

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

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

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 carvedilol, any of the components of COREG, or to 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

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. (7.6)
- Insulin and oral hypoglycemics action may be enhanced. (7.7)

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

Revised: December 2008
CRG:XXPI

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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 carvedilol, any of the components of
84 COREG, or to COREG CR

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 Anesthesia and Major Surgery**

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

180 **5.10 Thyrotoxicosis**

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

184 **5.11 Pheochromocytoma**

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

189 **5.12 Prinzmetal's Variant Angina**

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

195 **5.13 Risk of Anaphylactic Reaction**

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

200 **6 ADVERSE REACTIONS**

201 **6.1 Clinical Studies Experience**

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

211 Heart Failure: COREG has been evaluated for safety in heart failure in more than
212 4,500 patients worldwide of whom more than 2,100 participated in placebo-controlled clinical
213 trials. Approximately 60% of the total treated population in placebo-controlled clinical trials
214 received COREG for at least 6 months and 30% received COREG for at least 12 months. In the
215 COMET trial, 1,511 patients with mild-to-moderate heart failure were treated with COREG for
216 up to 5.9 years (mean 4.8 years). Both in US clinical trials in mild-to-moderate heart failure that
217 compared COREG in daily doses up to 100 mg (n = 765) to placebo (n = 437), and in a
218 multinational clinical trial in severe heart failure (COPERNICUS) that compared COREG in
219 daily doses up to 50 mg (n = 1,156) with placebo (n = 1,133), discontinuation rates for adverse
220 experiences were similar in carvedilol and placebo patients. In placebo-controlled clinical trials,
221 the only cause of discontinuation >1%, and occurring more often on carvedilol was dizziness
222 (1.3% on carvedilol, 0.6% on placebo in the COPERNICUS trial).

223 Table 1 shows adverse events reported in patients with mild-to-moderate heart failure
224 enrolled in US placebo-controlled clinical trials, and with severe heart failure enrolled in the
225 COPERNICUS trial. Shown are adverse events that occurred more frequently in drug-treated
226 patients than placebo-treated patients with an incidence of >3% in patients treated with
227 carvedilol regardless of causality. Median study medication exposure was 6.3 months for both
228 carvedilol and placebo patients in the trials of mild-to-moderate heart failure, and 10.4 months in
229 the trial of severe heart failure patients. The adverse event profile of COREG observed in the
230 long-term COMET study was generally similar to that observed in the US Heart Failure Trials.

231

232 **Table 1. Adverse Events (%) Occurring More Frequently With COREG Than With**
 233 **Placebo in Patients With Mild-to-Moderate Heart Failure (HF) Enrolled in US Heart**
 234 **Failure Trials or in Patients With Severe Heart Failure in the COPERNICUS Trial**
 235 **(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	—	—

236

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

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

242 **Incidence >1% to ≤3%**

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

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

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

247 *Gastrointestinal:* Melena, periodontitis.

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

249 *Metabolic and Nutritional:* Hyperuricemia, hypoglycemia, hyponatremia, increased
250 alkaline phosphatase, glycosuria, hypervolemia, diabetes mellitus, GGT increased, weight loss,
251 hyperkalemia, creatinine increased.

252 *Musculoskeletal:* Muscle cramps.

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

254 *Psychiatric:* Somnolence.

255 *Reproductive, male:* Impotence.

256 *Special Senses:* Blurred vision.

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

258 **Left Ventricular Dysfunction Following Myocardial Infarction:** COREG has been
259 evaluated for safety in survivors of an acute myocardial infarction with left ventricular
260 dysfunction in the CAPRICORN trial which involved 969 patients who received COREG and
261 980 who received placebo. Approximately 75% of the patients received COREG for at least
262 6 months and 53% received COREG for at least 12 months. Patients were treated for an average
263 of 12.9 months and 12.8 months with COREG and placebo, respectively.

264 The most common adverse events reported with COREG in the CAPRICORN trial were
265 consistent with the profile of the drug in the US heart failure trials and the COPERNICUS trial.
266 The only additional adverse events reported in CAPRICORN in >3% of the patients and more
267 commonly on carvedilol were dyspnea, anemia, and lung edema. The following adverse events
268 were reported with a frequency of >1% but ≤3% and more frequently with COREG: Flu
269 syndrome, cerebrovascular accident, peripheral vascular disorder, hypotonia, depression,
270 gastrointestinal pain, arthritis, and gout. The overall rates of discontinuations due to adverse
271 events were similar in both groups of patients. In this database, the only cause of discontinuation
272 >1%, and occurring more often on carvedilol was hypotension (1.5% on carvedilol, 0.2% on
273 placebo).

274 **Hypertension:** COREG has been evaluated for safety in hypertension in more than
275 2,193 patients in US clinical trials and in 2,976 patients in international clinical trials.
276 Approximately 36% of the total treated population received COREG for at least 6 months. Most

277 adverse events reported during therapy with COREG were of mild to moderate severity. In US
 278 controlled clinical trials directly comparing COREG in doses up to 50 mg (n = 1,142) to placebo
 279 (n = 462), 4.9% of patients receiving COREG discontinued for adverse events versus 5.2% of
 280 placebo patients. Although there was no overall difference in discontinuation rates,
 281 discontinuations were more common in the carvedilol group for postural hypotension (1% versus
 282 0). The overall incidence of adverse events in US placebo-controlled trials increased with
 283 increasing dose of COREG. For individual adverse events this could only be distinguished for
 284 dizziness, which increased in frequency from 2% to 5% as total daily dose increased from
 285 6.25 mg to 50 mg.

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

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

	COREG	Placebo
	(n = 1,142)	(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	—

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

293
 294 Dyspnea and fatigue were also reported in these studies, but the rates were equal or
 295 greater in patients who received placebo.

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

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

300 *Cardiovascular:* Peripheral ischemia, tachycardia.

301 *Central and Peripheral Nervous System:* Hypokinesia.

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

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

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

308 *Reproductive, male:* Decreased libido.

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

311 *Special Senses:* Tinnitus.

312 *Urinary System:* Micturition frequency increased.

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

314 *Metabolic and Nutritional:* Hypokalemia, hypertriglyceridemia.

315 *Hematologic:* Anemia, leukopenia.

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

321 **6.2 Laboratory Abnormalities**

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

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

334 **6.3 Postmarketing Experience**

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

339 Reports of aplastic anemia and severe skin reactions (Stevens-Johnson syndrome, toxic
340 epidermal necrolysis, and erythema multiforme) have been rare and received only when
341 carvedilol was administered concomitantly with other medications associated with such

342 reactions. Rare reports of hypersensitivity reactions (e.g., anaphylactic reaction, angioedema, and
343 urticaria) have been received for COREG and COREG CR[®], including cases occurring after the
344 initiation of COREG CR in patients previously treated with COREG. Urinary incontinence in
345 women (which resolved upon discontinuation of the medication) and interstitial pneumonitis
346 have been reported rarely.

347 **7 DRUG INTERACTIONS**

348 **7.1 CYP2D6 Inhibitors and Poor Metabolizers**

349 Interactions of carvedilol with potent inhibitors of CYP2D6 isoenzyme (such as
350 quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would
351 be expected to increase blood levels of the R(+) enantiomer of carvedilol [*see Clinical*
352 *Pharmacology (12.3)*]. Retrospective analysis of side effects in clinical trials showed that poor
353 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from
354 vasodilating effects of the higher concentrations of the α -blocking R(+) enantiomer.

355 **7.2 Hypotensive Agents**

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

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

364 **7.3 Cyclosporine**

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

373 **7.4 Digitalis Glycosides**

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

379 **7.5 Inducers/Inhibitors of Hepatic Metabolism**

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

383 **7.6 Amiodarone**

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

391 **7.7 Calcium Channel Blockers**

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

396 **7.8 Insulin or Oral Hypoglycemics**

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

400 **8 USE IN SPECIFIC POPULATIONS**

401 **8.1 Pregnancy**

402 Pregnancy Category C. Studies performed in pregnant rats and rabbits given carvedilol
403 revealed increased post-implantation loss in rats at doses of 300 mg/kg/day (50 times the
404 maximum recommended human dose [MRHD] as mg/m^2) and in rabbits at doses of
405 75 mg/kg/day (25 times the MRHD as mg/m^2). In the rats, there was also a decrease in fetal body
406 weight at the maternally toxic dose of 300 mg/kg/day (50 times the MRHD as mg/m^2), which
407 was accompanied by an elevation in the frequency of fetuses with delayed skeletal development
408 (missing or stunted 13th rib). In rats the no-observed-effect level for developmental toxicity was
409 60 mg/kg/day (10 times the MRHD as mg/m^2); in rabbits it was 15 mg/kg/day (5 times the
410 MRHD as mg/m^2). There are no adequate and well-controlled studies in pregnant women.
411 COREG should be used during pregnancy only if the potential benefit justifies the potential risk
412 to the fetus.

413 **8.3 Nursing Mothers**

414 It is not known whether this drug is excreted in human milk. Studies in rats have shown
415 that carvedilol and/or its metabolites (as well as other β -blockers) cross the placental barrier and
416 are excreted in breast milk. There was increased mortality at one week post-partum in neonates
417 from rats treated with 60 mg/kg/day (10 times the MRHD as mg/m^2) and above during the last

418 trimester through day 22 of lactation. Because many drugs are excreted in human milk and
419 because of the potential for serious adverse reactions in nursing infants from β -blockers,
420 especially bradycardia, a decision should be made whether to discontinue nursing or to
421 discontinue the drug, taking into account the importance of the drug to the mother. The effects of
422 other α - and β -blocking agents have included perinatal and neonatal distress.

423 **8.4 Pediatric Use**

424 Effectiveness of COREG in patients younger than 18 years of age has not been
425 established.

426 In a double-blind trial, 161 children (mean age 6 years, range 2 months to 17 years; 45%
427 less than 2 years old) with chronic heart failure [NYHA class II-IV, left ventricular ejection
428 fraction <40% for children with a systemic left ventricle (LV), and moderate-severe ventricular
429 dysfunction qualitatively by echo for those with a systemic ventricle that was not an LV] who
430 were receiving standard background treatment were randomized to placebo or to 2 dose levels of
431 carvedilol. These dose levels produced placebo-corrected heart rate reduction of 4-6 heart beats
432 per minute, indicative of β -blockade activity. Exposure appeared to be lower in pediatric subjects
433 than adults. After 8 months of follow-up, there was no significant effect of treatment on clinical
434 outcomes. Adverse reactions in this trial that occurred in greater than 10% of patients treated
435 with COREG and at twice the rate of placebo-treated patients included chest pain (17% versus
436 6%), dizziness (13% versus 2%), and dyspnea (11% versus 0%).

437 **8.5 Geriatric Use**

438 Of the 765 patients with heart failure randomized to COREG in US clinical trials, 31%
439 (235) were 65 years of age or older, and 7.3% (56) were 75 years of age or older. Of the
440 1,156 patients randomized to COREG in a long-term, placebo-controlled trial in severe heart
441 failure, 47% (547) were 65 years of age or older, and 15% (174) were 75 years of age or older.
442 Of 3,025 patients receiving COREG in heart failure trials worldwide, 42% were 65 years of age
443 or older.

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

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

449 With the exception of dizziness in hypertensive patients (incidence 8.8% in the elderly
450 versus 6% in younger patients), no overall differences in the safety or effectiveness (see Figures
451 2 and 4) were observed between the older subjects and younger subjects in each of these
452 populations. Similarly, other reported clinical experience has not identified differences in
453 responses between the elderly and younger subjects, but greater sensitivity of some older
454 individuals cannot be ruled out.

455 **10 OVERDOSAGE**

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

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

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

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

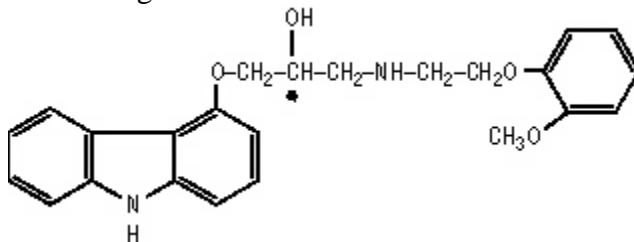
466 If peripheral vasodilation dominates, it may be necessary to administer adrenaline or
467 noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant
468 bradycardia, pacemaker therapy should be performed. For bronchospasm, β -sympathomimetics
469 (as aerosol or IV)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

471 NOTE: In the event of severe intoxication where there are symptoms of shock, treatment
472 with antidotes must be continued for a sufficiently long period of time consistent with the 7- to
473 10-hour half-life of carvedilol.

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

478 **11 DESCRIPTION**

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



482

483 COREG is a white, oval, film-coated tablet containing 3.125 mg, 6.25 mg, 12.5 mg, or
484 25 mg of carvedilol. The 6.25 mg, 12.5 mg, and 25 mg tablets are TILTAB[®] tablets. Inactive
485 ingredients consist of colloidal silicon dioxide, crospovidone, hypromellose, lactose, magnesium
486 stearate, polyethylene glycol, polysorbate 80, povidone, sucrose, and titanium dioxide.

487 Carvedilol is a white to off-white powder with a molecular weight of 406.5 and a
488 molecular formula of C₂₄H₂₆N₂O₄. It is freely soluble in dimethylsulfoxide; soluble in methylene

489 chloride and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in
490 ethyl ether; and practically insoluble in water, gastric fluid (simulated, TS, pH 1.1), and intestinal
491 fluid (simulated, TS without pancreatin, pH 7.5).

492 **12 CLINICAL PHARMACOLOGY**

493 **12.1 Mechanism of Action**

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

497 **12.2 Pharmacodynamics**

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

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

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

509 Among 839 patients with NYHA class II-III heart failure treated for 26 to 52 weeks in
510 4 US placebo-controlled trials, average left ventricular ejection fraction (EF) measured by
511 radionuclide ventriculography increased by 9 EF units (%) in patients receiving COREG and by
512 2 EF units in placebo patients at a target dose of 25-50 mg twice daily. The effects of carvedilol
513 on ejection fraction were related to dose. Doses of 6.25 mg twice daily, 12.5 mg twice daily, and
514 25 mg twice daily were associated with placebo-corrected increases in EF of 5 EF units, 6 EF
515 units, and 8 EF units, respectively; each of these effects were nominally statistically significant.

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

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

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

525 α_1 -adrenoreceptor blocking activity has been demonstrated in human and animal studies,
526 showing that carvedilol (1) attenuates the pressor effects of phenylephrine; (2) causes

527 vasodilation; and (3) reduces peripheral vascular resistance. These effects contribute to the
528 reduction of blood pressure and usually are seen within 30 minutes of drug administration.

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

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

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

542 **12.3 Pharmacokinetics**

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

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

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

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

567 The primary P450 enzymes responsible for the metabolism of both R(+) and
568 S(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent
569 CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and
570 5'-hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be
571 of primary importance in the O-methylation pathway of S(-)-carvedilol.

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

579 Carvedilol is more than 98% bound to plasma proteins, primarily with albumin. The
580 plasma-protein binding is independent of concentration over the therapeutic range. Carvedilol is
581 a basic, lipophilic compound with a steady-state volume of distribution of approximately 115 L,
582 indicating substantial distribution into extravascular tissues. Plasma clearance ranges from 500 to
583 700 mL/min.

584 **12.4 Specific Populations**

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

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

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

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

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

605 **12.5 Drug-Drug Interactions**

606 Since carvedilol undergoes substantial oxidative metabolism, the metabolism and
607 pharmacokinetics of carvedilol may be affected by induction or inhibition of cytochrome P450
608 enzymes.

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

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

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

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

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

626 Rifampin: In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin
627 (600 mg daily for 12 days) decreased the AUC and C_{max} of carvedilol by about 70% [see Drug
628 Interactions (7.5)].

629 Torsemide: In a study of 12 healthy subjects, combined oral administration of carvedilol
630 25 mg once daily and torsemide 5 mg once daily for 5 days did not result in any significant
631 differences in their pharmacokinetics compared with administration of the drugs alone.

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

635 **13 NONCLINICAL TOXICOLOGY**

636 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

648 **14 CLINICAL STUDIES**

649 **14.1 Heart Failure**

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

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

655 Four US multicenter, double-blind, placebo-controlled studies enrolled 1,094 patients
656 (696 randomized to carvedilol) with NYHA class II-III heart failure and ejection fraction ≤ 0.35 .
657 The vast majority were on digitalis, diuretics, and an ACE inhibitor at study entry. Patients were
658 assigned to the studies based upon exercise ability. An Australia-New Zealand double-blind,
659 placebo-controlled study enrolled 415 patients (half randomized to carvedilol) with less severe
660 heart failure. All protocols excluded patients expected to undergo cardiac transplantation during
661 the 7.5 to 15 months of double-blind follow-up. All randomized patients had tolerated a 2-week
662 course on carvedilol 6.25 mg twice daily.

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

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

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

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

680 *Functional Measures:* None of the multicenter studies had NYHA classification as a
681 primary end point, but all such studies had it as a secondary end point. There was at least a trend

682 toward improvement in NYHA class in all studies. Exercise tolerance was the primary end point
683 in 3 studies; in none was a statistically significant effect found.

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

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

690 *COMET Trial:* In this double-blind trial, 3,029 patients with NYHA class II-IV heart
691 failure (left ventricular ejection fraction $\leq 35\%$) were randomized to receive either carvedilol
692 (target dose: 25 mg twice daily) or immediate-release metoprolol tartrate (target dose: 50 mg
693 twice daily). The mean age of the patients was approximately 62 years, 80% were males, and the
694 mean left ventricular ejection fraction at baseline was 26%. Approximately 96% of the patients
695 had NYHA class II or III heart failure. Concomitant treatment included diuretics (99%), ACE
696 inhibitors (91%), digitalis (59%), aldosterone antagonists (11%), and “statin” lipid-lowering
697 agents (21%). The mean duration of follow-up was 4.8 years. The mean dose of carvedilol was
698 42 mg per day.

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

708

709 **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

710

711 It is not known whether this formulation of metoprolol at any dose or this low dose of
712 metoprolol in any formulation has any effect on survival or hospitalization in patients with heart
713 failure. Thus, this trial extends the time over which carvedilol manifests benefits on survival in

714 heart failure, but it is not evidence that carvedilol improves outcome over the formulation of
715 metoprolol (TOPROL-XL[®]) with benefits in heart failure.

716 **Severe Heart Failure (COPERNICUS):** In a double-blind study (COPERNICUS),
717 2,289 patients with heart failure at rest or with minimal exertion and left ventricular ejection
718 fraction <25% (mean 20%), despite digitalis (66%), diuretics (99%), and ACE inhibitors (89%)
719 were randomized to placebo or carvedilol. Carvedilol was titrated from a starting dose of
720 3.125 mg twice daily to the maximum tolerated dose or up to 25 mg twice daily over a minimum
721 of 6 weeks. Most subjects achieved the target dose of 25 mg. The study was conducted in
722 Eastern and Western Europe, the United States, Israel, and Canada. Similar numbers of subjects
723 per group (about 100) withdrew during the titration period.

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

731

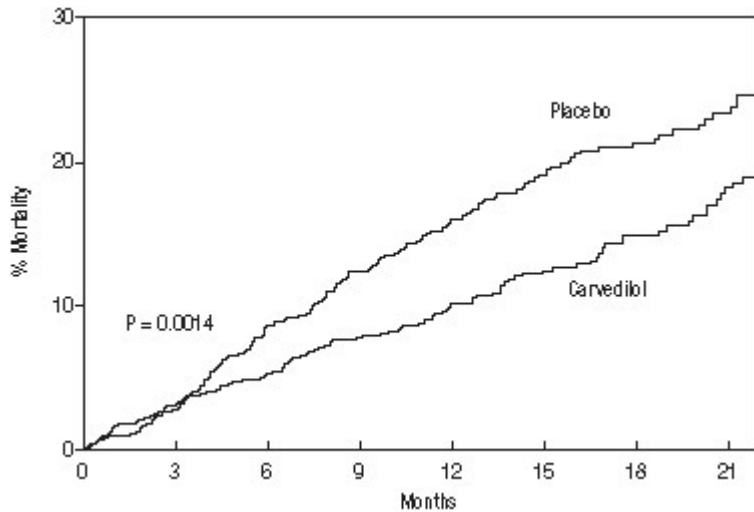
732 **Table 4. Results of COPERNICUS Trial in Patients With Severe Heart Failure**

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

733 Cardiovascular = CV; Heart failure = HF.

734

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



736
737

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

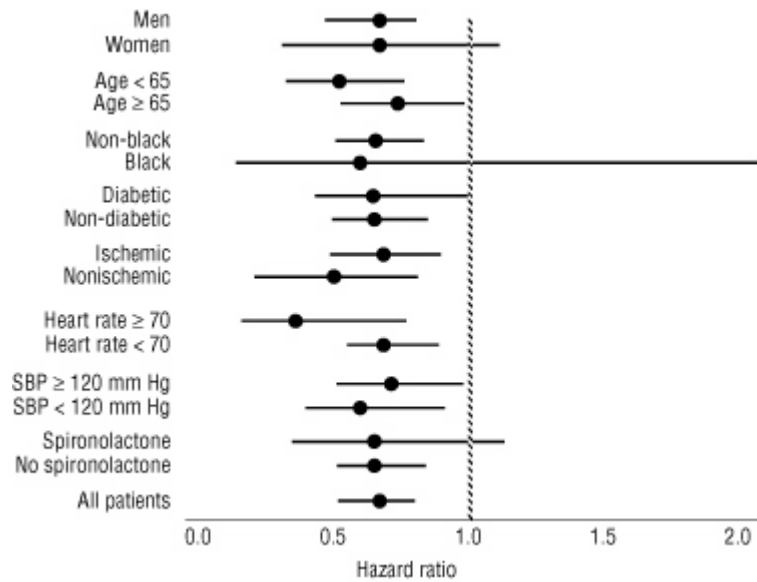
740 Patients' global assessments, in which carvedilol-treated patients were compared to
741 placebo, were based on pre-specified, periodic patient self-assessments regarding whether
742 clinical status post-treatment showed improvement, worsening or no change compared to
743 baseline. Patients treated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

745 The protocol also specified that hospitalizations would be assessed. Fewer patients on
746 COREG than on placebo were hospitalized for any reason (372 versus 432, $p = 0.0029$), for
747 cardiovascular reasons (246 versus 314, $p = 0.0003$), or for worsening heart failure (198 versus
748 268, $p = 0.0001$).

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

753
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Figure 2. Effects on Mortality for Subgroups in COPERNICUS



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757 **14.2 Left Ventricular Dysfunction Following Myocardial Infarction**

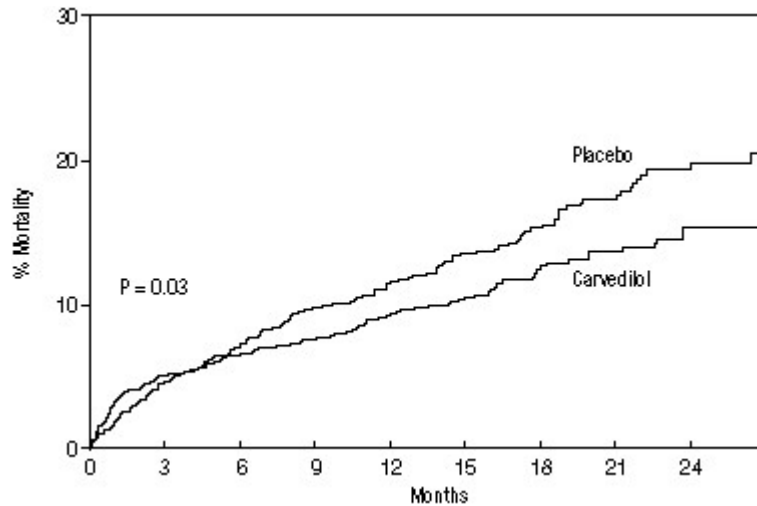
758 CAPRICORN was a double-blind study comparing carvedilol and placebo in
 759 1,959 patients with a recent myocardial infarction (within 21 days) and left ventricular ejection
 760 fraction of $\leq 40\%$, with (47%) or without symptoms of heart failure. Patients given carvedilol
 761 received 6.25 mg twice daily, titrated as tolerated to 25 mg twice daily. Patients had to have a
 762 systolic blood pressure >90 mm Hg, a sitting heart rate >60 beats/minute, and no
 763 contraindication to β -blocker use. Treatment of the index infarction included aspirin (85%), IV
 764 or oral β -blockers (37%), nitrates (73%), heparin (64%), thrombolytics (40%), and acute
 765 angioplasty (12%). Background treatment included ACE inhibitors or angiotensin receptor
 766 blockers (97%), anticoagulants (20%), lipid-lowering agents (23%), and diuretics (34%).
 767 Baseline population characteristics included an average age of 63 years, 74% male, 95%
 768 Caucasian, mean blood pressure 121/74 mm Hg, 22% with diabetes, and 54% with a history of
 769 hypertension. Mean dosage achieved of carvedilol was 20 mg twice daily; mean duration of
 770 follow-up was 15 months.

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

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

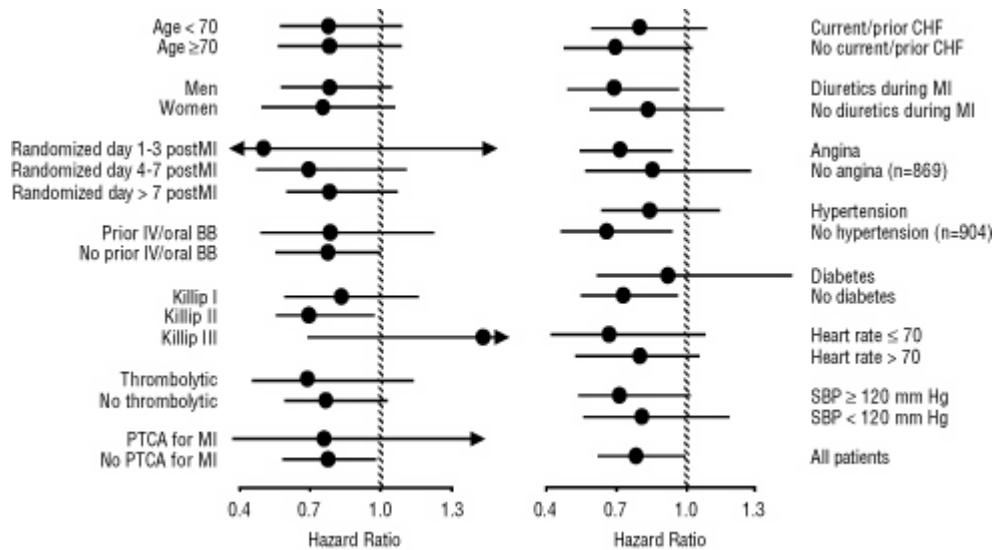
782

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



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Figure 4. Effects on Mortality for Subgroups in CAPRICORN



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14.3 Hypertension

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

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

801 **14.4 Hypertension With Type 2 Diabetes Mellitus**

802 In a double-blind study (GEMINI), COREG, added to an ACE inhibitor or angiotensin
803 receptor blocker, was evaluated in a population with mild-to-moderate hypertension and well-
804 controlled type 2 diabetes mellitus. The mean HbA1c at baseline was 7.2%. COREG was titrated
805 to a mean dose of 17.5 mg twice daily and maintained for 5 months. COREG had no adverse
806 effect on glycemic control, based on HbA1c measurements (mean change from baseline of
807 0.02%, 95% CI -0.06 to 0.10, p = NS) [*see Warnings and Precautions (5.6)*].

808 **16 HOW SUPPLIED/STORAGE AND HANDLING**

809 The white, oval, film-coated tablets are available in the following strengths: 3.125 mg–
810 engraved with 39 and SB, in bottles of 100; 6.25 mg–engraved with 4140 and SB, in bottles of
811 100; 12.5 mg–engraved with 4141 and SB, in bottles of 100; 25 mg–engraved with 4142 and SB,
812 in bottles of 100. The 6.25 mg, 12.5 mg, and 25 mg tablets are TILTAB tablets.

- 813 • 3.125 mg 100's: NDC 0007-4139-20
- 814 • 6.25 mg 100's: NDC 0007-4140-20
- 815 • 12.5 mg 100's: NDC 0007-4141-20
- 816 • 25 mg 100's: NDC 0007-4142-20

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

818 **17 PATIENT COUNSELING INFORMATION**

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

820 **17.1 Patient Advice**

821 Patients taking COREG should be advised of the following:

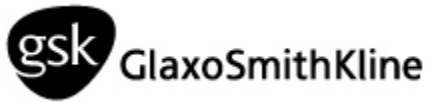
- 822 • Patients should take COREG with food.
- 823 • Patients should not interrupt or discontinue using COREG without a physician's advice.
- 824 • Patients with heart failure should consult their physician if they experience signs or
825 symptoms of worsening heart failure such as weight gain or increasing shortness of breath.
- 826 • Patients may experience a drop in blood pressure when standing, resulting in dizziness and,
827 rarely, fainting. Patients should sit or lie down when these symptoms of lowered blood
828 pressure occur.
- 829 • If experiencing dizziness or fatigue, patients should avoid driving or hazardous tasks.
- 830 • Patients should consult a physician if they experience dizziness or faintness, in case the
831 dosage should be adjusted.
- 832 • Diabetic patients should report any changes in blood sugar levels to their physician.
- 833 • Contact lens wearers may experience decreased lacrimation.

834

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

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

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838

839 GlaxoSmithKline

840 Research Triangle Park, NC 27709

841

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17.2 FDA-Approved Patient Labeling

PATIENT INFORMATION
COREG[®] (Co-REG)
Carvedilol Tablets

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

What is COREG?

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

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

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

Who should not take COREG?

Do not take COREG if you:

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

What should I tell my doctor before taking COREG?

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

- Have asthma or other lung problems (such as bronchitis or emphysema)
- Have problems with blood flow in your feet and legs (peripheral vascular disease) COREG can make some of your symptoms worse.
- Have diabetes
- Have thyroid problems
- Have a condition called pheochromocytoma

- 883 • Have had severe allergic reactions
884 • Are pregnant or trying to become pregnant. It is not known if COREG is safe for your unborn
885 baby. You and your doctor should talk about the best way to control your high blood pressure
886 during pregnancy.
887 • Are breastfeeding. It is not known if COREG passes into your breast milk. You should not
888 breastfeed while using COREG.
889 • Are scheduled for surgery and will be given anesthetic agents
890 • Are taking prescription or non-prescription medicines, vitamins, and herbal supplements.
891 COREG and certain other medicines can affect each other and cause serious side effects.
892 COREG may affect the way other medicines work. Also, other medicines may affect how
893 well COREG works.

894

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

897

898 **How should I take COREG?**

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

- 903 • Take COREG exactly as prescribed. Your doctor will tell you how many tablets to take and
904 how often. In order to minimize possible side effects, your doctor might begin with a low
905 dose and then slowly increase the dose.
906 • **Do not stop taking COREG and do not change the amount of COREG you take without**
907 **talking to your doctor.**
908 • Tell your doctor if you gain weight or have trouble breathing while taking COREG.
909 • Take COREG with food.
910 • If you miss a dose of COREG, take your dose as soon as you remember, unless it is time to
911 take your next dose. Take your next dose at the usual time. Do not take 2 doses at the same
912 time.
913 • If you take too much COREG, call your doctor or poison control center right away.

914

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

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

918

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

- 920 • **Low blood pressure (which may cause dizziness or fainting when you stand up).** If
921 these happen, sit or lie down right away and tell your doctor.

- 922 • **Tiredness.** If you feel tired or dizzy you should not drive, use machinery, or do anything
923 that needs you to be alert.
- 924 • **Slow heartbeat.**
- 925 • **Changes in your blood sugar. If you have diabetes, tell your doctor if you have any**
926 **changes in your blood sugar levels.**
- 927 • COREG may hide some of the symptoms of low blood sugar, especially a fast heartbeat.
- 928 • COREG may mask the symptoms of hyperthyroidism (overactive thyroid).
- 929 • **Worsening of severe allergic reactions.**

930

931 Other side effects of COREG include shortness of breath, weight gain, diarrhea, and fewer tears
932 or dry eyes that become bothersome if you wear contact lenses. Rare serious allergic reactions
933 have happened in patients who were on COREG.

934

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

936

937 **How should I store COREG?**

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

941

942 **General Information about COREG**

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

946

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

951

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

953 Active Ingredient: Carvedilol.

954

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

957

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

959

960 COREG is a registered trademark of GlaxoSmithKline.



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967 Revised: April 2008
968 CRG:2PIL
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