

## 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

#### 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  $\beta$ -blockers. (4) However, if deemed necessary, use with caution and at lowest effective dose. (5.5)
- Diabetes: Monitor glucose as  $\beta$ -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](http://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  $\beta$ -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: October 2010

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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  $\beta$ -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  $\beta$ -blockers. The last 2**

91 **complications may occur with or without preceding exacerbation of the angina pectoris. As**

92 **with other  $\beta$ -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  $\beta$ -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  $\beta$ -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,  $\beta$ -blockers may mask some of the manifestations of hypoglycemia,  
151 particularly tachycardia. Nonselective  $\beta$ -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  $\beta$ -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  $\beta$ -adrenergic blockade may mask clinical signs of hyperthyroidism, such as tachycardia.  
181 Abrupt withdrawal of  $\beta$ -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  $\alpha$ -blocking agent should be initiated prior to the  
185 use of any  $\beta$ -blocking agent. Although carvedilol has both  $\alpha$ - and  $\beta$ -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  $\beta$ -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  $\alpha$ -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  $\beta$ -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 **6 ADVERSE REACTIONS**

### 200 **6.1 Clinical Studies Experience**

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

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

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

230

231 **Table 1. Adverse Events (%) Occurring More Frequently With COREG Than With**  
 232 **Placebo in Patients With Mild-to-Moderate Heart Failure (HF) Enrolled in US Heart**  
 233 **Failure Trials or in Patients With Severe Heart Failure in the COPERNICUS Trial**  
 234 **(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)
<b>Body as a Whole</b>				
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	—	—
<b>Cardiovascular</b>				
Bradycardia	9	1	10	3
Hypotension	9	3	14	8
Syncope	3	3	8	5
Angina pectoris	2	3	6	4
<b>Central Nervous System</b>				
Dizziness	32	19	24	17
Headache	8	7	5	3
<b>Gastrointestinal</b>				
Diarrhea	12	6	5	3
Nausea	9	5	4	3
Vomiting	6	4	1	2
<b>Metabolic</b>				
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
<b>Musculoskeletal</b>				
Arthralgia	6	5	1	1
<b>Respiratory</b>				
Cough increased	8	9	5	4
Rales	4	4	4	2
<b>Vision</b>				
Vision abnormal	5	2	—	—

235

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

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

241 **Incidence >1% to ≤3%**

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

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

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

246 *Gastrointestinal:* Melena, periodontitis.

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

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

251 *Musculoskeletal:* Muscle cramps.

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

253 *Psychiatric:* Somnolence.

254 *Reproductive, male:* Impotence.

255 *Special Senses:* Blurred vision.

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

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

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

273 **Hypertension:** COREG has been evaluated for safety in hypertension in more than  
274 2,193 patients in US clinical trials and in 2,976 patients in international clinical trials.

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

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

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

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

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

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

292  
 293 Dyspnea and fatigue were also reported in these studies, but the rates were equal or  
 294 greater in patients who received placebo.

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

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

299 *Cardiovascular:* Peripheral ischemia, tachycardia.

300 *Central and Peripheral Nervous System:* Hypokinesia.

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

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

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

307 *Reproductive, male:* Decreased libido.

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

310 *Special Senses:* Tinnitus.

311 *Urinary System:* Micturition frequency increased.

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

313 *Metabolic and Nutritional:* Hypokalemia, hypertriglyceridemia.

314 *Hematologic:* Anemia, leukopenia.

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

## 320 **6.2 Laboratory Abnormalities**

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

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

## 333 **6.3 Postmarketing Experience**

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

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

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

## 346 **7 DRUG INTERACTIONS**

### 347 **7.1 CYP2D6 Inhibitors and Poor Metabolizers**

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

### 354 **7.2 Hypotensive Agents**

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

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

### 363 **7.3 Cyclosporine**

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

### 372 **7.4 Digitalis Glycosides**

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

378 **7.5 Inducers/Inhibitors of Hepatic Metabolism**

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

382 **7.6 Amiodarone**

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

390 **7.7 Calcium Channel Blockers**

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

395 **7.8 Insulin or Oral Hypoglycemics**

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

400 **7.9 Anesthesia**

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

404 **8 USE IN SPECIFIC POPULATIONS**

405 **8.1 Pregnancy**

406 Pregnancy Category C. Studies performed in pregnant rats and rabbits given carvedilol  
407 revealed increased post-implantation loss in rats at doses of 300 mg/kg/day (50 times the  
408 maximum recommended human dose [MRHD] as  $mg/m^2$ ) and in rabbits at doses of  
409 75 mg/kg/day (25 times the MRHD as  $mg/m^2$ ). In the rats, there was also a decrease in fetal body  
410 weight at the maternally toxic dose of 300 mg/kg/day (50 times the MRHD as  $mg/m^2$ ), which  
411 was accompanied by an elevation in the frequency of fetuses with delayed skeletal development  
412 (missing or stunted 13th rib). In rats the no-observed-effect level for developmental toxicity was  
413 60 mg/kg/day (10 times the MRHD as  $mg/m^2$ ); in rabbits it was 15 mg/kg/day (5 times the  
414 MRHD as  $mg/m^2$ ). There are no adequate and well-controlled studies in pregnant women.  
415 COREG should be used during pregnancy only if the potential benefit justifies the potential risk  
416 to the fetus.

417 **8.3 Nursing Mothers**

418 It is not known whether this drug is excreted in human milk. Studies in rats have shown  
419 that carvedilol and/or its metabolites (as well as other  $\beta$ -blockers) cross the placental barrier and  
420 are excreted in breast milk. There was increased mortality at one week post-partum in neonates  
421 from rats treated with 60 mg/kg/day (10 times the MRHD as mg/m<sup>2</sup>) and above during the last  
422 trimester through day 22 of lactation. Because many drugs are excreted in human milk and  
423 because of the potential for serious adverse reactions in nursing infants from  $\beta$ -blockers,  
424 especially bradycardia, a decision should be made whether to discontinue nursing or to  
425 discontinue the drug, taking into account the importance of the drug to the mother. The effects of  
426 other  $\alpha$ - and  $\beta$ -blocking agents have included perinatal and neonatal distress.

427 **8.4 Pediatric Use**

428 Effectiveness of COREG in patients younger than 18 years of age has not been  
429 established.

430 In a double-blind trial, 161 children (mean age 6 years, range 2 months to 17 years; 45%  
431 less than 2 years old) with chronic heart failure [NYHA class II-IV, left ventricular ejection  
432 fraction <40% for children with a systemic left ventricle (LV), and moderate-severe ventricular  
433 dysfunction qualitatively by echo for those with a systemic ventricle that was not an LV] who  
434 were receiving standard background treatment were randomized to placebo or to 2 dose levels of  
435 carvedilol. These dose levels produced placebo-corrected heart rate reduction of 4-6 heart beats  
436 per minute, indicative of  $\beta$ -blockade activity. Exposure appeared to be lower in pediatric subjects  
437 than adults. After 8 months of follow-up, there was no significant effect of treatment on clinical  
438 outcomes. Adverse reactions in this trial that occurred in greater than 10% of patients treated  
439 with COREG and at twice the rate of placebo-treated patients included chest pain (17% versus  
440 6%), dizziness (13% versus 2%), and dyspnea (11% versus 0%).

441 **8.5 Geriatric Use**

442 Of the 765 patients with heart failure randomized to COREG in US clinical trials, 31%  
443 (235) were 65 years of age or older, and 7.3% (56) were 75 years of age or older. Of the  
444 1,156 patients randomized to COREG in a long-term, placebo-controlled trial in severe heart  
445 failure, 47% (547) were 65 years of age or older, and 15% (174) were 75 years of age or older.  
446 Of 3,025 patients receiving COREG in heart failure trials worldwide, 42% were 65 years of age  
447 or older.

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

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

453 With the exception of dizziness in hypertensive patients (incidence 8.8% in the elderly  
454 versus 6% in younger patients), no overall differences in the safety or effectiveness (see Figures  
455 2 and 4) were observed between the older subjects and younger subjects in each of these  
456 populations. Similarly, other reported clinical experience has not identified differences in

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

## 459 **10 OVERDOSAGE**

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

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

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

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

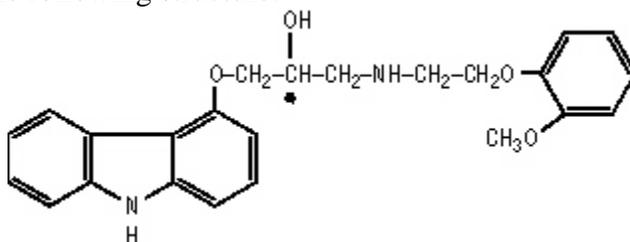
470 If peripheral vasodilation dominates, it may be necessary to administer adrenaline or  
471 noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant  
472 bradycardia, pacemaker therapy should be performed. For bronchospasm,  $\beta$ -sympathomimetics  
473 (as aerosol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

475 NOTE: In the event of severe intoxication where there are symptoms of shock, treatment  
476 with antidotes must be continued for a sufficiently long period of time consistent with the 7- to  
477 10-hour half-life of carvedilol.

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

## 482 **11 DESCRIPTION**

483 Carvedilol is a nonselective  $\beta$ -adrenergic blocking agent with  $\alpha_1$ -blocking activity. It is  
484 ( $\pm$ )-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol. Carvedilol is a  
485 racemic mixture with the following structure:



486

487 COREG is a white, oval, film-coated tablet containing 3.125 mg, 6.25 mg, 12.5 mg, or  
488 25 mg of carvedilol. The 6.25 mg, 12.5 mg, and 25 mg tablets are TILTAB<sup>®</sup> tablets. Inactive  
489 ingredients consist of colloidal silicon dioxide, crospovidone, hypromellose, lactose, magnesium  
490 stearate, polyethylene glycol, polysorbate 80, povidone, sucrose, and titanium dioxide.

491 Carvedilol is a white to off-white powder with a molecular weight of 406.5 and a  
492 molecular formula of C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>. It is freely soluble in dimethylsulfoxide; soluble in methylene  
493 chloride and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in  
494 ethyl ether; and practically insoluble in water, gastric fluid (simulated, TS, pH 1.1), and intestinal  
495 fluid (simulated, TS without pancreatin, pH 7.5).

## 496 **12 CLINICAL PHARMACOLOGY**

### 497 **12.1 Mechanism of Action**

498 COREG is a racemic mixture in which nonselective  $\beta$ -adrenoreceptor blocking activity is  
499 present in the S(-) enantiomer and  $\alpha_1$ -adrenergic blocking activity is present in both R(+) and  
500 S(-) enantiomers at equal potency. COREG has no intrinsic sympathomimetic activity.

### 501 **12.2 Pharmacodynamics**

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

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

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

513 Among 839 patients with NYHA class II-III heart failure treated for 26 to 52 weeks in  
514 4 US placebo-controlled trials, average left ventricular ejection fraction (EF) measured by  
515 radionuclide ventriculography increased by 9 EF units (%) in patients receiving COREG and by  
516 2 EF units in placebo patients at a target dose of 25-50 mg twice daily. The effects of carvedilol  
517 on ejection fraction were related to dose. Doses of 6.25 mg twice daily, 12.5 mg twice daily, and  
518 25 mg twice daily were associated with placebo-corrected increases in EF of 5 EF units, 6 EF  
519 units, and 8 EF units, respectively; each of these effects were nominally statistically significant.

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

523 Hypertension: The mechanism by which  $\beta$ -blockade produces an antihypertensive effect  
524 has not been established.

525  $\beta$ -adrenoreceptor blocking activity has been demonstrated in animal and human studies  
526 showing that carvedilol (1) reduces cardiac output in normal subjects; (2) reduces exercise-  
527 and/or isoproterenol-induced tachycardia; and (3) reduces reflex orthostatic tachycardia.  
528 Significant  $\beta$ -adrenoreceptor blocking effect is usually seen within 1 hour of drug administration.

529  $\alpha_1$ -adrenoreceptor blocking activity has been demonstrated in human and animal studies,  
530 showing that carvedilol (1) attenuates the pressor effects of phenylephrine; (2) causes  
531 vasodilation; and (3) reduces peripheral vascular resistance. These effects contribute to the  
532 reduction of blood pressure and usually are seen within 30 minutes of drug administration.

533 Due to the  $\alpha_1$ -receptor blocking activity of carvedilol, blood pressure is lowered more in  
534 the standing than in the supine position, and symptoms of postural hypotension (1.8%), including  
535 rare instances of syncope, can occur. Following oral administration, when postural hypotension  
536 has occurred, it has been transient and is uncommon when COREG is administered with food at  
537 the recommended starting dose and titration increments are closely followed [*see Dosage and*  
538 *Administration (2)*].

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

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

### 546 **12.3 Pharmacokinetics**

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

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

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

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

569 administration in healthy subjects. The mean apparent terminal elimination half-lives for  
570 R(+)-carvedilol range from 5 to 9 hours compared with 7 to 11 hours for the S(-)-enantiomer.

571 The primary P450 enzymes responsible for the metabolism of both R(+) and  
572 S(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent  
573 CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4' - and  
574 5'-hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be  
575 of primary importance in the O-methylation pathway of S(-)-carvedilol.

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

583 Carvedilol is more than 98% bound to plasma proteins, primarily with albumin. The  
584 plasma-protein binding is independent of concentration over the therapeutic range. Carvedilol is  
585 a basic, lipophilic compound with a steady-state volume of distribution of approximately 115 L,  
586 indicating substantial distribution into extravascular tissues. Plasma clearance ranges from 500 to  
587 700 mL/min.

## 588 **12.4 Specific Populations**

589 Heart Failure: Steady-state plasma concentrations of carvedilol and its enantiomers  
590 increased proportionally over the 6.25 to 50 mg dose range in patients with heart failure.  
591 Compared to healthy subjects, heart failure patients had increased mean AUC and C<sub>max</sub> values  
592 for carvedilol and its enantiomers, with up to 50% to 100% higher values observed in 6 patients  
593 with NYHA class IV heart failure. The mean apparent terminal elimination half-life for  
594 carvedilol was similar to that observed in healthy subjects.

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

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

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

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

609 **12.5 Drug-Drug Interactions**

610 Since carvedilol undergoes substantial oxidative metabolism, the metabolism and  
611 pharmacokinetics of carvedilol may be affected by induction or inhibition of cytochrome P450  
612 enzymes.

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

617 Cimetidine: In a pharmacokinetic study conducted in 10 healthy male subjects,  
618 cimetidine (1,000 mg/day) increased the steady-state AUC of carvedilol by 30% with no change  
619 in C<sub>max</sub> [see Drug Interactions (7.5)].

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

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

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

630 Rifampin: In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin  
631 (600 mg daily for 12 days) decreased the AUC and C<sub>max</sub> of carvedilol by about 70% [see Drug  
632 Interactions (7.5)].

633 Torsemide: In a study of 12 healthy subjects, combined oral administration of carvedilol  
634 25 mg once daily and torsemide 5 mg once daily for 5 days did not result in any significant  
635 differences in their pharmacokinetics compared with administration of the drugs alone.

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

639 **13 NONCLINICAL TOXICOLOGY**

640 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

647 At doses  $\geq 200$  mg/kg/day ( $\geq 32$  times the MRHD as mg/m<sup>2</sup>) carvedilol was toxic to adult  
648 rats (sedation, reduced weight gain) and was associated with a reduced number of successful  
649 matings, prolonged mating time, significantly fewer corpora lutea and implants per dam, and  
650 complete resorption of 18% of the litters. The no-observed-effect dose level for overt toxicity  
651 and impairment of fertility was 60 mg/kg/day (10 times the MRHD as mg/m<sup>2</sup>).

## 652 **14 CLINICAL STUDIES**

### 653 **14.1 Heart Failure**

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

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

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

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

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

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

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

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

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

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

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

694 *COMET Trial:* In this double-blind trial, 3,029 patients with NYHA class II-IV heart  
695 failure (left ventricular ejection fraction  $\leq 35\%$ ) were randomized to receive either carvedilol  
696 (target dose: 25 mg twice daily) or immediate-release metoprolol tartrate (target dose: 50 mg  
697 twice daily). The mean age of the patients was approximately 62 years, 80% were males, and the  
698 mean left ventricular ejection fraction at baseline was 26%. Approximately 96% of the patients  
699 had NYHA class II or III heart failure. Concomitant treatment included diuretics (99%), ACE  
700 inhibitors (91%), digitalis (59%), aldosterone antagonists (11%), and "statin" lipid-lowering  
701 agents (21%). The mean duration of follow-up was 4.8 years. The mean dose of carvedilol was  
702 42 mg per day.

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

712

713 **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

714

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

718 heart failure, but it is not evidence that carvedilol improves outcome over the formulation of  
719 metoprolol (TOPROL-XL<sup>®</sup>) with benefits in heart failure.

720 **Severe Heart Failure (COPERNICUS):** In a double-blind study (COPERNICUS),  
721 2,289 patients with heart failure at rest or with minimal exertion and left ventricular ejection  
722 fraction <25% (mean 20%), despite digitalis (66%), diuretics (99%), and ACE inhibitors (89%)  
723 were randomized to placebo or carvedilol. Carvedilol was titrated from a starting dose of  
724 3.125 mg twice daily to the maximum tolerated dose or up to 25 mg twice daily over a minimum  
725 of 6 weeks. Most subjects achieved the target dose of 25 mg. The study was conducted in  
726 Eastern and Western Europe, the United States, Israel, and Canada. Similar numbers of subjects  
727 per group (about 100) withdrew during the titration period.

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

735

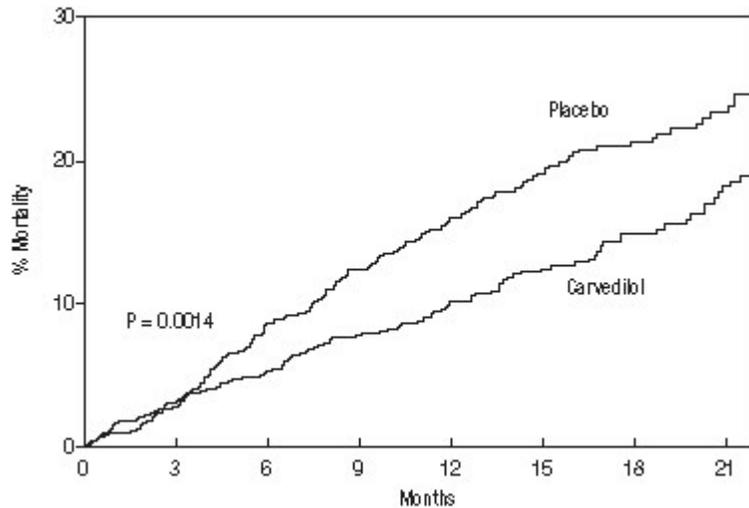
736 **Table 4. Results of COPERNICUS Trial in Patients With Severe Heart Failure**

<b>End point</b>	<b>Placebo (N = 1,133)</b>	<b>Carvedilol (N = 1,156)</b>	<b>Hazard ratio (95% CI)</b>	<b>% Reduction</b>	<b>Nominal p value</b>
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

737 Cardiovascular = CV; Heart failure = HF.

738

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



740  
741

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

744

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

749

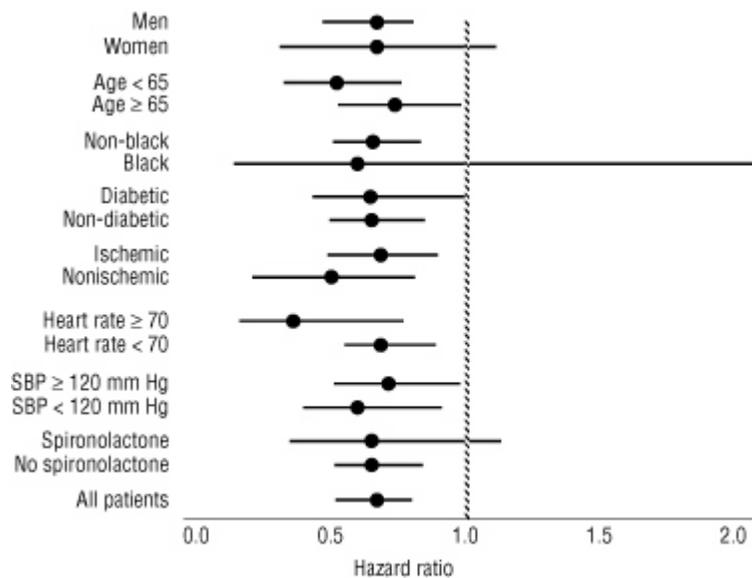
750 The protocol also specified that hospitalizations would be assessed. Fewer patients on  
751 COREG than on placebo were hospitalized for any reason (372 versus 432,  $p = 0.0029$ ), for  
752 cardiovascular reasons (246 versus 314,  $p = 0.0003$ ), or for worsening heart failure (198 versus  
753 268,  $p = 0.0001$ ).

753

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

757

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



759  
760

#### 761 14.2 Left Ventricular Dysfunction Following Myocardial Infarction

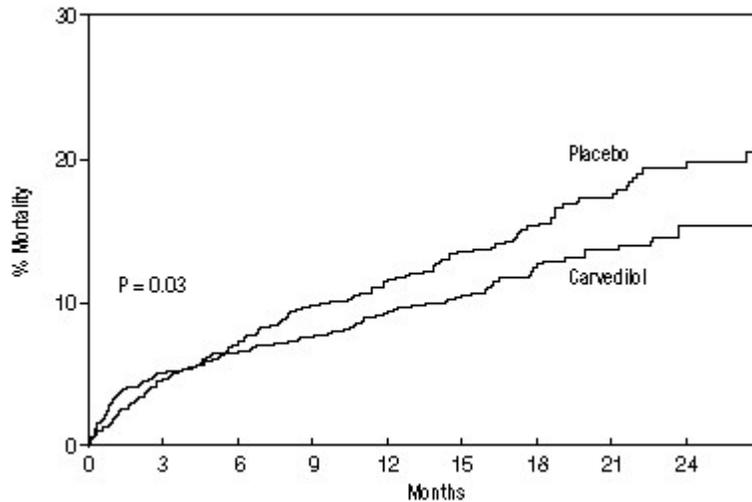
762 CAPRICORN was a double-blind study comparing carvedilol and placebo in  
763 1,959 patients with a recent myocardial infarction (within 21 days) and left ventricular ejection  
764 fraction of  $\leq 40\%$ , with (47%) or without symptoms of heart failure. Patients given carvedilol  
765 received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

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

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

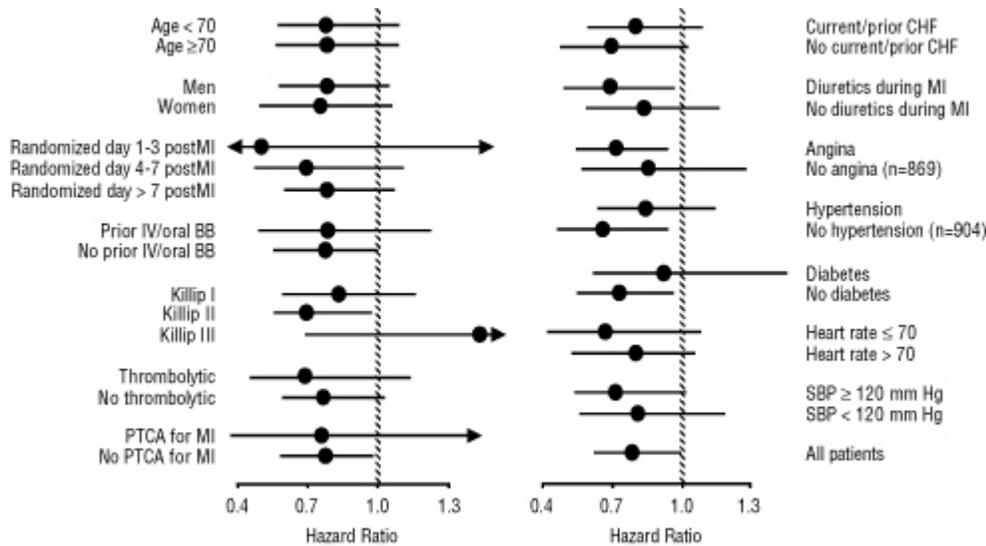
786

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



788  
789

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



791  
792

793 **14.3 Hypertension**

794 COREG was studied in 2 placebo-controlled trials that utilized twice-daily dosing, at  
 795 total daily doses of 12.5 to 50 mg. In these and other studies, the starting dose did not exceed  
 796 12.5 mg. At 50 mg/day, COREG reduced sitting trough (12-hour) blood pressure by about  
 797 9/5.5 mm Hg; at 25 mg/day the effect was about 7.5/3.5 mm Hg. Comparisons of trough to peak  
 798 blood pressure showed a trough to peak ratio for blood pressure response of about 65%. Heart  
 799 rate fell by about 7.5 beats/minute at 50 mg/day. In general, as is true for other β-blockers,  
 800 responses were smaller in black than non-black patients. There were no age- or gender-related  
 801 differences in response.

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

#### 805 **14.4 Hypertension With Type 2 Diabetes Mellitus**

806 In a double-blind study (GEMINI), COREG, added to an ACE inhibitor or angiotensin  
807 receptor blocker, was evaluated in a population with mild-to-moderate hypertension and well-  
808 controlled type 2 diabetes mellitus. The mean HbA1c at baseline was 7.2%. COREG was titrated  
809 to a mean dose of 17.5 mg twice daily and maintained for 5 months. COREG had no adverse  
810 effect on glycemic control, based on HbA1c measurements (mean change from baseline of  
811 0.02%, 95% CI -0.06 to 0.10, p = NS) [*see Warnings and Precautions (5.6)*].

### 812 **16 HOW SUPPLIED/STORAGE AND HANDLING**

813 The white, oval, film-coated tablets are available in the following strengths: 3.125 mg–  
814 engraved with 39 and SB, in bottles of 100; 6.25 mg–engraved with 4140 and SB, in bottles of  
815 100; 12.5 mg–engraved with 4141 and SB, in bottles of 100; 25 mg–engraved with 4142 and SB,  
816 in bottles of 100. The 6.25 mg, 12.5 mg, and 25 mg tablets are TILTAB tablets.

- 817 • 3.125 mg 100's: NDC 0007-4139-20
- 818 • 6.25 mg 100's: NDC 0007-4140-20
- 819 • 12.5 mg 100's: NDC 0007-4141-20
- 820 • 25 mg 100's: NDC 0007-4142-20

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

### 822 **17 PATIENT COUNSELING INFORMATION**

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

#### 824 **17.1 Patient Advice**

825 Patients taking COREG should be advised of the following:

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

838

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

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

841



842

843 Manufactured for

844 **GlaxoSmithKline**

845 Research Triangle Park, NC 27709

846 Manufactured by

847 **Patheon Puerto Rico, Inc.**

848 Manati, PR 00674 USA

849

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852 October 2010

853 CRG: 19PI

**17.2 FDA-Approved Patient Labeling**

**PATIENT INFORMATION**  
**COREG<sup>®</sup> (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 certain types of heart failure
- To treat patients who had a heart attack that worsened how well the heart pumps
- To treat patients with high blood pressure (hypertension)

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

- 894 • Have had severe allergic reactions  
895 • Are pregnant or trying to become pregnant. It is not known if COREG is safe for your unborn  
896 baby. You and your doctor should talk about the best way to control your high blood pressure  
897 during pregnancy.  
898 • Are breastfeeding. It is not known if COREG passes into your breast milk. You should not  
899 breastfeed while using COREG.  
900 • Are scheduled for surgery and will be given anesthetic agents  
901 • Are taking prescription or non-prescription medicines, vitamins, and herbal supplements.  
902 COREG and certain other medicines can affect each other and cause serious side effects.  
903 COREG may affect the way other medicines work. Also, other medicines may affect how  
904 well COREG works.  
905

906 Keep a list of all the medicines you take. Show this list to your doctor and pharmacist before you  
907 start a new medicine.  
908

#### 909 **How should I take COREG?**

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

- 914 • Take COREG exactly as prescribed. Your doctor will tell you how many tablets to take and  
915 how often. In order to minimize possible side effects, your doctor might begin with a low  
916 dose and then slowly increase the dose.  
917 • **Do not stop taking COREG and do not change the amount of COREG you take without**  
918 **talking to your doctor.**  
919 • Tell your doctor if you gain weight or have trouble breathing while taking COREG.  
920 • Take COREG with food.  
921 • If you miss a dose of COREG, take your dose as soon as you remember, unless it is time to  
922 take your next dose. Take your next dose at the usual time. Do not take 2 doses at the same  
923 time.  
924 • If you take too much COREG, call your doctor or poison control center right away.  
925

#### 926 **What should I avoid while taking COREG?**

- 927 • COREG can cause you to feel dizzy, tired, or faint. Do not drive a car, use machinery, or  
928 do anything that needs you to be alert if you have these symptoms.  
929

#### 930 **What are possible side effects of COREG?**

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

- 935 • Slow heartbeat.
- 936 • Changes in your blood sugar. If you have diabetes, tell your doctor if you have any
- 937 changes in your blood sugar levels.
- 938 • COREG may hide some of the symptoms of low blood sugar, especially a fast heartbeat.
- 939 • COREG may mask the symptoms of hyperthyroidism (overactive thyroid).
- 940 • Worsening of severe allergic reactions.
- 941 • Rare but serious allergic reactions (including hives or swelling of the face, lips, tongue,
- 942 and/or throat that may cause difficulty in breathing or swallowing) have happened in
- 943 patients who were on COREG. These reactions can be life-threatening.

944

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

947

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

949

### 950 **How should I store COREG?**

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

954

### 955 **General Information about COREG**

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

959

960 This leaflet summarizes the most important information about COREG. If you would like more  
961 information, talk with your doctor. You can ask your doctor or pharmacist for information about  
962 COREG that is written for healthcare professionals. You can also find out more about COREG  
963 by visiting the website [www.COREG.com](http://www.COREG.com) or calling 1-888-825-5249. This call is free.

964

### 965 **What are the ingredients in COREG?**

966 Active Ingredient: Carvedilol.

967

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

970

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

972

### 973 **What is high blood pressure (hypertension)?**

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

976 | makes the heart work harder to pump blood through the body and causes damage to blood  
977 | vessels. COREG can help your blood vessels relax so your blood pressure is lower. Medicines  
978 | that lower blood pressure may lower your chance of having a stroke or heart attack.  
979

980 COREG is a registered trademark of GlaxoSmithKline.



981  
982 Manufactured for  
983 **GlaxoSmithKline**  
984 Research Triangle Park, NC 27709

985 Manufactured by  
986 **Patheon Puerto Rico, Inc.**  
987 Manati, PR 00674 USA

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991 Revised: November 2010

992 | CRG:XPIL

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