

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

COREG® (carvedilol) tablets

Initial U.S. Approval: 1995

RECENT MAJOR CHANGES

Warnings and Precautions, Major Surgery (5.9) October 2010
Warnings and Precautions, Intraoperative Floppy Iris Syndrome (5.14) January 2011

INDICATIONS AND USAGE

COREG 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. Individualize dosage and monitor during up-titration. (2)

- Heart failure: Start at 3.125 mg twice daily and increase to 6.25, 12.5, and then 25 mg twice 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 6.25 mg twice daily and increase to 12.5 mg then 25 mg twice daily after intervals of 3 to 10 days. A lower starting dose or slower titration may be used. (2.2)
- Hypertension: Start at 6.25 mg twice daily and increase if needed for blood pressure control to 12.5 mg then 25 mg twice daily over intervals of 1 to 2 weeks. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 3.125, 6.25, 12.5, 25 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 any component of this medication or other medications containing carvedilol. (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

Most common adverse events (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: February 2011

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1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

3 1.1 Heart Failure

4 COREG is indicated for the treatment of mild-to-severe chronic heart failure of ischemic
5 or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitors, and digitalis, to
6 increase survival and, also, to reduce the risk of hospitalization [*see Drug Interactions (7.4) and*
7 *Clinical Studies (14.1)*].

8 1.2 Left Ventricular Dysfunction Following Myocardial Infarction

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

12 1.3 Hypertension

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

16 2 DOSAGE AND ADMINISTRATION

17 COREG should be taken with food to slow the rate of absorption and reduce the
18 incidence of orthostatic effects.

19 2.1 Heart Failure

20 DOSAGE MUST BE INDIVIDUALIZED AND CLOSELY MONITORED BY A
21 PHYSICIAN DURING UP-TITRATION. Prior to initiation of COREG, it is recommended that
22 fluid retention be minimized. The recommended starting dose of COREG is 3.125 mg twice
23 daily for 2 weeks. If tolerated, patients may have their dose increased to 6.25, 12.5, and 25 mg
24 twice daily over successive intervals of at least 2 weeks. Patients should be maintained on lower
25 doses if higher doses are not tolerated. A maximum dose of 50 mg twice daily has been
26 administered to patients with mild-to-moderate heart failure weighing over 85 kg (187 lbs).

27 Patients should be advised that initiation of treatment and (to a lesser extent) dosage
28 increases may be associated with transient symptoms of dizziness or lightheadedness (and rarely
29 syncope) within the first hour after dosing. During these periods, patients should avoid situations
30 such as driving or hazardous tasks, where symptoms could result in injury. Vasodilatory
31 symptoms often do not require treatment, but it may be useful to separate the time of dosing of
32 COREG from that of the ACE inhibitor or to reduce temporarily the dose of the ACE inhibitor.
33 The dose of COREG should not be increased until symptoms of worsening heart failure or
34 vasodilation have been stabilized.

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

37 The dose of COREG should be reduced if patients experience bradycardia (heart rate
38 < 55 beats/minute).

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

42 **2.2 Left Ventricular Dysfunction Following Myocardial Infarction**

43 **DOSAGE MUST BE INDIVIDUALIZED AND MONITORED DURING**
44 **UP-TITRATION.** Treatment with COREG may be started as an inpatient or outpatient and
45 should be started after the patient is hemodynamically stable and fluid retention has been
46 minimized. It is recommended that COREG be started at 6.25 mg twice daily and increased after
47 3 to 10 days, based on tolerability, to 12.5 mg twice daily, then again to the target dose of 25 mg
48 twice daily. A lower starting dose may be used (3.125 mg twice daily) and/or the rate of
49 up-titration may be slowed if clinically indicated (e.g., due to low blood pressure or heart rate, or
50 fluid retention). Patients should be maintained on lower doses if higher doses are not tolerated.
51 The recommended dosing regimen need not be altered in patients who received treatment with an
52 IV or oral β -blocker during the acute phase of the myocardial infarction.

53 **2.3 Hypertension**

54 **DOSAGE MUST BE INDIVIDUALIZED.** The recommended starting dose of COREG
55 is 6.25 mg twice daily. If this dose is tolerated, using standing systolic pressure measured about
56 1 hour after dosing as a guide, the dose should be maintained for 7 to 14 days, and then increased
57 to 12.5 mg twice daily if needed, based on trough blood pressure, again using standing systolic
58 pressure one hour after dosing as a guide for tolerance. This dose should also be maintained for 7
59 to 14 days and can then be adjusted upward to 25 mg twice daily if tolerated and needed. The full
60 antihypertensive effect of COREG is seen within 7 to 14 days. Total daily dose should not
61 exceed 50 mg.

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

64 **2.4 Hepatic Impairment**

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

67 **3 DOSAGE FORMS AND STRENGTHS**

68 The white, oval, film-coated tablets are available in the following strengths: 3.125 mg–
69 engraved with 39 and SB, 6.25 mg–engraved with 4140 and SB, 12.5 mg–engraved with 4141
70 and SB, and 25 mg–engraved with 4142 and SB.

71 **4 CONTRAINDICATIONS**

72 COREG is contraindicated in the following conditions:

- 73 • Bronchial asthma or related bronchospastic conditions. Deaths from status asthmaticus have
74 been reported following single doses of COREG.
- 75 • Second- or third-degree AV block
- 76 • Sick sinus syndrome
- 77 • Severe bradycardia (unless a permanent pacemaker is in place)

- 78 • Patients with cardiogenic shock or who have decompensated heart failure requiring the use of
79 intravenous inotropic therapy. Such patients should first be weaned from intravenous therapy
80 before initiating COREG.
- 81 • Patients with severe hepatic impairment
- 82 • Patients with a history of a serious hypersensitivity reaction (e.g., Stevens-Johnson
83 syndrome, anaphylactic reaction, angioedema) to any component of this medication or other
84 medications containing carvedilol.

85 **5 WARNINGS AND PRECAUTIONS**

86 **5.1 Cessation of Therapy**

87 **Patients with coronary artery disease, who are being treated with COREG, should**
88 **be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and**
89 **the occurrence of myocardial infarction and ventricular arrhythmias have been reported in**
90 **angina patients following the abrupt discontinuation of therapy with β -blockers. The last 2**
91 **complications may occur with or without preceding exacerbation of the angina pectoris. As**
92 **with other β -blockers, when discontinuation of COREG is planned, the patients should be**
93 **carefully observed and advised to limit physical activity to a minimum. COREG should be**
94 **discontinued over 1 to 2 weeks whenever possible. If the angina worsens or acute coronary**
95 **insufficiency develops, it is recommended that COREG be promptly reinstated, at least**
96 **temporarily. Because coronary artery disease is common and may be unrecognized, it may**
97 **be prudent not to discontinue therapy with COREG abruptly even in patients treated only**
98 **for hypertension or heart failure.**

99 **5.2 Bradycardia**

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

103 **5.3 Hypotension**

104 In clinical trials of primarily mild-to-moderate heart failure, hypotension and postural
105 hypotension occurred in 9.7% and syncope in 3.4% of patients receiving COREG compared to
106 3.6% and 2.5% of placebo patients, respectively. The risk for these events was highest during the
107 first 30 days of dosing, corresponding to the up-titration period and was a cause for
108 discontinuation of therapy in 0.7% of patients receiving COREG, compared to 0.4% of placebo
109 patients. In a long-term, placebo-controlled trial in severe heart failure (COPERNICUS),
110 hypotension and postural hypotension occurred in 15.1% and syncope in 2.9% of heart failure
111 patients receiving COREG compared to 8.7% and 2.3% of placebo patients, respectively. These
112 events were a cause for discontinuation of therapy in 1.1% of patients receiving COREG,
113 compared to 0.8% of placebo patients.

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

117 In the CAPRICORN study of survivors of an acute myocardial infarction, hypotension or
118 postural hypotension occurred in 20.2% of patients receiving COREG compared to 12.6% of
119 placebo patients. Syncope was reported in 3.9% and 1.9% of patients, respectively. These events
120 were a cause for discontinuation of therapy in 2.5% of patients receiving COREG, compared to
121 0.2% of placebo patients.

122 Starting with a low dose, administration with food, and gradual up-titration should
123 decrease the likelihood of syncope or excessive hypotension [*see Dosage and Administration*
124 (2.1, 2.2, 2.3)]. During initiation of therapy, the patient should be cautioned to avoid situations
125 such as driving or hazardous tasks, where injury could result should syncope occur.

126 **5.4 Heart Failure/Fluid Retention**

127 Worsening heart failure or fluid retention may occur during up-titration of carvedilol. If
128 such symptoms occur, diuretics should be increased and the carvedilol dose should not be
129 advanced until clinical stability resumes [*see Dosage and Administration (2)*]. Occasionally it is
130 necessary to lower the carvedilol dose or temporarily discontinue it. Such episodes do not
131 preclude subsequent successful titration of, or a favorable response to, carvedilol. In a
132 placebo-controlled trial of patients with severe heart failure, worsening heart failure during the
133 first 3 months was reported to a similar degree with carvedilol and with placebo. When treatment
134 was maintained beyond 3 months, worsening heart failure was reported less frequently in
135 patients treated with carvedilol than with placebo. Worsening heart failure observed during
136 long-term therapy is more likely to be related to the patients' underlying disease than to
137 treatment with carvedilol.

138 **5.5 Non-allergic Bronchospasm**

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

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

149 **5.6 Glycemic Control in Type 2 Diabetes**

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

155 In heart failure patients with diabetes, carvedilol therapy may lead to worsening
156 hyperglycemia, which responds to intensification of hypoglycemic therapy. It is recommended

157 that blood glucose be monitored when carvedilol dosing is initiated, adjusted, or discontinued.
158 Studies designed to examine the effects of carvedilol on glycemic control in patients with
159 diabetes and heart failure have not been conducted.

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

164 **5.7 Peripheral Vascular Disease**

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

167 **5.8 Deterioration of Renal Function**

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

175 **5.9 Major Surgery**

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

179 **5.10 Thyrotoxicosis**

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

183 **5.11 Pheochromocytoma**

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

188 **5.12 Prinzmetal's Variant Angina**

189 Agents with non-selective β -blocking activity may provoke chest pain in patients with
190 Prinzmetal's variant angina. There has been no clinical experience with carvedilol in these
191 patients although the α -blocking activity may prevent such symptoms. However, caution should
192 be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant
193 angina.

194 **5.13 Risk of Anaphylactic Reaction**

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

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

199 **5.14 Intraoperative Floppy Iris Syndrome**

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

209 **6 ADVERSE REACTIONS**

210 **6.1 Clinical Studies Experience**

211 COREG has been evaluated for safety in patients with heart failure (mild, moderate, and
212 severe), in patients with left ventricular dysfunction following myocardial infarction and in
213 hypertensive patients. The observed adverse event profile was consistent with the pharmacology
214 of the drug and the health status of the patients in the clinical trials. Adverse events reported for
215 each of these patient populations are provided below. Excluded are adverse events considered
216 too general to be informative, and those not reasonably associated with the use of the drug
217 because they were associated with the condition being treated or are very common in the treated
218 population. Rates of adverse events were generally similar across demographic subsets (men and
219 women, elderly and non-elderly, blacks and non-blacks).

220 Heart Failure: COREG has been evaluated for safety in heart failure in more than
221 4,500 patients worldwide of whom more than 2,100 participated in placebo-controlled clinical
222 trials. Approximately 60% of the total treated population in placebo-controlled clinical trials
223 received COREG for at least 6 months and 30% received COREG for at least 12 months. In the
224 COMET trial, 1,511 patients with mild-to-moderate heart failure were treated with COREG for
225 up to 5.9 years (mean 4.8 years). Both in US clinical trials in mild-to-moderate heart failure that
226 compared COREG in daily doses up to 100 mg (n = 765) to placebo (n = 437), and in a
227 multinational clinical trial in severe heart failure (COPERNICUS) that compared COREG in
228 daily doses up to 50 mg (n = 1,156) with placebo (n = 1,133), discontinuation rates for adverse
229 experiences were similar in carvedilol and placebo patients. In placebo-controlled clinical trials,
230 the only cause of discontinuation >1%, and occurring more often on carvedilol was dizziness
231 (1.3% on carvedilol, 0.6% on placebo in the COPERNICUS trial).

232 Table 1 shows adverse events reported in patients with mild-to-moderate heart failure
233 enrolled in US placebo-controlled clinical trials, and with severe heart failure enrolled in the
234 COPERNICUS trial. Shown are adverse events that occurred more frequently in drug-treated
235 patients than placebo-treated patients with an incidence of >3% in patients treated with

236 carvedilol regardless of causality. Median study medication exposure was 6.3 months for both
237 carvedilol and placebo patients in the trials of mild-to-moderate heart failure, and 10.4 months in
238 the trial of severe heart failure patients. The adverse event profile of COREG observed in the
239 long-term COMET study was generally similar to that observed in the US Heart Failure Trials.
240

241 **Table 1. Adverse Events (%) Occurring More Frequently With COREG Than With**
 242 **Placebo in Patients With Mild-to-Moderate Heart Failure (HF) Enrolled in US Heart**
 243 **Failure Trials or in Patients With Severe Heart Failure in the COPERNICUS Trial**
 244 **(Incidence >3% in Patients Treated With Carvedilol, Regardless of Causality)**

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

245

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

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

251 **Incidence >1% to ≤3%**

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

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

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

256 *Gastrointestinal:* Melena, periodontitis.

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

258 *Metabolic and Nutritional:* Hyperuricemia, hypoglycemia, hyponatremia, increased
259 alkaline phosphatase, glycosuria, hypervolemia, diabetes mellitus, GGT increased, weight loss,
260 hyperkalemia, creatinine increased.

261 *Musculoskeletal:* Muscle cramps.

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

263 *Psychiatric:* Somnolence.

264 *Reproductive, male:* Impotence.

265 *Special Senses:* Blurred vision.

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

267 **Left Ventricular Dysfunction Following Myocardial Infarction:** COREG has been
268 evaluated for safety in survivors of an acute myocardial infarction with left ventricular
269 dysfunction in the CAPRICORN trial which involved 969 patients who received COREG and
270 980 who received placebo. Approximately 75% of the patients received COREG for at least
271 6 months and 53% received COREG for at least 12 months. Patients were treated for an average
272 of 12.9 months and 12.8 months with COREG and placebo, respectively.

273 The most common adverse events reported with COREG in the CAPRICORN trial were
274 consistent with the profile of the drug in the US heart failure trials and the COPERNICUS trial.
275 The only additional adverse events reported in CAPRICORN in >3% of the patients and more
276 commonly on carvedilol were dyspnea, anemia, and lung edema. The following adverse events
277 were reported with a frequency of >1% but ≤3% and more frequently with COREG: Flu
278 syndrome, cerebrovascular accident, peripheral vascular disorder, hypotonia, depression,
279 gastrointestinal pain, arthritis, and gout. The overall rates of discontinuations due to adverse
280 events were similar in both groups of patients. In this database, the only cause of discontinuation
281 >1%, and occurring more often on carvedilol was hypotension (1.5% on carvedilol, 0.2% on
282 placebo).

283 **Hypertension:** COREG has been evaluated for safety in hypertension in more than
284 2,193 patients in US clinical trials and in 2,976 patients in international clinical trials.

285 Approximately 36% of the total treated population received COREG for at least 6 months. Most

286 adverse events reported during therapy with COREG were of mild to moderate severity. In US
287 controlled clinical trials directly comparing COREG in doses up to 50 mg (n = 1,142) to placebo
288 (n = 462), 4.9% of patients receiving COREG discontinued for adverse events versus 5.2% of
289 placebo patients. Although there was no overall difference in discontinuation rates,
290 discontinuations were more common in the carvedilol group for postural hypotension (1% versus
291 0). The overall incidence of adverse events in US placebo-controlled trials increased with
292 increasing dose of COREG. For individual adverse events this could only be distinguished for
293 dizziness, which increased in frequency from 2% to 5% as total daily dose increased from
294 6.25 mg to 50 mg.

295 Table 2 shows adverse events in US placebo-controlled clinical trials for hypertension
296 that occurred with an incidence of $\geq 1\%$ regardless of causality, and that were more frequent in
297 drug-treated patients than placebo-treated patients.

298

299 **Table 2. Adverse Events (%) Occurring in US Placebo-Controlled Hypertension Trials**
300 **(Incidence $\geq 1\%$, Regardless of Causality)***

	COREG (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	—

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

302

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

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

308

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

309

Cardiovascular: Peripheral ischemia, tachycardia.

310

Central and Peripheral Nervous System: Hypokinesia.

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

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

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

317 *Reproductive, male:* Decreased libido.

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

320 *Special Senses:* Tinnitus.

321 *Urinary System:* Micturition frequency increased.

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

323 *Metabolic and Nutritional:* Hypokalemia, hypertriglyceridemia.

324 *Hematologic:* Anemia, leukopenia.

325 The following events were reported in $\leq 0.1\%$ of patients and are potentially important:

326 Complete AV block, bundle branch block, myocardial ischemia, cerebrovascular disorder,
327 convulsions, migraine, neuralgia, paresis, anaphylactoid reaction, alopecia, exfoliative
328 dermatitis, amnesia, GI hemorrhage, bronchospasm, pulmonary edema, decreased hearing,
329 respiratory alkalosis, increased BUN, decreased HDL, pancytopenia, and atypical lymphocytes.

330 **6.2 Laboratory Abnormalities**

331 Reversible elevations in serum transaminases (ALT or AST) have been observed during
332 treatment with COREG. Rates of transaminase elevations (2- to 3-times the upper limit of
333 normal) observed during controlled clinical trials have generally been similar between patients
334 treated with COREG and those treated with placebo. However, transaminase elevations,
335 confirmed by rechallenge, have been observed with COREG. In a long-term, placebo-controlled
336 trial in severe heart failure, patients treated with COREG had lower values for hepatic
337 transaminases than patients treated with placebo, possibly because improvements in cardiac
338 function induced by COREG led to less hepatic congestion and/or improved hepatic blood flow.

339 COREG has not been associated with clinically significant changes in serum potassium,
340 total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or
341 creatinine. No clinically relevant changes were noted in fasting serum glucose in hypertensive
342 patients; fasting serum glucose was not evaluated in the heart failure clinical trials.

343 **6.3 Postmarketing Experience**

344 The following adverse reactions have been identified during post-approval use of
345 COREG. Because these reactions are reported voluntarily from a population of uncertain size, it
346 is not always possible to reliably estimate their frequency or establish a causal relationship to
347 drug exposure.

348

349 *Blood and Lymphatic System Disorders:* Aplastic anemia.

350

351 *Immune System Disorders:* Hypersensitivity (e.g., anaphylactic reactions, angioedema,
352 urticaria).

353

354 *Renal and Urinary Disorders:* Urinary incontinence.

355

356 *Respiratory, Thoracic and Mediastinal Disorders:* Interstitial pneumonitis.

357

358 *Skin and Subcutaneous Tissue Disorders:* Stevens-Johnson syndrome, toxic epidermal
359 necrolysis, erythema multiforme.

360

361 **7 DRUG INTERACTIONS**

362 **7.1 CYP2D6 Inhibitors and Poor Metabolizers**

363 Interactions of carvedilol with potent inhibitors of CYP2D6 isoenzyme (such as
364 quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would
365 be expected to increase blood levels of the R(+) enantiomer of carvedilol [see *Clinical*
366 *Pharmacology (12.3)*]. Retrospective analysis of side effects in clinical trials showed that poor
367 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from
368 vasodilating effects of the higher concentrations of the α -blocking R(+) enantiomer.

369 **7.2 Hypotensive Agents**

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

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

378 **7.3 Cyclosporine**

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

387 **7.4 Digitalis Glycosides**

388 Both digitalis glycosides and β -blockers slow atrioventricular conduction and decrease
389 heart rate. Concomitant use can increase the risk of bradycardia. Digoxin concentrations are
390 increased by about 15% when digoxin and carvedilol are administered concomitantly. Therefore,

391 increased monitoring of digoxin is recommended when initiating, adjusting, or discontinuing
392 COREG [see *Clinical Pharmacology (12.5)*].

393 **7.5 Inducers/Inhibitors of Hepatic Metabolism**

394 Rifampin reduced plasma concentrations of carvedilol by about 70% [see *Clinical*
395 *Pharmacology (12.5)*]. Cimetidine increased AUC by about 30% but caused no change in C_{max}
396 [see *Clinical Pharmacology (12.5)*].

397 **7.6 Amiodarone**

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

405 **7.7 Calcium Channel Blockers**

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

410 **7.8 Insulin or Oral Hypoglycemics**

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

414 **7.9 Anesthesia**

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

418 **8 USE IN SPECIFIC POPULATIONS**

419 **8.1 Pregnancy**

420 Pregnancy Category C. Studies performed in pregnant rats and rabbits given carvedilol
421 revealed increased post-implantation loss in rats at doses of 300 mg/kg/day (50 times the
422 maximum recommended human dose [MRHD] as mg/m²) and in rabbits at doses of
423 75 mg/kg/day (25 times the MRHD as mg/m²). In the rats, there was also a decrease in fetal body
424 weight at the maternally toxic dose of 300 mg/kg/day (50 times the MRHD as mg/m²), which
425 was accompanied by an elevation in the frequency of fetuses with delayed skeletal development
426 (missing or stunted 13th rib). In rats the no-observed-effect level for developmental toxicity was
427 60 mg/kg/day (10 times the MRHD as mg/m²); in rabbits it was 15 mg/kg/day (5 times the
428 MRHD as mg/m²). There are no adequate and well-controlled studies in pregnant women.

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

431 **8.3 Nursing Mothers**

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

441 **8.4 Pediatric Use**

442 Effectiveness of COREG in patients younger than 18 years of age has not been
443 established.

444 In a double-blind trial, 161 children (mean age 6 years, range 2 months to 17 years; 45%
445 less than 2 years old) with chronic heart failure [NYHA class II-IV, left ventricular ejection
446 fraction <40% for children with a systemic left ventricle (LV), and moderate-severe ventricular
447 dysfunction qualitatively by echo for those with a systemic ventricle that was not an LV] who
448 were receiving standard background treatment were randomized to placebo or to 2 dose levels of
449 carvedilol. These dose levels produced placebo-corrected heart rate reduction of 4-6 heart beats
450 per minute, indicative of β -blockade activity. Exposure appeared to be lower in pediatric subjects
451 than adults. After 8 months of follow-up, there was no significant effect of treatment on clinical
452 outcomes. Adverse reactions in this trial that occurred in greater than 10% of patients treated
453 with COREG and at twice the rate of placebo-treated patients included chest pain (17% versus
454 6%), dizziness (13% versus 2%), and dyspnea (11% versus 0%).

455 **8.5 Geriatric Use**

456 Of the 765 patients with heart failure randomized to COREG in US clinical trials, 31%
457 (235) were 65 years of age or older, and 7.3% (56) were 75 years of age or older. Of the
458 1,156 patients randomized to COREG in a long-term, placebo-controlled trial in severe heart
459 failure, 47% (547) were 65 years of age or older, and 15% (174) were 75 years of age or older.
460 Of 3,025 patients receiving COREG in heart failure trials worldwide, 42% were 65 years of age
461 or older.

462 Of the 975 myocardial infarction patients randomized to COREG in the CAPRICORN
463 trial, 48% (468) were 65 years of age or older, and 11% (111) were 75 years of age or older.

464 Of the 2,065 hypertensive patients in US clinical trials of efficacy or safety who were
465 treated with COREG, 21% (436) were 65 years of age or older. Of 3,722 patients receiving
466 COREG in hypertension clinical trials conducted worldwide, 24% were 65 years of age or older.

467 With the exception of dizziness in hypertensive patients (incidence 8.8% in the elderly
468 versus 6% in younger patients), no overall differences in the safety or effectiveness (see Figures

469 2 and 4) were observed between the older subjects and younger subjects in each of these
470 populations. Similarly, other reported clinical experience has not identified differences in
471 responses between the elderly and younger subjects, but greater sensitivity of some older
472 individuals cannot be ruled out.

473 10 OVERDOSAGE

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

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

480 *for excessive bradycardia:* Atropine, 2 mg IV.

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

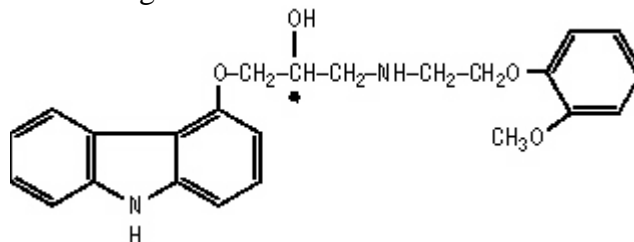
484 If peripheral vasodilation dominates, it may be necessary to administer adrenaline or
485 noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant
486 bradycardia, pacemaker therapy should be performed. For bronchospasm, β -sympathomimetics
487 (as aerosol or IV)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

489 NOTE: In the event of severe intoxication where there are symptoms of shock, treatment
490 with antidotes must be continued for a sufficiently long period of time consistent with the 7- to
491 10-hour half-life of carvedilol.

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

496 11 DESCRIPTION

497 Carvedilol is a nonselective β -adrenergic blocking agent with α_1 -blocking activity. It is
498 (\pm)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol. Carvedilol is a
499 racemic mixture with the following structure:



500

501 COREG is a white, oval, film-coated tablet containing 3.125 mg, 6.25 mg, 12.5 mg, or
502 25 mg of carvedilol. The 6.25 mg, 12.5 mg, and 25 mg tablets are TILTAB[®] tablets. Inactive

503 ingredients consist of colloidal silicon dioxide, crospovidone, hypromellose, lactose, magnesium
504 stearate, polyethylene glycol, polysorbate 80, povidone, sucrose, and titanium dioxide.

505 Carvedilol is a white to off-white powder with a molecular weight of 406.5 and a
506 molecular formula of $C_{24}H_{26}N_2O_4$. It is freely soluble in dimethylsulfoxide; soluble in methylene
507 chloride and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in
508 ethyl ether; and practically insoluble in water, gastric fluid (simulated, TS, pH 1.1), and intestinal
509 fluid (simulated, TS without pancreatin, pH 7.5).

510 **12 CLINICAL PHARMACOLOGY**

511 **12.1 Mechanism of Action**

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

515 **12.2 Pharmacodynamics**

516 Heart Failure: The basis for the beneficial effects of COREG in heart failure is not
517 established.

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

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

527 Among 839 patients with NYHA class II-III heart failure treated for 26 to 52 weeks in
528 4 US placebo-controlled trials, average left ventricular ejection fraction (EF) measured by
529 radionuclide ventriculography increased by 9 EF units (%) in patients receiving COREG and by
530 2 EF units in placebo patients at a target dose of 25-50 mg twice daily. The effects of carvedilol
531 on ejection fraction were related to dose. Doses of 6.25 mg twice daily, 12.5 mg twice daily, and
532 25 mg twice daily were associated with placebo-corrected increases in EF of 5 EF units, 6 EF
533 units, and 8 EF units, respectively; each of these effects were nominally statistically significant.

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

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

539 β -adrenoreceptor blocking activity has been demonstrated in animal and human studies
540 showing that carvedilol (1) reduces cardiac output in normal subjects; (2) reduces exercise-

541 and/or isoproterenol-induced tachycardia; and (3) reduces reflex orthostatic tachycardia.
542 Significant β -adrenoreceptor blocking effect is usually seen within 1 hour of drug administration.
543 α_1 -adrenoreceptor blocking activity has been demonstrated in human and animal studies,
544 showing that carvedilol (1) attenuates the pressor effects of phenylephrine; (2) causes
545 vasodilation; and (3) reduces peripheral vascular resistance. These effects contribute to the
546 reduction of blood pressure and usually are seen within 30 minutes of drug administration.

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

553 In hypertensive patients with normal renal function, therapeutic doses of COREG
554 decreased renal vascular resistance with no change in glomerular filtration rate or renal plasma
555 flow. Changes in excretion of sodium, potassium, uric acid, and phosphorus in hypertensive
556 patients with normal renal function were similar after COREG and placebo.

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

560 **12.3 Pharmacokinetics**

561 COREG is rapidly and extensively absorbed following oral administration, with absolute
562 bioavailability of approximately 25% to 35% due to a significant degree of first-pass
563 metabolism. Following oral administration, the apparent mean terminal elimination half-life of
564 carvedilol generally ranges from 7 to 10 hours. Plasma concentrations achieved are proportional
565 to the oral dose administered. When administered with food, the rate of absorption is slowed, as
566 evidenced by a delay in the time to reach peak plasma levels, with no significant difference in
567 extent of bioavailability. Taking COREG with food should minimize the risk of orthostatic
568 hypotension.

569 Carvedilol is extensively metabolized. Following oral administration of radiolabelled
570 carvedilol to healthy volunteers, carvedilol accounted for only about 7% of the total radioactivity
571 in plasma as measured by area under the curve (AUC). Less than 2% of the dose was excreted
572 unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and
573 glucuronidation. The oxidative metabolites are further metabolized by conjugation via
574 glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile
575 into the feces. Demethylation and hydroxylation at the phenol ring produce 3 active metabolites
576 with β -receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl metabolite
577 is approximately 13 times more potent than carvedilol for β -blockade.

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

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

585 The primary P450 enzymes responsible for the metabolism of both R(+) and
586 S(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent
587 CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and
588 5'-hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be
589 of primary importance in the O-methylation pathway of S(-)-carvedilol.

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

597 Carvedilol is more than 98% bound to plasma proteins, primarily with albumin. The
598 plasma-protein binding is independent of concentration over the therapeutic range. Carvedilol is
599 a basic, lipophilic compound with a steady-state volume of distribution of approximately 115 L,
600 indicating substantial distribution into extravascular tissues. Plasma clearance ranges from 500 to
601 700 mL/min.

602 **12.4 Specific Populations**

603 Heart Failure: Steady-state plasma concentrations of carvedilol and its enantiomers
604 increased proportionally over the 6.25 to 50 mg dose range in patients with heart failure.
605 Compared to healthy subjects, heart failure patients had increased mean AUC and C_{max} values
606 for carvedilol and its enantiomers, with up to 50% to 100% higher values observed in 6 patients
607 with NYHA class IV heart failure. The mean apparent terminal elimination half-life for
608 carvedilol was similar to that observed in healthy subjects.

609 Geriatric: Plasma levels of carvedilol average about 50% higher in the elderly compared
610 to young subjects.

611 Hepatic Impairment: Compared to healthy subjects, patients with severe liver
612 impairment (cirrhosis) exhibit a 4- to 7-fold increase in carvedilol levels. Carvedilol is
613 contraindicated in patients with severe liver impairment.

614 Renal Impairment: Although carvedilol is metabolized primarily by the liver, plasma
615 concentrations of carvedilol have been reported to be increased in patients with renal
616 impairment. Based on mean AUC data, approximately 40% to 50% higher plasma concentrations
617 of carvedilol were observed in hypertensive patients with moderate to severe renal impairment
618 compared to a control group of hypertensive patients with normal renal function. However, the
619 ranges of AUC values were similar for both groups. Changes in mean peak plasma levels were
620 less pronounced, approximately 12% to 26% higher in patients with impaired renal function.

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

623 **12.5 Drug-Drug Interactions**

624 Since carvedilol undergoes substantial oxidative metabolism, the metabolism and
625 pharmacokinetics of carvedilol may be affected by induction or inhibition of cytochrome P450
626 enzymes.

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

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

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

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

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

644 Rifampin: In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin
645 (600 mg daily for 12 days) decreased the AUC and C_{max} of carvedilol by about 70% [*see Drug*
646 *Interactions (7.5)*].

647 Torsemide: In a study of 12 healthy subjects, combined oral administration of carvedilol
648 25 mg once daily and torsemide 5 mg once daily for 5 days did not result in any significant
649 differences in their pharmacokinetics compared with administration of the drugs alone.

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

653 **13 NONCLINICAL TOXICOLOGY**

654 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

666 **14 CLINICAL STUDIES**

667 **14.1 Heart Failure**

668 A total of 6,975 patients with mild to severe heart failure were evaluated in
669 placebo-controlled studies of carvedilol.

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

673 Four US multicenter, double-blind, placebo-controlled studies enrolled 1,094 patients
674 (696 randomized to carvedilol) with NYHA class II-III heart failure and ejection fraction ≤ 0.35 .
675 The vast majority were on digitalis, diuretics, and an ACE inhibitor at study entry. Patients were
676 assigned to the studies based upon exercise ability. An Australia-New Zealand double-blind,
677 placebo-controlled study enrolled 415 patients (half randomized to carvedilol) with less severe
678 heart failure. All protocols excluded patients expected to undergo cardiac transplantation during
679 the 7.5 to 15 months of double-blind follow-up. All randomized patients had tolerated a 2-week
680 course on carvedilol 6.25 mg twice daily.

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

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

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

694 In the Australia-New Zealand study, death and total hospitalizations were reduced by
695 about 25% over 18 to 24 months. In the 3 largest US studies, death and total hospitalizations

696 were reduced by 19%, 39%, and 49%, nominally statistically significant in the last 2 studies. The
697 Australia-New Zealand results were statistically borderline.

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

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

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

708 *COMET Trial:* In this double-blind trial, 3,029 patients with NYHA class II-IV heart
709 failure (left ventricular ejection fraction $\leq 35\%$) were randomized to receive either carvedilol
710 (target dose: 25 mg twice daily) or immediate-release metoprolol tartrate (target dose: 50 mg
711 twice daily). The mean age of the patients was approximately 62 years, 80% were males, and the
712 mean left ventricular ejection fraction at baseline was 26%. Approximately 96% of the patients
713 had NYHA class II or III heart failure. Concomitant treatment included diuretics (99%), ACE
714 inhibitors (91%), digitalis (59%), aldosterone antagonists (11%), and “statin” lipid-lowering
715 agents (21%). The mean duration of follow-up was 4.8 years. The mean dose of carvedilol was
716 42 mg per day.

717 The study had 2 primary end points: All-cause mortality and the composite of death plus
718 hospitalization for any reason. The results of COMET are presented in Table 3 below. All-cause
719 mortality carried most of the statistical weight and was the primary determinant of the study size.
720 All-cause mortality was 34% in the patients treated with carvedilol and was 40% in the
721 immediate-release metoprolol group ($p = 0.0017$; hazard ratio = 0.83, 95% CI 0.74-0.93). The
722 effect on mortality was primarily due to a reduction in cardiovascular death. The difference
723 between the 2 groups with respect to the composite end point was not significant ($p = 0.122$).
724 The estimated mean survival was 8.0 years with carvedilol and 6.6 years with immediate-release
725 metoprolol.

726

727

Table 3. 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

728

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

734 **Severe Heart Failure (COPERNICUS):** In a double-blind study (COPERNICUS),
735 2,289 patients with heart failure at rest or with minimal exertion and left ventricular ejection
736 fraction <25% (mean 20%), despite digitalis (66%), diuretics (99%), and ACE inhibitors (89%)
737 were randomized to placebo or carvedilol. Carvedilol was titrated from a starting dose of
738 3.125 mg twice daily to the maximum tolerated dose or up to 25 mg twice daily over a minimum
739 of 6 weeks. Most subjects achieved the target dose of 25 mg. The study was conducted in
740 Eastern and Western Europe, the United States, Israel, and Canada. Similar numbers of subjects
741 per group (about 100) withdrew during the titration period.

742 The primary end point of the trial was all-cause mortality, but cause-specific mortality
743 and the risk of death or hospitalization (total, cardiovascular [CV], or heart failure [HF]) were
744 also examined. The developing trial data were followed by a data monitoring committee, and
745 mortality analyses were adjusted for these multiple looks. The trial was stopped after a median
746 follow-up of 10 months because of an observed 35% reduction in mortality (from 19.7% per
747 patient year on placebo to 12.8% on carvedilol, hazard ratio 0.65, 95% CI 0.52 – 0.81,
748 p = 0.0014, adjusted) (see Figure 1). The results of COPERNICUS are shown in Table 4.

749

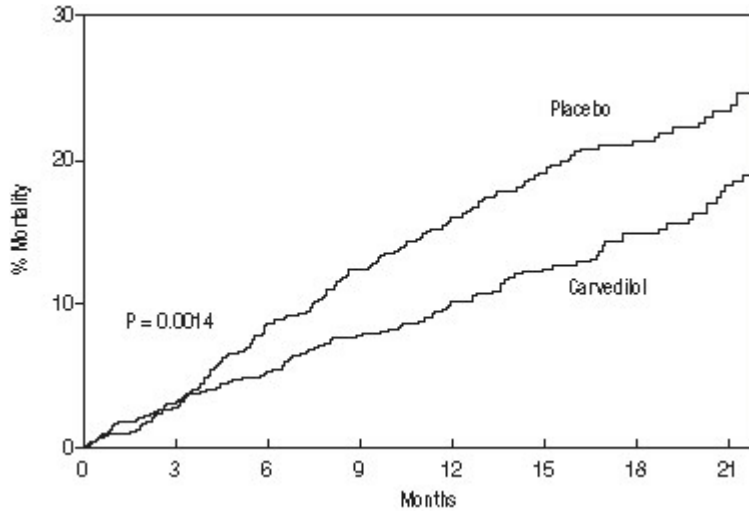
750 **Table 4. Results of COPERNICUS Trial in Patients With Severe Heart Failure**

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

751 Cardiovascular = CV; Heart failure = HF.

752

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



754

755

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

758

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

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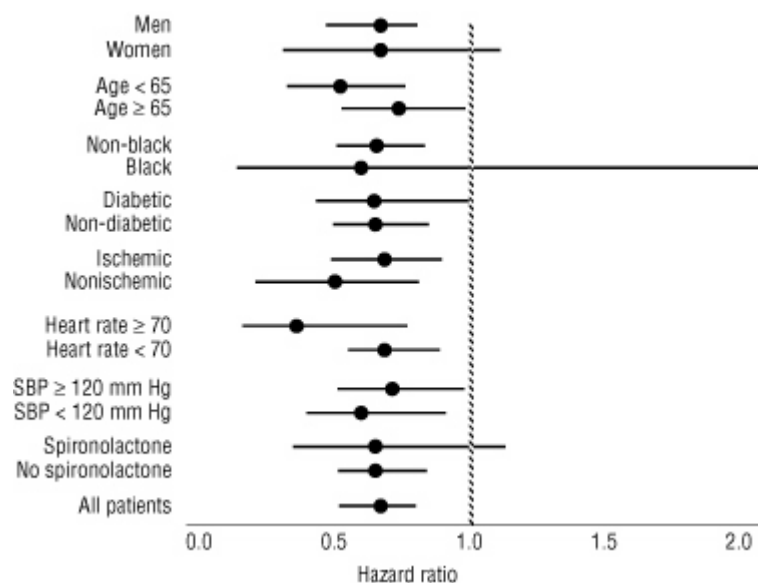
765 The protocol also specified that hospitalizations would be assessed. Fewer patients on
766 COREG than on placebo were hospitalized for any reason (372 versus 432, $p = 0.0029$), for
767 cardiovascular reasons (246 versus 314, $p = 0.0003$), or for worsening heart failure (198 versus
768 268, $p = 0.0001$).

769

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

774

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



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14.2 Left Ventricular Dysfunction Following Myocardial Infarction

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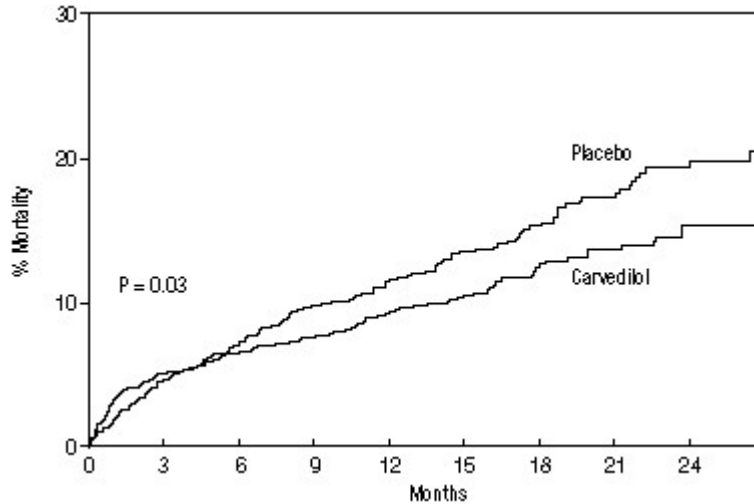
800

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

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

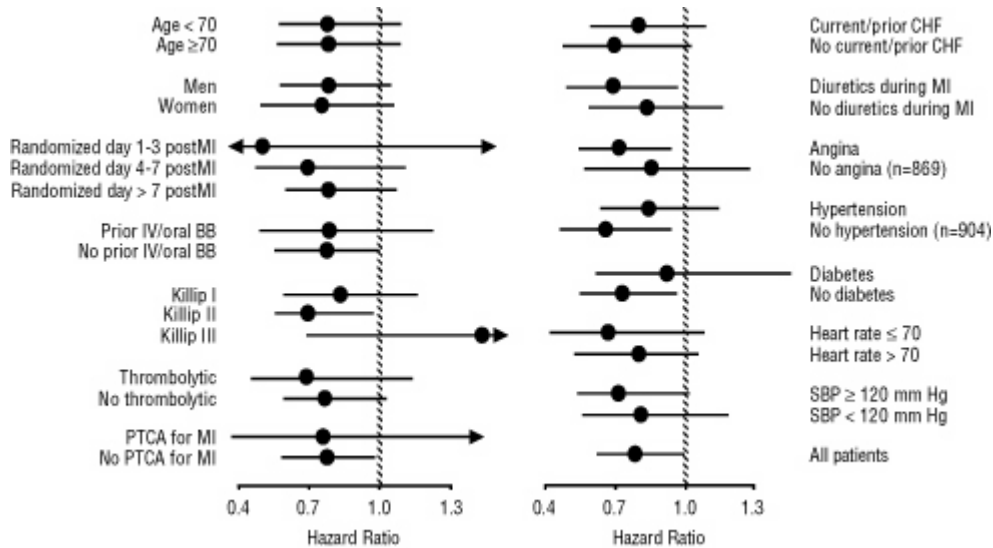
There was also a significant 40% reduction in fatal or non-fatal myocardial infarction observed in the group treated with carvedilol (95% CI 11% to 60%, $p = 0.01$). A similar reduction in the risk of myocardial infarction was also observed in a meta-analysis of placebo-controlled trials of carvedilol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

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



802
803

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



805
806

807 **14.3 Hypertension**

808 COREG was studied in 2 placebo-controlled trials that utilized twice-daily dosing, at
 809 total daily doses of 12.5 to 50 mg. In these and other studies, the starting dose did not exceed
 810 12.5 mg. At 50 mg/day, COREG reduced sitting trough (12-hour) blood pressure by about
 811 9/5.5 mm Hg; at 25 mg/day the effect was about 7.5/3.5 mm Hg. Comparisons of trough to peak
 812 blood pressure showed a trough to peak ratio for blood pressure response of about 65%. Heart
 813 rate fell by about 7.5 beats/minute at 50 mg/day. In general, as is true for other β-blockers,
 814 responses were smaller in black than non-black patients. There were no age- or gender-related
 815 differences in response.

816 The peak antihypertensive effect occurred 1 to 2 hours after a dose. The dose-related
817 blood pressure response was accompanied by a dose-related increase in adverse effects [*see*
818 *Adverse Reactions (6)*].

819 **14.4 Hypertension With Type 2 Diabetes Mellitus**

820 In a double-blind study (GEMINI), COREG, added to an ACE inhibitor or angiotensin
821 receptor blocker, was evaluated in a population with mild-to-moderate hypertension and well-
822 controlled type 2 diabetes mellitus. The mean HbA1c at baseline was 7.2%. COREG was titrated
823 to a mean dose of 17.5 mg twice daily and maintained for 5 months. COREG had no adverse
824 effect on glycemic control, based on HbA1c measurements (mean change from baseline of
825 0.02%, 95% CI -0.06 to 0.10, p = NS) [*see Warnings and Precautions (5.6)*].

826 **16 HOW SUPPLIED/STORAGE AND HANDLING**

827 The white, oval, film-coated tablets are available in the following strengths: 3.125 mg–
828 engraved with 39 and SB, in bottles of 100; 6.25 mg–engraved with 4140 and SB, in bottles of
829 100; 12.5 mg–engraved with 4141 and SB, in bottles of 100; 25 mg–engraved with 4142 and SB,
830 in bottles of 100. The 6.25 mg, 12.5 mg, and 25 mg tablets are TILTAB tablets.

- 831 • 3.125 mg 100's: NDC 0007-4139-20
- 832 • 6.25 mg 100's: NDC 0007-4140-20
- 833 • 12.5 mg 100's: NDC 0007-4141-20
- 834 • 25 mg 100's: NDC 0007-4142-20

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

836 **17 PATIENT COUNSELING INFORMATION**

837 *See FDA-Approved Patient Labeling (17.2).*

838 **17.1 Patient Advice**

839 Patients taking COREG should be advised of the following:

- 840 • Patients should take COREG with food.
- 841 • Patients should not interrupt or discontinue using COREG without a physician's advice.
- 842 • Patients with heart failure should consult their physician if they experience signs or
843 symptoms of worsening heart failure such as weight gain or increasing shortness of breath.
- 844 • Patients may experience a drop in blood pressure when standing, resulting in dizziness and,
845 rarely, fainting. Patients should sit or lie down when these symptoms of lowered blood
846 pressure occur.
- 847 • If experiencing dizziness or fatigue, patients should avoid driving or hazardous tasks.
- 848 • Patients should consult a physician if they experience dizziness or faintness, in case the
849 dosage should be adjusted.
- 850 • Diabetic patients should report any changes in blood sugar levels to their physician.
- 851 • Contact lens wearers may experience decreased lacrimation.

852 **17.2 FDA-Approved Patient Labeling**

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

855

856 COREG, COREG CR, and TILTAB are registered trademarks of GlaxoSmithKline.

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

858



859

860 Manufactured for

861 **GlaxoSmithKline**

862 Research Triangle Park, NC 27709

863 Manufactured by

864 **Patheon Puerto Rico, Inc.**

865 Manati, PR 00674 USA

866

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869 February 2011

870 CRG:21PI

871 PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

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873

874

PATIENT INFORMATION

875

COREG[®] (Co-REG)

876

Carvedilol Tablets

877

878 Read the Patient Information that comes with COREG before you start taking it and each time

879 you get a refill. There may be new information. This information does not take the place of

880 talking with your doctor about your medical condition or your treatment. If you have any

881 questions about COREG, ask your doctor or pharmacist.

882

883 **What is COREG?**

884 COREG is a prescription medicine that belongs to a group of medicines called “beta-blockers”.

885 COREG is used, often with other medicines, for the following conditions:

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

889

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

891

892 **Who should not take COREG?**

893 Do not take COREG if you:

- 894 • Have severe heart failure and are hospitalized in the intensive care unit or require certain
- 895 intravenous medications that help support circulation (inotropic medications)
- 896 • Are prone to asthma or other breathing problems
- 897 • Have a slow heartbeat or a heart that skips a beat (irregular heartbeat)
- 898 • Have liver problems
- 899 • Are allergic to any of the ingredients in COREG. The active ingredient is carvedilol. See the
- 900 end of this leaflet for a list of all the ingredients in COREG.

901

902 **What should I tell my doctor before taking COREG?**

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

- 904 • Have asthma or other lung problems (such as bronchitis or emphysema)
- 905 • Have problems with blood flow in your feet and legs (peripheral vascular disease) COREG
- 906 can make some of your symptoms worse.
- 907 • Have diabetes
- 908 • Have thyroid problems
- 909 • Have a condition called pheochromocytoma
- 910 • Have had severe allergic reactions

- 911 • Are pregnant or trying to become pregnant. It is not known if COREG is safe for your unborn
912 baby. You and your doctor should talk about the best way to control your high blood pressure
913 during pregnancy.
- 914 • Are breastfeeding. It is not known if COREG passes into your breast milk. You should not
915 breastfeed while using COREG.
- 916 • Are scheduled for surgery and will be given anesthetic agents
- 917 • Are scheduled for cataract surgery and have taken or are currently taking COREG.
- 918 • Are taking prescription or non-prescription medicines, vitamins, and herbal supplements.
919 COREG and certain other medicines can affect each other and cause serious side effects.
920 COREG may affect the way other medicines work. Also, other medicines may affect how
921 well COREG works.

922

923 Keep a list of all the medicines you take. Show this list to your doctor and pharmacist before you
924 start a new medicine.

925

926 **How should I take COREG?**

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

- 931 • Take COREG exactly as prescribed. Your doctor will tell you how many tablets to take and
932 how often. In order to minimize possible side effects, your doctor might begin with a low
933 dose and then slowly increase the dose.
- 934 • **Do not stop taking COREG and do not change the amount of COREG you take without**
935 **talking to your doctor.**
- 936 • Tell your doctor if you gain weight or have trouble breathing while taking COREG.
- 937 • Take COREG with food.
- 938 • If you miss a dose of COREG, take your dose as soon as you remember, unless it is time to
939 take your next dose. Take your next dose at the usual time. Do not take 2 doses at the same
940 time.
- 941 • If you take too much COREG, call your doctor or poison control center right away.

942

943 **What should I avoid while taking COREG?**

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

946

947 **What are possible side effects of COREG?**

- 948 • Low blood pressure (which may cause dizziness or fainting when you stand up). If these
949 happen, sit or lie down right away and tell your doctor.
- 950 • **Tiredness.** If you feel tired or dizzy you should not drive, use machinery, or do anything that
951 needs you to be alert.

- 952 • Slow heartbeat.
953 • Changes in your blood sugar. If you have diabetes, tell your doctor if you have any changes
954 in your blood sugar levels.
955 • COREG may hide some of the symptoms of low blood sugar, especially a fast heartbeat.
956 • COREG may mask the symptoms of hyperthyroidism (overactive thyroid).
957 • Worsening of severe allergic reactions.
958 • Rare but serious allergic reactions (including hives or swelling of the face, lips, tongue,
959 and/or throat that may cause difficulty in breathing or swallowing) have happened in patients
960 who were on COREG. These reactions can be life-threatening.

961

962 Other side effects of COREG include shortness of breath, weight gain, diarrhea, and fewer tears
963 or dry eyes that become bothersome if you wear contact lenses.

964

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

966

967 **How should I store COREG?**

- 968 • Store COREG at less than 86°F (30°C). Keep the tablets dry.
969 • Safely, throw away COREG that is out of date or no longer needed.
970 • Keep COREG and all medicines out of the reach of children.

971

972 **General Information about COREG**

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

976

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

981

982 **What are the ingredients in COREG?**

983 Active Ingredient: Carvedilol.

984

985 Inactive Ingredients: Colloidal silicon dioxide, crospovidone, hypromellose, lactose, magnesium
986 stearate, polyethylene glycol, polysorbate 80, povidone, sucrose, and titanium dioxide.

987

988 Carvedilol tablets come in the following strengths: 3.125 mg, 6.25 mg, 12.5 mg, 25 mg.

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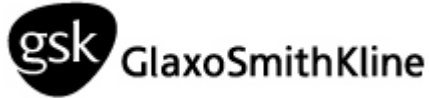
990 **What is high blood pressure (hypertension)?**

991 Blood pressure is the force of blood in your blood vessels when your heart beats and when your
992 heart rests. You have high blood pressure when the force is too much. High blood pressure

993 makes the heart work harder to pump blood through the body and causes damage to blood
994 vessels. COREG can help your blood vessels relax so your blood pressure is lower. Medicines
995 that lower blood pressure may lower your chance of having a stroke or heart attack.

996

997 COREG is a registered trademark of GlaxoSmithKline.



998

999 Manufactured for

1000 **GlaxoSmithKline**

1001 Research Triangle Park, NC 27709

1002 Manufactured by

1003 **Patheon Puerto Rico, Inc.**

1004 Manati, PR 00674 USA

1005

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1008 January 2011

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