
595 older. Of the 975 myocardial infarction patients randomized to carvedilol in the CAPRICORN
596 trial, 48% (468) were 65 years of age or older, and 11% (111) were 75 years of age or older. Of
597 the 2,065 hypertensive patients in US clinical trials of efficacy or safety who were treated with
598 carvedilol, 21% (436) were 65 years of age or older. Of 3,722 patients receiving immediate-
599 release carvedilol in hypertension clinical trials conducted worldwide, 24% were 65 years of age
600 or older.

601 With the exception of dizziness in hypertensive patients (incidence 8.8% in the elderly
602 versus 6% in younger patients), no overall differences in the safety or effectiveness (see Figures
603 2 and 4) were observed between the older subjects and younger subjects in each of these
604 populations. Similarly, other reported clinical experience has not identified differences in

605 responses between the elderly and younger subjects, but greater sensitivity of some older
606 individuals cannot be ruled out.

607 10 OVERDOSAGE

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

611 The patient should be placed in a supine position and, where necessary, kept under
612 observation and treated under intensive-care conditions. Gastric lavage or pharmacologically
613 induced emesis may be used shortly after ingestion. The following agents may be administered:
614 *for excessive bradycardia:* atropine, 2 mg IV.

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

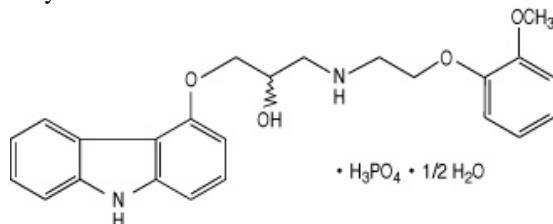
618 If peripheral vasodilation dominates, it may be necessary to administer adrenaline or
619 noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant
620 bradycardia, pacemaker therapy should be performed. For bronchospasm, β -sympathomimetics
621 (as aerosol or IV)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

623 NOTE: In the event of severe intoxication where there are symptoms of shock, treatment
624 with antidotes must be continued for a sufficiently long period of time consistent with the 7- to
625 10-hour half-life of carvedilol.

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

630 11 DESCRIPTION

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



634 Carvedilol phosphate is a white to almost-white solid with a molecular weight of 513.5
635 (406.5 carvedilol free base) and a molecular formula of $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_4 \cdot \text{H}_3\text{PO}_4 \cdot \frac{1}{2} \text{H}_2\text{O}$.

637 COREG CR is available for once-a-day administration as controlled-release oral capsules
638 containing 10, 20, 40, or 80 mg carvedilol phosphate. COREG CR hard gelatin capsules are

639 filled with carvedilol phosphate immediate-release and controlled-release microparticles that are
640 drug-layered and then coated with methacrylic acid copolymers. Inactive ingredients include
641 crospovidone, hydrogenated castor oil, hydrogenated vegetable oil, magnesium stearate,
642 methacrylic acid copolymers, microcrystalline cellulose, and povidone.

643 **12 CLINICAL PHARMACOLOGY**

644 **12.1 Mechanism of Action**

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

648 **12.2 Pharmacodynamics**

649 Heart Failure and Left Ventricular Dysfunction Following Myocardial Infarction:

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

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

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

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

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

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

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

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

681 **12.3 Pharmacokinetics**

682 Absorption: Carvedilol is rapidly and extensively absorbed following oral administration
683 of immediate-release carvedilol tablets, with an absolute bioavailability of approximately 25% to
684 35% due to a significant degree of first-pass metabolism. COREG CR extended-release capsules
685 have approximately 85% of the bioavailability of immediate-release carvedilol tablets. For
686 corresponding dosages [*see Dosage and Administration (2)*], the exposure (AUC, C_{max} , trough
687 concentration) of carvedilol as COREG CR extended-release capsules is equivalent to those of
688 immediate-release carvedilol tablets when both are administered with food. The absorption of
689 carvedilol from COREG CR is slower and more prolonged compared to the immediate-release
690 carvedilol tablet with peak concentrations achieved approximately 5 hours after administration.
691 Plasma concentrations of carvedilol increase in a dose-proportional manner over the dosage
692 range of COREG CR 10 to 80 mg. Within-subject and between-subject variability for AUC and
693 C_{max} is similar for COREG CR and immediate-release carvedilol.

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

699 In a study with adult subjects, sprinkling the contents of the COREG CR capsule on
700 applesauce did not appear to have a significant effect on overall exposure (AUC) compared to
701 administration of the intact capsule following a standard meal but did result in a decrease in C_{max}
702 (18%).

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

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

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

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

723 The primary P450 enzymes responsible for the metabolism of both R(+) and
724 S(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent
725 CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and
726 5'-hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be
727 of primary importance in the O-methylation pathway of S(-)-carvedilol.

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

735 **12.4 Specific Populations**

736 Heart Failure: Following administration of immediate-release carvedilol tablets,
737 steady-state plasma concentrations of carvedilol and its enantiomers increased proportionally
738 over the dose range in patients with heart failure. Compared to healthy subjects, heart failure
739 patients had increased mean AUC and C_{max} values for carvedilol and its enantiomers, with up to
740 50% to 100% higher values observed in 6 patients with NYHA class IV heart failure. The mean
741 apparent terminal elimination half-life for carvedilol was similar to that observed in healthy
742 subjects.

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

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

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

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

757 Renal Impairment: No studies have been performed with COREG CR in patients with
758 renal impairment. Although carvedilol is metabolized primarily by the liver, plasma
759 concentrations of carvedilol have been reported to be increased in patients with renal impairment

760 after dosing with immediate-release carvedilol. Based on mean AUC data, approximately 40% to
761 50% higher plasma concentrations of carvedilol were observed in hypertensive patients with
762 moderate to severe renal impairment compared to a control group of hypertensive patients with
763 normal renal function. However, the ranges of AUC values were similar for both groups.
764 Changes in mean peak plasma levels were less pronounced, approximately 12% to 26% higher in
765 patients with impaired renal function.

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

768 **12.5 Drug-Drug Interactions**

769 Since carvedilol undergoes substantial oxidative metabolism, the metabolism and
770 pharmacokinetics of carvedilol may be affected by induction or inhibition of cytochrome P450
771 enzymes.

772 The following drug interaction studies were performed with immediate-release carvedilol
773 tablets.

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

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

781 Digoxin: Following concomitant administration of carvedilol (25 mg once daily) and
782 digoxin (0.25 mg once daily) for 14 days, steady-state AUC and trough concentrations of digoxin
783 were increased by 14% and 16%, respectively, in 12 hypertensive patients [see *Drug*
784 *Interactions (7.4)*].

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

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

791 Rifampin: In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin
792 (600 mg daily for 12 days) decreased the AUC and C_{max} of carvedilol by about 70% [see *Drug*
793 *Interactions (7.5)*].

794 Torsemide: In a study of 12 healthy subjects, combined oral administration of carvedilol
795 25 mg once daily and torsemide 5 mg once daily for 5 days did not result in any significant
796 differences in their pharmacokinetics compared with administration of the drugs alone.

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

800 **13 NONCLINICAL TOXICOLOGY**

801 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

813 **14 CLINICAL STUDIES**

814 Support for the use of COREG CR extended-release capsules for the treatment of mild-
815 to-severe heart failure and for patients with left ventricular dysfunction following myocardial
816 infarction is based on the equivalence of pharmacokinetic and pharmacodynamic (β_1 -blockade)
817 parameters between COREG CR and immediate-release carvedilol [*see Clinical Pharmacology*
818 (12.2, 12.3)].

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

821 **14.1 Heart Failure**

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

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

827 Four US multicenter, double-blind, placebo-controlled studies enrolled 1,094 patients
828 (696 randomized to carvedilol) with NYHA class II-III heart failure and ejection fraction ≤ 0.35 .
829 The vast majority were on digitalis, diuretics, and an ACE inhibitor at study entry. Patients were
830 assigned to the studies based upon exercise ability. An Australia-New Zealand double-blind,
831 placebo-controlled study enrolled 415 patients (half randomized to immediate-release carvedilol)
832 with less severe heart failure. All protocols excluded patients expected to undergo cardiac
833 transplantation during the 7.5 to 15 months of double-blind follow-up. All randomized patients
834 had tolerated a 2-week course on immediate-release carvedilol 6.25 mg twice daily.

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

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

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

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

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

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

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

859 *Mortality:* Death was not a pre-specified end point in any study, but was analyzed in all
860 studies. Overall, in these 4 US trials, mortality was reduced, nominally significantly so in
861 2 studies.

862 **The COMET Trial:** In this double-blind trial, 3,029 patients with NYHA class II-IV
863 heart failure (left ventricular ejection fraction $\leq 35\%$) were randomized to receive either
864 carvedilol (target dose: 25 mg twice daily) or immediate-release metoprolol tartrate (target dose:
865 50 mg twice daily). The mean age of the patients was approximately 62 years, 80% were males,
866 and the mean left ventricular ejection fraction at baseline was 26%. Approximately 96% of the
867 patients had NYHA class II or III heart failure. Concomitant treatment included diuretics (99%),
868 ACE inhibitors (91%), digitalis (59%), aldosterone antagonists (11%), and "statin" lipid-
869 lowering agents (21%). The mean duration of follow-up was 4.8 years. The mean dose of
870 carvedilol was 42 mg per day.

871 The study had 2 primary end points: all-cause mortality and the composite of death plus
872 hospitalization for any reason. The results of COMET are presented in Table 5 below. All-cause
873 mortality carried most of the statistical weight and was the primary determinant of the study size.
874 All-cause mortality was 34% in the patients treated with carvedilol and was 40% in the
875 immediate-release metoprolol group ($p = 0.0017$; hazard ratio = 0.83, 95% CI 0.74–0.93). The
876 effect on mortality was primarily due to a reduction in cardiovascular death. The difference
877 between the 2 groups with respect to the composite end point was not significant ($p = 0.122$).
878 The estimated mean survival was 8.0 years with carvedilol and 6.6 years with immediate-release
879 metoprolol.

880

881 **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

882

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

888 **Severe Heart Failure (COPERNICUS):** In a double-blind study, 2,289 patients with
889 heart failure at rest or with minimal exertion and left ventricular ejection fraction <25% (mean
890 20%), despite digitalis (66%), diuretics (99%), and ACE inhibitors (89%) were randomized to
891 placebo or carvedilol. Carvedilol was titrated from a starting dose of 3.125 mg twice daily to the
892 maximum tolerated dose or up to 25 mg twice daily over a minimum of 6 weeks. Most subjects
893 achieved the target dose of 25 mg. The study was conducted in Eastern and Western Europe, the
894 United States, Israel, and Canada. Similar numbers of subjects per group (about 100) withdrew
895 during the titration period.

896 The primary end point of the trial was all-cause mortality, but cause-specific mortality
897 and the risk of death or hospitalization (total, cardiovascular [CV], or heart failure [HF]) were
898 also examined. The developing trial data were followed by a data monitoring committee, and
899 mortality analyses were adjusted for these multiple looks. The trial was stopped after a median
900 follow-up of 10 months because of an observed 35% reduction in mortality (from 19.7% per
901 patient year on placebo to 12.8% on carvedilol, hazard ratio 0.65, 95% CI 0.52 – 0.81,
902 $p = 0.0014$, adjusted) (see Figure 1). The results of COPERNICUS are shown in Table 6.

903

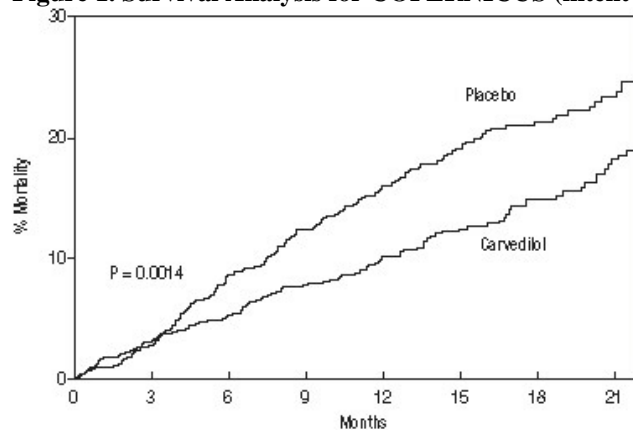
904 **Table 6. Results of COPERNICUS Trial in Patients With Severe Heart Failure**

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

905 Cardiovascular = CV; Heart failure = HF

906

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



908

909

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

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

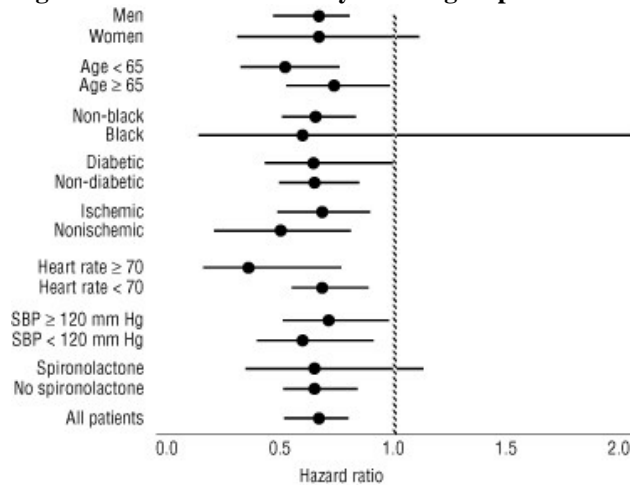
917 The protocol also specified that hospitalizations would be assessed. Fewer patients on
 918 immediate-release carvedilol than on placebo were hospitalized for any reason (372 versus 432,
 919 $p = 0.0029$), for cardiovascular reasons (246 versus 314, $p = 0.0003$), or for worsening heart
 920 failure (198 versus 268, $p = 0.0001$).

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

924 women, elderly and non-elderly, blacks and non-blacks, and diabetics and non-diabetics (see
 925 Figure 2).

926

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



928

929

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

933 **14.2 Left Ventricular Dysfunction Following Myocardial Infarction**

934 CAPRICORN was a double-blind study comparing carvedilol and placebo in 1,959
 935 patients with a recent myocardial infarction (within 21 days) and left ventricular ejection fraction
 936 of ≤40%, with (47%) or without symptoms of heart failure. Patients given carvedilol received
 937 6.25 mg twice daily, titrated as tolerated to 25 mg twice daily. Patients had to have a systolic
 938 blood pressure >90 mm Hg, a sitting heart rate >60 beats/minute, and no contraindication to
 939 β-blocker use. Treatment of the index infarction included aspirin (85%), IV or oral β-blockers
 940 (37%), nitrates (73%), heparin (64%), thrombolytics (40%), and acute angioplasty (12%).
 941 Background treatment included ACE inhibitors or angiotensin receptor blockers (97%),
 942 anticoagulants (20%), lipid-lowering agents (23%), and diuretics (34%). Baseline population
 943 characteristics included an average age of 63 years, 74% male, 95% Caucasian, mean blood
 944 pressure 121/74 mm Hg, 22% with diabetes, and 54% with a history of hypertension. Mean
 945 dosage achieved of carvedilol was 20 mg twice daily; mean duration of follow-up was
 946 15 months.

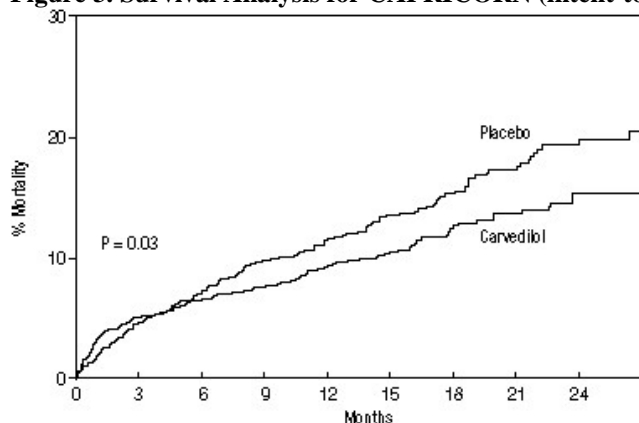
947 All-cause mortality was 15% in the placebo group and 12% in the carvedilol group,
 948 indicating a 23% risk reduction in patients treated with carvedilol (95% CI 2% to 40%, p = 0.03),
 949 as shown in Figure 3. The effects on mortality in various subgroups are shown in Figure 4.
 950 Nearly all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

952 carvedilol). Another study end point, total mortality and all-cause hospitalization, did not show a
 953 significant improvement.

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

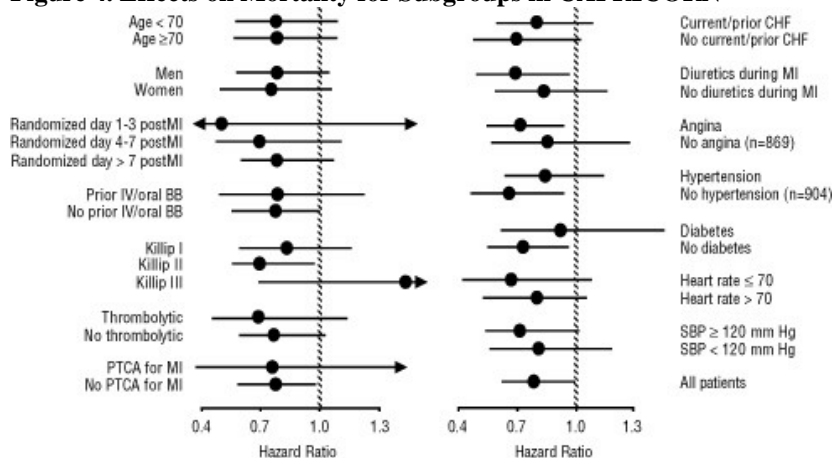
958
 959

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



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 961
 962

Figure 4. Effects on Mortality for Subgroups in CAPRICORN



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 968

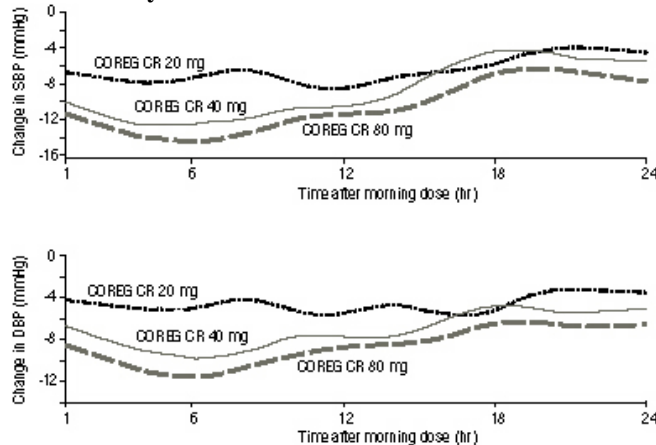
Although the clinical trials used twice-daily dosing, clinical pharmacologic and
 pharmacokinetic data provide a reasonable basis for concluding that once-daily dosing with
 COREG CR should be adequate in the treatment of left ventricular dysfunction following
 myocardial infarction.

969 **14.3 Hypertension**

970 A double-blind, randomized, placebo-controlled, 8-week trial evaluated the blood
971 pressure lowering effects of COREG CR 20 mg, 40 mg, and 80 mg once daily in 338 patients
972 with essential hypertension (sitting diastolic blood pressure [DBP] ≥ 90 and ≤ 109 mm Hg). Of
973 337 evaluable patients, a total of 273 patients (81%) completed the study. Of the 64 (19%)
974 patients withdrawn from the study, 10 (3%) were due to adverse events, 10 (3%) were due to
975 lack of efficacy; the remaining 44 (13%) withdrew for other reasons. The mean age of the
976 patients was approximately 53 years, 66% were male, and the mean sitting systolic blood
977 pressure (SBP) and DBP at baseline were 150 mm Hg and 99 mm Hg, respectively. Dose
978 titration occurred at 2-week intervals.

979 Statistically significant reductions in blood pressure as measured by 24-hour ambulatory
980 blood pressure monitoring (ABPM) were observed with each dose of COREG CR compared to
981 placebo. Placebo-subtracted mean changes from baseline in mean SBP/DBP were
982 -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
983 80 mg, respectively. Placebo-subtracted mean changes from baseline in mean trough (average of
984 hours 20-24) SBP/DBP were -3.3/-2.8 mm Hg, -4.9/-5.2 mm Hg, and -8.4/-7.4 mm Hg for
985 COREG CR 20 mg, 40 mg, and 80 mg, respectively. The placebo-corrected trough to peak
986 (3-7 hr) ratio was approximately 0.6 for COREG CR 80 mg. In this study, assessments of
987 24-hour ABPM monitoring demonstrated statistically significant blood pressure reductions with
988 COREG CR throughout the dosing period (Figure 5).

989
990 **Figure 5. Changes from Baseline in Systolic Blood Pressure and Diastolic Blood Pressure**
991 **Measured by 24-Hour ABPM**



992 Lines smoothed using locally weighted regression smoothing methodology.

993

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

997 pressure by about 9/5.5 mm Hg; at 25 mg/day the effect was about 7.5/3.5 mm Hg. Comparisons
998 of trough-to-peak blood pressure showed a trough-to-peak ratio for blood pressure response of
999 about 65%. Heart rate fell by about 7.5 beats/minute at 50 mg/day. In general, as is true for other
1000 β -blockers, responses were smaller in black than non-black patients. There were no age- or
1001 gender-related differences in response. The dose-related blood pressure response was
1002 accompanied by a dose-related increase in adverse effects [see *Adverse Reactions (6)*].

1003 **14.4 Hypertension With Type 2 Diabetes Mellitus**

1004 In a double-blind study (GEMINI), carvedilol, added to an ACE inhibitor or angiotensin
1005 receptor blocker, was evaluated in a population with mild-to-moderate hypertension and well-
1006 controlled type 2 diabetes mellitus. The mean HbA1c at baseline was 7.2%. COREG was titrated
1007 to a mean dose of 17.5 mg twice daily and maintained for 5 months. COREG had no adverse
1008 effect on glycemic control, based on HbA1c measurements (mean change from baseline of
1009 0.02%, 95% CI -0.06 to 0.10, p = NS) [see *Warnings and Precautions (5.6)*].

1010 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1011 The hard gelatin capsules are available in the following strengths:

- 1012 • 10 mg – white and green capsule shell printed with GSK COREG CR and 10 mg
- 1013 • 20 mg – white and yellow capsule shell printed with GSK COREG CR and 20 mg
- 1014 • 40 mg – yellow and green capsule shell printed with GSK COREG CR and 40 mg
- 1015 • 80 mg – white capsule shell printed with GSK COREG CR and 80 mg

- 1016
- 1017 • 10 mg 30's: NDC 0007-3370-13
- 1018 • 10 mg 90's: NDC 0007-3370-59
- 1019 • 20 mg 30's: NDC 0007-3371-13
- 1020 • 20 mg 90's: NDC 0007-3371-59
- 1021 • 40 mg 30's: NDC 0007-3372-13
- 1022 • 40 mg 90's: NDC 0007-3372-59
- 1023 • 80 mg 30's: NDC 0007-3373-13
- 1024 • 80 mg 90's: NDC 0007-3373-59

1025 Store at 25°C (77°F); excursions 15° to 30°C (59° to 86°F). Dispense in a tight,
1026 light-resistant container.

1027 **17 PATIENT COUNSELING INFORMATION**

1028 See FDA-Approved Patient Labeling (17.2).

1029 **17.1 Patient Advice**

1030 Patients taking COREG CR should be advised of the following:

- 1031 • Patients should not interrupt or discontinue using COREG CR without a physician's advice.
- 1032 • Patients with heart failure should consult their physician if they experience signs or
1033 symptoms of worsening heart failure such as weight gain or increasing shortness of breath.

- 1034 • Patients may experience a drop in blood pressure when standing, resulting in dizziness and,
1035 rarely, fainting. Patients should sit or lie down when these symptoms of lowered blood
1036 pressure occur.
- 1037 • If experiencing dizziness or fatigue, patients should avoid driving or hazardous tasks.
- 1038 • Patients should consult a physician if they experience dizziness or faintness, in case the
1039 dosage should be adjusted.
- 1040 • Patients should not crush or chew COREG CR capsules.
- 1041 • Patients should take COREG CR with food.
- 1042 • Diabetic patients should report any changes in blood sugar levels to their physician.
- 1043 • Contact lens wearers may experience decreased lacrimation.

1044 **17.2 FDA-Approved Patient Labeling**

1045 Patient labeling is provided as a tear-off leaflet at the end of this full prescribing
1046 information.

1047
1048 COREG CR and COREG are registered trademarks of GlaxoSmithKline.

1049 TOPROL-XL is a registered trademark of the AstraZeneca group of companies.

1050



1051

1052 GlaxoSmithKline

1053 Research Triangle Park, NC 27709

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1055

1056 November 2010

1057 CCR: 12PI

1058 **PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT**

1059 -----

1060 **PATIENT INFORMATION LEAFLET**
1061 **COREG CR[®] (Co-REG)**
1062 **(carvedilol phosphate) Extended-release Capsules**

1063

1064 Read the Patient Information that comes with COREG CR before you start taking it and each
1065 time you get a refill. There may be new information. This information does not take the place of
1066 talking with your doctor about your medical condition or your treatment. If you have any
1067 questions about COREG CR, ask your doctor or pharmacist.

1068

1069 **What is the most important information I should know about COREG CR?**

1070 **It is important for you to take your medicine every day as directed by your doctor. If you**
1071 **stop taking COREG CR suddenly, you could have chest pain and a heart attack. If your**
1072 **doctor decides that you should stop taking COREG CR, your doctor may slowly lower**
1073 **your dose over time before stopping it completely.**

1074

1075 **What is COREG CR?**

1076 COREG CR is a prescription medicine that belongs to a group of medicines called “beta-
1077 blockers”. COREG CR is used, often with other medicines, for the following conditions:

- 1078 • to treat patients with certain types of heart failure
1079 • to treat patients who had a heart attack that worsened how well the heart pumps
1080 • to treat patients with high blood pressure (hypertension)

1081

1082 COREG CR is not approved for use in children under 18 years of age.

1083

1084 **Who should not take COREG CR?**

1085 Do not take COREG CR if you:

- 1086 • have severe heart failure and require certain intravenous medicines that help support
1087 circulation.
1088 • have asthma or other breathing problems.
1089 • have a slow heartbeat or certain conditions that cause your heart to skip a beat (irregular
1090 heartbeat).
1091 • have liver problems.
1092 • are allergic to any of the ingredients in COREG CR. See “What are the ingredients in
1093 COREG CR?”

1094

1095 **What should I tell my doctor before taking COREG CR?**

1096 Tell your doctor about all of your medical conditions, including if you:

- 1097 • have asthma or other lung problems (such as bronchitis or emphysema).

- 1098 • have problems with blood flow in your feet and legs (peripheral vascular disease).
1099 COREG CR can make some of your symptoms worse.
- 1100 • have diabetes.
1101 • have thyroid problems.
1102 • have a condition called pheochromocytoma.
1103 • have had severe allergic reactions.
1104 • are scheduled for surgery and will be given anesthetic agents.
1105 • are pregnant or trying to become pregnant. It is not known if COREG CR is safe for your
1106 unborn baby. You and your doctor should talk about the best way to control your high blood
1107 pressure during pregnancy.
1108 • are breastfeeding. It is not known if COREG CR passes into your breast milk. You should
1109 not breastfeed while using COREG CR.

1110
1111 **Tell your doctor about all of the medicines you take** including prescription and non-
1112 prescription medicines, vitamins, and herbal supplements. COREG CR and certain other
1113 medicines can affect each other and cause serious side effects. COREG CR may affect the way
1114 other medicines work. Also, other medicines may affect how well COREG CR works.

1115
1116 Know the medicines you take. Keep a list of your medicines and show it to your doctor and
1117 pharmacist before you start a new medicine.

1118
1119 **How should I take COREG CR?**

- 1120 • Take COREG CR exactly as prescribed. Take COREG CR **one** time each day with food. **It is**
1121 **important that you take COREG CR only one time each day.** To lessen possible side
1122 effects, your doctor might begin with a low dose and then slowly increase the dose.
1123 • Swallow COREG CR capsules whole. Do not chew or crush COREG CR capsules.
1124 • If you have trouble swallowing COREG CR whole:
1125 • The capsule may be carefully opened and the beads sprinkled over a spoonful of
1126 applesauce which should be eaten right away. The applesauce should not be warm.
1127 • Do not sprinkle beads on foods other than applesauce.
1128 • **Do not stop taking COREG CR and do not change the amount of COREG CR you take**
1129 **without talking to your doctor.**
1130 • If you miss a dose of COREG CR, take your dose as soon as you remember, unless it is time
1131 to take your next dose. Take your next dose at the usual time. Do not take 2 doses at the same
1132 time.
1133 • If you take too much COREG CR, call your doctor or poison control center right away.

1134
1135 **What should I avoid while taking COREG CR?**

1136 COREG CR can cause you to feel dizzy, tired, or faint. Do not drive a car, use machinery, or do
1137 anything that needs you to be alert if you have these symptoms.

1138

1139 **What are possible side effects of COREG CR?**

1140 Serious side effects of COREG CR include:

- 1141 • **chest pain and heart attack if you suddenly stop taking COREG CR.** See “What is the
1142 *most important information I should know about COREG CR?*”
- 1143 • **slow heart beat.**
- 1144 • **low blood pressure (which may cause dizziness or fainting when you stand up).** If these
1145 happen, sit or lie down, and tell your doctor right away.
- 1146 • **worsening heart failure.** Tell your doctor right away if you have signs and symptoms that
1147 your heart failure may be worse, such as weight gain or increased shortness of breath.
- 1148 • **changes in your blood sugar. If you have diabetes, tell your doctor if you have any**
1149 **changes in your blood sugar levels.**
- 1150 • masking (hiding) the symptoms of low blood sugar, especially a fast heartbeat.
- 1151 • **new or worsening symptoms of peripheral vascular disease.**
- 1152 • leg pain that happens when you walk, but goes away when you rest
- 1153 • no feeling (numbness) in your legs or feet while you are resting
- 1154 • cold legs or feet
- 1155 • masking the symptoms of hyperthyroidism (overactive thyroid), such as a fast heartbeat.
- 1156 • **worsening of severe allergic reactions.** Medicines to treat a severe allergic reaction may not
1157 work as well while you are taking COREG CR.
- 1158 • **rare but serious allergic reactions** (including hives or swelling of the face, lips, tongue,
1159 and/or throat that may cause difficulty in breathing or swallowing) have happened in patients
1160 who were on COREG or COREG CR. These reactions can be life-threatening. In some cases,
1161 these reactions happened in patients who had been on COREG before taking COREG CR.

1162

1163 Common side effects of COREG CR include shortness of breath, weight gain, diarrhea, and
1164 tiredness. If you wear contact lenses, you may have fewer tears or dry eyes that can become
1165 bothersome.

1166

1167 Call your doctor if you have any side effects that bother you or don't go away.

1168

1169 **How should I store COREG CR?**

1170 Store COREG CR at less than 86°F (30°C).

1171 Safely throw away COREG CR that is out of date or no longer needed.

1172 **Keep COREG CR and all medicines out of the reach of children.**

1173

1174 **General information about COREG CR**

1175 Medicines are sometimes prescribed for conditions other than those described in patient
1176 information leaflets. Do not use COREG CR for a condition for which it was not prescribed. Do
1177 not give COREG CR to other people, even if they have the same symptoms you have. It may
1178 harm them.

1179

1180 This leaflet summarizes the most important information about COREG CR. If you would like
1181 more information, talk with your doctor. You can ask your doctor or pharmacist for information
1182 about COREG CR that is written for healthcare professionals. You can also find out more about
1183 COREG CR by visiting the website www.COREGCR.com or calling 1-888-825-5249. This call
1184 is free.

1185

1186 **What are the ingredients in COREG CR?**

1187 Active ingredient: carvedilol phosphate

1188 Inactive ingredients: crospovidone, hydrogenated castor oil, hydrogenated vegetable oil,
1189 magnesium stearate, methacrylic acid copolymers, microcrystalline cellulose, and povidone
1190 COREG CR capsules come in the following strengths: 10 mg, 20 mg, 40 mg, 80 mg.

1191

1192 **What is high blood pressure (hypertension)?**

1193 Blood pressure is the force of blood in your blood vessels when your heart beats and when your
1194 heart rests. You have high blood pressure when the force is too much. High blood pressure
1195 makes the heart work harder to pump blood through the body and causes damage to blood
1196 vessels. COREG CR can help your blood vessels relax so your blood pressure is lower.
1197 Medicines that lower blood pressure may lower your chance of having a stroke or heart attack.

1198

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