

## 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 for oral use

Initial U.S. Approval: 1995

#### 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 mg, 6.25 mg, 12.5 mg, 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: XX/XXXX

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

- 1.1 Heart Failure
- 1.2 Left Ventricular Dysfunction following Myocardial Infarction
- 1.3 Hypertension

### 2 DOSAGE AND ADMINISTRATION

- 2.1 Heart Failure
- 2.2 Left Ventricular Dysfunction following Myocardial Infarction
- 2.3 Hypertension
- 2.4 Hepatic Impairment

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Cessation of Therapy
- 5.2 Bradycardia
- 5.3 Hypotension
- 5.4 Heart Failure/Fluid Retention
- 5.5 Non-allergic Bronchospasm
- 5.6 Glycemic Control in Type 2 Diabetes
- 5.7 Peripheral Vascular Disease
- 5.8 Deterioration of Renal Function
- 5.9 Major Surgery
- 5.10 Thyrotoxicosis
- 5.11 Pheochromocytoma
- 5.12 Prinzmetal's Variant Angina
- 5.13 Risk of Anaphylactic Reaction
- 5.14 Intraoperative Floppy Iris Syndrome

### 6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience
- 6.2 Laboratory Abnormalities
- 6.3 Postmarketing Experience

### 7 DRUG INTERACTIONS

- 7.1 CYP2D6 Inhibitors and Poor Metabolizers

- 7.2 Hypotensive Agents
- 7.3 Cyclosporine
- 7.4 Digitalis Glycosides
- 7.5 Inducers/Inhibitors of Hepatic Metabolism
- 7.6 Amiodarone
- 7.7 Calcium Channel Blockers
- 7.8 Insulin or Oral Hypoglycemics
- 7.9 Anesthesia

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

### 10 OVERDOSAGE

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Specific Populations
- 12.5 Drug-Drug Interactions

### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### 14 CLINICAL STUDIES

- 14.1 Heart Failure
- 14.2 Left Ventricular Dysfunction following Myocardial Infarction
- 14.3 Hypertension
- 14.4 Hypertension with Type 2 Diabetes Mellitus

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

---

## 1 FULL PRESCRIBING INFORMATION

### 2 1 INDICATIONS AND USAGE

#### 3 1.1 Heart Failure

4 COREG<sup>®</sup> is indicated for the treatment of mild-to-severe chronic heart failure of ischemic or  
5 cardiomyopathic origin, usually in addition to diuretics, ACE inhibitors, and digitalis, to increase  
6 survival and, also, to reduce the risk of hospitalization [*see Drug Interactions (7.4) and Clinical*  
7 *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 have  
10 survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction  
11 of less than or equal to 40% (with or without symptomatic heart failure) [*see Clinical Studies*  
12 *(14.2)*].

#### 13 1.3 Hypertension

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

## 17 2 DOSAGE AND ADMINISTRATION

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

### 20 2.1 Heart Failure

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

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

34 COREG should not be increased until symptoms of worsening heart failure or vasodilation have  
35 been stabilized.

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

38 The dose of COREG should be reduced if patients experience bradycardia (heart rate less than  
39 55 beats per minute).

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

## 43 **2.2 Left Ventricular Dysfunction following Myocardial Infarction**

44 DOSAGE MUST BE INDIVIDUALIZED AND MONITORED DURING UP-TITRATION.

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

## 54 **2.3 Hypertension**

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

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

## 65 **2.4 Hepatic Impairment**

66 COREG should not be given to patients with severe hepatic impairment [*see Contraindications*  
67 (4)].

### 68 **3 DOSAGE FORMS AND STRENGTHS**

69 The white, oval, film-coated tablets are available in the following strengths:

- 70 • 3.125 mg – engraved with “39” and “SB”
- 71 • 6.25 mg – engraved with “4140” and “SB”
- 72 • 12.5 mg – engraved with “4141” and “SB”
- 73 • 25 mg – engraved with “4142” and “SB”

### 74 **4 CONTRAINDICATIONS**

75 COREG is contraindicated in the following conditions:

- 76 • Bronchial asthma or related bronchospastic conditions. Deaths from status asthmaticus have  
77 been reported following single doses of COREG.
- 78 • Second- or third-degree AV block.
- 79 • Sick sinus syndrome.
- 80 • Severe bradycardia (unless a permanent pacemaker is in place).
- 81 • Patients with cardiogenic shock or who have decompensated heart failure requiring the use of  
82 intravenous inotropic therapy. Such patients should first be weaned from intravenous therapy  
83 before initiating COREG.
- 84 • Patients with severe hepatic impairment.
- 85 • Patients with a history of a serious hypersensitivity reaction (e.g., Stevens-Johnson  
86 syndrome, anaphylactic reaction, angioedema) to any component of this medication or other  
87 medications containing carvedilol.

### 88 **5 WARNINGS AND PRECAUTIONS**

#### 89 **5.1 Cessation of Therapy**

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

## 102 **5.2 Bradycardia**

103 In clinical trials, COREG caused bradycardia in about 2% of hypertensive subjects, 9% of heart  
104 failure subjects, and 6.5% of myocardial infarction subjects with left ventricular dysfunction. If  
105 pulse rate drops below 55 beats per minute, the dosage should be reduced.

## 106 **5.3 Hypotension**

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

117 Postural hypotension occurred in 1.8% and syncope in 0.1% of hypertensive subjects, primarily  
118 following the initial dose or at the time of dose increase and was a cause for discontinuation of  
119 therapy in 1% of subjects.

120 In the CAPRICORN trial of survivors of an acute myocardial infarction, hypotension or postural  
121 hypotension occurred in 20.2% of subjects receiving COREG compared with 12.6% of placebo  
122 subjects. Syncope was reported in 3.9% and 1.9% of subjects, respectively. These events were a  
123 cause for discontinuation of therapy in 2.5% of subjects receiving COREG, compared with 0.2%  
124 of placebo subjects.

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

## 129 **5.4 Heart Failure/Fluid Retention**

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

138 carvedilol than with placebo. Worsening heart failure observed during long-term therapy is more  
139 likely to be related to the patients' underlying disease than to treatment with carvedilol.

## 140 **5.5 Non-allergic Bronchospasm**

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

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

## 151 **5.6 Glycemic Control in Type 2 Diabetes**

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

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

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

## 165 **5.7 Peripheral Vascular Disease**

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

## 168 **5.8 Deterioration of Renal Function**

169 Rarely, use of carvedilol in patients with heart failure has resulted in deterioration of renal  
170 function. Patients at risk appear to be those with low blood pressure (systolic blood pressure less  
171 than 100 mm Hg), ischemic heart disease and diffuse vascular disease, and/or underlying renal  
172 insufficiency. Renal function has returned to baseline when carvedilol was stopped. In patients

173 with these risk factors it is recommended that renal function be monitored during up-titration of  
174 carvedilol and the drug discontinued or dosage reduced if worsening of renal function occurs.

## 175 **5.9 Major Surgery**

176 Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major  
177 surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may  
178 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. Abrupt  
181 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 use of  
185 any  $\beta$ -blocking agent. Although carvedilol has both  $\alpha$ - and  $\beta$ -blocking pharmacologic activities,  
186 there has been no experience with its use in this condition. Therefore, caution should be taken in  
187 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 variety of  
196 allergens may be more reactive to repeated challenge, either accidental, diagnostic, or  
197 therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat  
198 allergic reaction.

## 199 **5.14 Intraoperative Floppy Iris Syndrome**

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

209 **6 ADVERSE REACTIONS**

210 **6.1 Clinical Studies Experience**

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

220 Heart Failure

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

233 Table 1 shows adverse events reported in subjects with mild-to-moderate heart failure enrolled in  
234 US placebo-controlled clinical trials, and with severe heart failure enrolled in the COPERNICUS  
235 trial. Shown are adverse events that occurred more frequently in drug-treated subjects than  
236 placebo-treated subjects with an incidence of greater than 3% in subjects treated with carvedilol  
237 regardless of causality. Median trial medication exposure was 6.3 months for both carvedilol and  
238 placebo subjects in the trials of mild-to-moderate heart failure, and 10.4 months in the trial of  
239 severe heart failure subjects. The adverse event profile of COREG observed in the long-term  
240 COMET trial was generally similar to that observed in the US Heart Failure Trials.

241



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

Body System/ Adverse Event	Mild-to-Moderate HF		Severe HF	
	COREG (n = 765)	Placebo (n = 437)	COREG (n = 1,156)	Placebo (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	—	—

246

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

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

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

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

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

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

258 *Gastrointestinal:* Melena, periodontitis.

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

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

263 *Musculoskeletal:* Muscle cramps.

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

265 *Psychiatric:* Somnolence.

266 *Reproductive, male:* Impotence.

267 *Special Senses:* Blurred vision.

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

269 **Left Ventricular Dysfunction following Myocardial Infarction**

270 COREG has been evaluated for safety in survivors of an acute myocardial infarction with left  
271 ventricular dysfunction in the CAPRICORN trial which involved 969 subjects who received  
272 COREG and 980 who received placebo. Approximately 75% of the subjects received COREG  
273 for at least 6 months and 53% received COREG for at least 12 months. Subjects were treated for  
274 an average of 12.9 months and 12.8 months with COREG and placebo, respectively.

275 The most common adverse events reported with COREG in the CAPRICORN trial were  
276 consistent with the profile of the drug in the US heart failure trials and the COPERNICUS trial.

277 The only additional adverse events reported in CAPRICORN in greater than 3% of the subjects  
278 and more commonly on carvedilol were dyspnea, anemia, and lung edema. The following

279 adverse events were reported with a frequency of greater than 1% but less than or equal to 3%  
280 and more frequently with COREG: flu syndrome, cerebrovascular accident, peripheral vascular  
281 disorder, hypotonia, depression, gastrointestinal pain, arthritis, and gout. The overall rates of  
282 discontinuations due to adverse events were similar in both groups of subjects. In this database,  
283 the only cause of discontinuation greater than 1%, and occurring more often on carvedilol was  
284 hypotension (1.5% on carvedilol, 0.2% on placebo).

### 285 Hypertension

286 COREG has been evaluated for safety in hypertension in more than 2,193 subjects in US clinical  
287 trials and in 2,976 subjects in international clinical trials. Approximately 36% of the total treated  
288 population received COREG for at least 6 months. Most adverse events reported during therapy  
289 with COREG were of mild to moderate severity. In US controlled clinical trials directly  
290 comparing COREG in doses up to 50 mg (n = 1,142) with placebo (n = 462), 4.9% of subjects  
291 receiving COREG discontinued for adverse events versus 5.2% of placebo subjects. Although  
292 there was no overall difference in discontinuation rates, discontinuations were more common in  
293 the carvedilol group for postural hypotension (1% versus 0). The overall incidence of adverse  
294 events in US placebo-controlled trials increased with increasing dose of COREG. For individual  
295 adverse events this could only be distinguished for dizziness, which increased in frequency from  
296 2% to 5% as total daily dose increased from 6.25 mg to 50 mg.

297 Table 2 shows adverse events in US placebo-controlled clinical trials for hypertension that  
298 occurred with an incidence of greater than or equal to 1% regardless of causality, and that were  
299 more frequent in drug-treated subjects than placebo-treated subjects.

300

301 **Table 2. Adverse Events (%) Occurring in US Placebo-Controlled Hypertension Trials**  
 302 **(Incidence  $\geq$ 1%, Regardless of Causality)<sup>a</sup>**

<b>Body System/ Adverse Event</b>	<b>COREG (n = 1,142)</b>	<b>Placebo (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	—

303 <sup>a</sup> Shown are events with rate >1% rounded to nearest integer.

304

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

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

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

311 *Cardiovascular:* Peripheral ischemia, tachycardia.

312 *Central and Peripheral Nervous System:* Hypokinesia.

313 *Gastrointestinal:* Bilirubinemia, increased hepatic enzymes (0.2% of hypertension patients and  
 314 0.4% of heart failure patients were discontinued from therapy because of increases in hepatic  
 315 enzymes) [see Adverse Reactions (6.2)].

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

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

319 *Reproductive, male:* Decreased libido.

320 *Skin and Appendages:* Pruritus, rash erythematous, rash maculopapular, rash psoriaform,  
 321 photosensitivity reaction.

322 *Special Senses:* Tinnitus.

323 *Urinary System:* Micturition frequency increased.

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

325 *Metabolic and Nutritional:* Hypokalemia, hypertriglyceridemia.

326 *Hematologic:* Anemia, leukopenia.

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

## 332 **6.2 Laboratory Abnormalities**

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

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

## 345 **6.3 Postmarketing Experience**

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

### 350 Blood and Lymphatic System Disorders

351 Aplastic anemia.

### 352 Immune System Disorders

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

### 354 Renal and Urinary Disorders

355 Urinary incontinence.

356 Respiratory, Thoracic, and Mediastinal Disorders

357 Interstitial pneumonitis.

358 Skin and Subcutaneous Tissue Disorders

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

360 **7 DRUG INTERACTIONS**

361 **7.1 CYP2D6 Inhibitors and Poor Metabolizers**

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

368 **7.2 Hypotensive Agents**

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

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

377 **7.3 Cyclosporine**

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

386 **7.4 Digitalis Glycosides**

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

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

## 392 **7.5 Inducers/Inhibitors of Hepatic Metabolism**

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

## 396 **7.6 Amiodarone**

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

## 404 **7.7 Calcium Channel Blockers**

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

## 409 **7.8 Insulin or Oral Hypoglycemics**

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

## 413 **7.9 Anesthesia**

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

# 417 **8 USE IN SPECIFIC POPULATIONS**

## 418 **8.1 Pregnancy**

419 Pregnancy Category C. Studies performed in pregnant rats and rabbits given carvedilol revealed  
420 increased post-implantation loss in rats at doses of 300 mg per kg per day (50 times the  
421 maximum recommended human dose [MRHD] as mg per  $m^2$ ) and in rabbits at doses of 75 mg  
422 per kg per day (25 times the MRHD as mg per  $m^2$ ). In the rats, there was also a decrease in fetal  
423 body weight at the maternally toxic dose of 300 mg per kg per day (50 times the MRHD as mg  
424 per  $m^2$ ), which was accompanied by an elevation in the frequency of fetuses with delayed

425 skeletal development (missing or stunted 13th rib). In rats the no-observed-effect level for  
426 developmental toxicity was 60 mg per kg per day (10 times the MRHD as mg per m<sup>2</sup>); in rabbits  
427 it was 15 mg per kg per day (5 times the MRHD as mg per m<sup>2</sup>). There are no adequate and  
428 well-controlled studies in pregnant women. COREG should be used during pregnancy only if the  
429 potential benefit justifies the potential risk to the fetus.

### 430 **8.3 Nursing Mothers**

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

### 440 **8.4 Pediatric Use**

441 Effectiveness of COREG in patients younger than 18 years has not been established.

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

### 453 **8.5 Geriatric Use**

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

459 Of the 975 myocardial infarction subjects randomized to COREG in the CAPRICORN trial, 48%  
460 (468) were aged 65 years or older, and 11% (111) were aged 75 years or older.



461 Of the 2,065 hypertensive subjects in US clinical trials of efficacy or safety who were treated  
462 with COREG, 21% (436) were aged 65 years or older. Of 3,722 subjects receiving COREG in  
463 hypertension clinical trials conducted worldwide, 24% were aged 65 years or older.

464 With the exception of dizziness in hypertensive subjects (incidence 8.8% in the elderly versus  
465 6% in younger subjects), no overall differences in the safety or effectiveness (see Figures 2 and  
466 4) were observed between the older subjects and younger subjects in each of these populations.  
467 Similarly, other reported clinical experience has not identified differences in responses between  
468 the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled  
469 out.

## 470 **10 OVERDOSAGE**

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

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

476 *For excessive bradycardia:* Atropine, 2 mg IV.

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

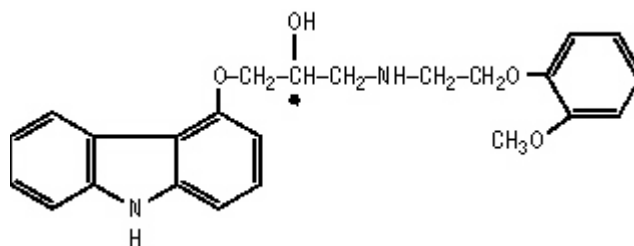
480 If peripheral vasodilation dominates, it may be necessary to administer adrenaline or  
481 noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant  
482 bradycardia, pacemaker therapy should be performed. For bronchospasm,  $\beta$ -sympathomimetics  
483 (as aerosol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

485 NOTE: In the event of severe intoxication where there are symptoms of shock, treatment with  
486 antidotes must be continued for a sufficiently long period of time consistent with the 7- to  
487 10-hour half-life of carvedilol.

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

## 492 **11 DESCRIPTION**

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



496

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

501 Carvedilol is a white to off-white powder with a molecular weight of 406.5 and a molecular  
 502 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 chloride  
 503 and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in ethyl ether;  
 504 and practically insoluble in water, gastric fluid (simulated, TS, pH 1.1), and intestinal fluid  
 505 (simulated, TS without pancreatin, pH 7.5).

## 506 12 CLINICAL PHARMACOLOGY

### 507 12.1 Mechanism of Action

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

### 511 12.2 Pharmacodynamics

#### 512 Heart Failure

513 The basis for the beneficial effects of COREG in heart failure is not established.

514 Two placebo-controlled trials compared the acute hemodynamic effects of COREG with baseline  
 515 measurements in 59 and 49 subjects with NYHA class II-IV heart failure receiving diuretics,  
 516 ACE inhibitors, and digitalis. There were significant reductions in systemic blood pressure,  
 517 pulmonary artery pressure, pulmonary capillary wedge pressure, and heart rate. Initial effects on  
 518 cardiac output, stroke volume index, and systemic vascular resistance were small and variable.

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

522 Among 839 subjects with NYHA class II-III heart failure treated for 26 to 52 weeks in 4 US  
 523 placebo-controlled trials, average left ventricular ejection fraction (EF) measured by radionuclide  
 524 ventriculography increased by 9 EF units (%) in subjects receiving COREG and by 2 EF units in  
 525 placebo subjects at a target dose of 25 to 50 mg twice daily. The effects of carvedilol on ejection

526 fraction were related to dose. Doses of 6.25 mg twice daily, 12.5 mg twice daily, and 25 mg  
527 twice daily were associated with placebo-corrected increases in EF of 5 EF units, 6 EF units, and  
528 8 EF units, respectively; each of these effects were nominally statistically significant.

### 529 Left Ventricular Dysfunction following Myocardial Infarction

530 The basis for the beneficial effects of COREG in patients with left ventricular dysfunction  
531 following an acute myocardial infarction is not established.

### 532 Hypertension

533 The mechanism by which  $\beta$ -blockade produces an antihypertensive effect has not been  
534 established.

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

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

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

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

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

### 556 **12.3 Pharmacokinetics**

557 COREG is rapidly and extensively absorbed following oral administration, with absolute  
558 bioavailability of approximately 25% to 35% due to a significant degree of first-pass  
559 metabolism. Following oral administration, the apparent mean terminal elimination half-life of  
560 carvedilol generally ranges from 7 to 10 hours. Plasma concentrations achieved are proportional  
561 to the oral dose administered. When administered with food, the rate of absorption is slowed, as

562 evidenced by a delay in the time to reach peak plasma levels, with no significant difference in  
563 extent of bioavailability. Taking COREG with food should minimize the risk of orthostatic  
564 hypotension.

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

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

577 Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R(+)-carvedilol  
578 approximately 2 to 3 times higher than S(-)-carvedilol following oral administration in healthy  
579 subjects. The mean apparent terminal elimination half-lives for R(+)-carvedilol range from 5 to  
580 9 hours compared with 7 to 11 hours for the S(-)-enantiomer.

581 The primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-carvedilol in  
582 human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19,  
583 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and 5'-hydroxylation of  
584 carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be of primary  
585 importance in the O-methylation pathway of S(-)-carvedilol.

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

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

## 598 **12.4 Specific Populations**

### 599 Heart Failure

600 Steady-state plasma concentrations of carvedilol and its enantiomers increased proportionally  
601 over the 6.25- to 50- mg dose range in subjects with heart failure. Compared with healthy  
602 subjects, heart failure subjects had increased mean AUC and C<sub>max</sub> values for carvedilol and its  
603 enantiomers, with up to 50% to 100% higher values observed in 6 subjects with NYHA class IV  
604 heart failure. The mean apparent terminal elimination half-life for carvedilol was similar to that  
605 observed in healthy subjects.

### 606 Geriatric

607 Plasma levels of carvedilol average about 50% higher in the elderly compared with young  
608 subjects.

### 609 Hepatic Impairment

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

### 613 Renal Impairment

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

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

## 623 **12.5 Drug-Drug Interactions**

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

### 627 Amiodarone

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

632 Cimetidine

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

636 Digoxin

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

640 Glyburide

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

644 Hydrochlorothiazide

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

648 Rifampin

649 In a pharmacokinetic trial conducted in 8 healthy male subjects, rifampin (600 mg daily for  
650 12 days) decreased the AUC and  $C_{max}$  of carvedilol by about 70% [see *Drug Interactions (7.5)*].

651 Torsemide

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

655 Warfarin

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

659 **13 NONCLINICAL TOXICOLOGY**

660 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

661 In 2-year studies conducted in rats given carvedilol at doses up to 75 mg per kg per day (12 times  
662 the MRHD when compared on a mg per  $m^2$  basis) or in mice given up to 200 mg per kg per day  
663 (16 times the MRHD on a mg per  $m^2$  basis), carvedilol had no carcinogenic effect.

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

667 At doses greater than or equal to 200 mg per kg per day (greater than or equal to 32 times the  
668 MRHD as mg per m<sup>2</sup>) carvedilol was toxic to adult rats (sedation, reduced weight gain) and was  
669 associated with a reduced number of successful matings, prolonged mating time, significantly  
670 fewer corpora lutea and implants per dam, and complete resorption of 18% of the litters. The  
671 no-observed-effect dose level for overt toxicity and impairment of fertility was 60 mg per kg per  
672 day (10 times the MRHD as mg per m<sup>2</sup>).

## 673 **14 CLINICAL STUDIES**

### 674 **14.1 Heart Failure**

675 A total of 6,975 subjects with mild to severe heart failure were evaluated in placebo-controlled  
676 trials of carvedilol.

#### 677 Mild-to-Moderate Heart Failure

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

680 Four US multicenter, double-blind, placebo-controlled trials enrolled 1,094 subjects  
681 (696 randomized to carvedilol) with NYHA class II-III heart failure and ejection fraction less  
682 than or equal to 0.35. The vast majority were on digitalis, diuretics, and an ACE inhibitor at trial  
683 entry. Patients were assigned to the trials based upon exercise ability. An Australia-New Zealand  
684 double-blind, placebo-controlled trial enrolled 415 subjects (half randomized to carvedilol) with  
685 less severe heart failure. All protocols excluded subjects expected to undergo cardiac  
686 transplantation during the 7.5 to 15 months of double-blind follow-up. All randomized subjects  
687 had tolerated a 2-week course on carvedilol 6.25 mg twice daily.

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

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

697 ***Slowing Progression of Heart Failure:*** One US multicenter trial (366 subjects) had as its  
698 primary end point the sum of cardiovascular mortality, cardiovascular hospitalization, and

699 sustained increase in heart failure medications. Heart failure progression was reduced, during an  
700 average follow-up of 7 months, by 48% ( $P = 0.008$ ).

701 In the Australia-New Zealand trial, death and total hospitalizations were reduced by about 25%  
702 over 18 to 24 months. In the 3 largest US trials, death and total hospitalizations were reduced by  
703 19%, 39%, and 49%, nominally statistically significant in the last 2 trials. The Australia-New  
704 Zealand results were statistically borderline.

705 **Functional Measures:** None of the multicenter trials had NYHA classification as a primary end  
706 point, but all such trials had it as a secondary end point. There was at least a trend toward  
707 improvement in NYHA class in all trials. Exercise tolerance was the primary end point in  
708 3 trials; in none was a statistically significant effect found.

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

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

#### 714 The COMET Trial

715 In this double-blind trial, 3,029 subjects with NYHA class II-IV heart failure (left ventricular  
716 ejection fraction less than or equal to 35%) were randomized to receive either carvedilol (target  
717 dose: 25 mg twice daily) or immediate-release metoprolol tartrate (target dose: 50 mg twice  
718 daily). The mean age of the subjects was approximately 62 years, 80% were males, and the mean  
719 left ventricular ejection fraction at baseline was 26%. Approximately 96% of the subjects had  
720 NYHA class II or III heart failure. Concomitant treatment included diuretics (99%), ACE  
721 inhibitors (91%), digitalis (59%), aldosterone antagonists (11%), and "statin" lipid-lowering  
722 agents (21%). The mean duration of follow-up was 4.8 years. The mean dose of carvedilol was  
723 42 mg per day.

724 The trial had 2 primary end points: all-cause mortality and the composite of death plus  
725 hospitalization for any reason. The results of COMET are presented in Table 3 below. All-cause  
726 mortality carried most of the statistical weight and was the primary determinant of the trial size.  
727 All-cause mortality was 34% in the subjects treated with carvedilol and was 40% in the  
728 immediate-release metoprolol group ( $P = 0.0017$ ; hazard ratio = 0.83, 95% CI: 0.74 to 0.93). The  
729 effect on mortality was primarily due to a reduction in cardiovascular death. The difference  
730 between the 2 groups with respect to the composite end point was not significant ( $P = 0.122$ ).  
731 The estimated mean survival was 8.0 years with carvedilol and 6.6 years with immediate-release  
732 metoprolol.  
733



734 **Table 3. Results of COMET**

<b>End point</b>	<b>Carvedilol N = 1,511</b>	<b>Metoprolol N = 1,518</b>	<b>Hazard Ratio</b>	<b>(95% CI)</b>
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

735  
736 It is not known whether this formulation of metoprolol at any dose or this low dose of metoprolol  
737 in any formulation has any effect on survival or hospitalization in patients with heart failure.  
738 Thus, this trial extends the time over which carvedilol manifests benefits on survival in heart  
739 failure, but it is not evidence that carvedilol improves outcome over the formulation of  
740 metoprolol (TOPROL-XL<sup>®</sup>) with benefits in heart failure.

741 **Severe Heart Failure (COPERNICUS)**

742 In a double-blind trial (COPERNICUS), 2,289 subjects with heart failure at rest or with minimal  
743 exertion and left ventricular ejection fraction less than 25% (mean 20%), despite digitalis (66%),  
744 diuretics (99%), and ACE inhibitors (89%) were randomized to placebo or carvedilol. Carvedilol  
745 was titrated from a starting dose of 3.125 mg twice daily to the maximum tolerated dose or up to  
746 25 mg twice daily over a minimum of 6 weeks. Most subjects achieved the target dose of 25 mg.  
747 The trial was conducted in Eastern and Western Europe, the United States, Israel, and Canada.  
748 Similar numbers of subjects per group (about 100) withdrew during the titration period.

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

756

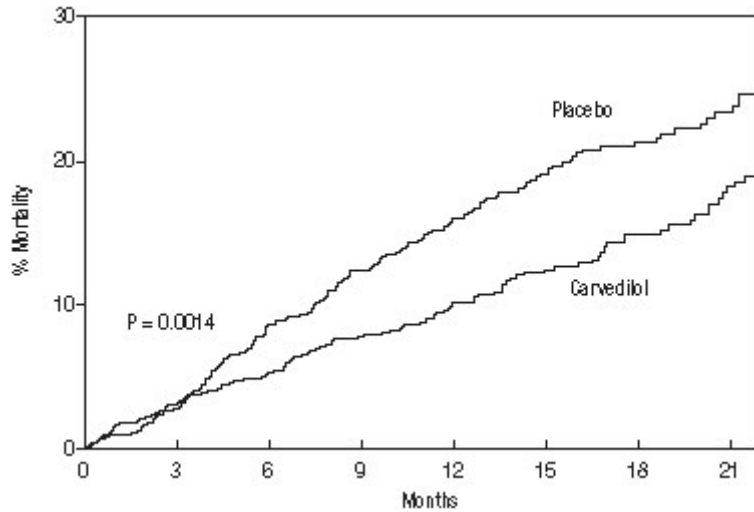
757 **Table 4. Results of COPERNICUS Trial in Subjects with Severe Heart Failure**

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

758 Cardiovascular = CV; Heart failure = HF.

759

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



761

762

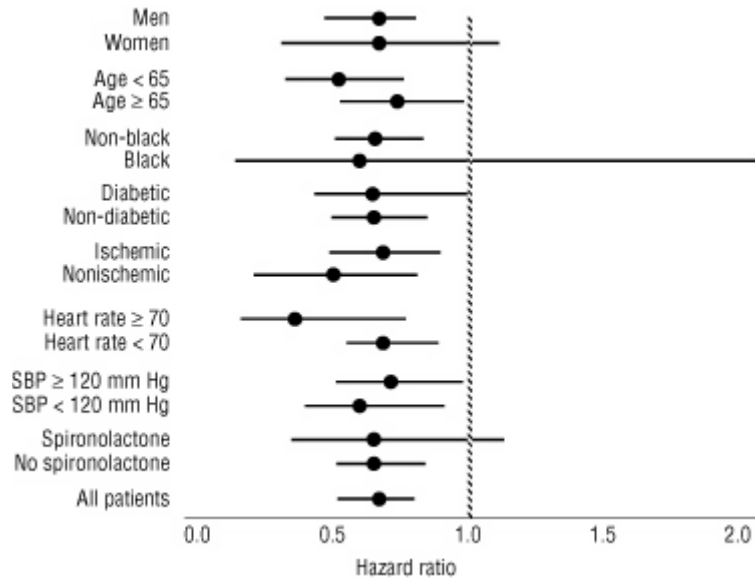
763 The effect on mortality was principally the result of a reduction in the rate of sudden death  
764 among subjects without worsening heart failure.

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

770 The protocol also specified that hospitalizations would be assessed. Fewer subjects on COREG  
771 than on placebo were hospitalized for any reason (372 versus 432,  $P = 0.0029$ ), for  
772 cardiovascular reasons (246 versus 314,  $P = 0.0003$ ), or for worsening heart failure (198 versus  
773 268,  $P = 0.0001$ ).

774 COREG had a consistent and beneficial effect on all-cause mortality as well as the combined end  
 775 points of all-cause mortality plus hospitalization (total, CV, or for heart failure) in the overall  
 776 trial population and in all subgroups examined, including men and women, elderly and  
 777 non-elderly, blacks and non-blacks, and diabetics and non-diabetics (see Figure 2).  
 778

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



780  
781

782 **14.2 Left Ventricular Dysfunction following Myocardial Infarction**

783 CAPRICORN was a double-blind trial comparing carvedilol and placebo in 1,959 subjects with a  
 784 recent myocardial infarction (within 21 days) and left ventricular ejection fraction of less than or  
 785 equal to 40%, with (47%) or without symptoms of heart failure. Subjects given carvedilol  
 786 received 6.25 mg twice daily, titrated as tolerated to 25 mg twice daily. Subjects had to have a  
 787 systolic blood pressure greater than 90 mm Hg, a sitting heart rate greater than 60 beats per  
 788 minute, and no contraindication to  $\beta$ -blocker use. Treatment of the index infarction included  
 789 aspirin (85%), IV or oral  $\beta$ -blockers (37%), nitrates (73%), heparin (64%), thrombolytics (40%),  
 790 and acute angioplasty (12%). Background treatment included ACE inhibitors or angiotensin-  
 791 receptor blockers (97%), anticoagulants (20%), lipid-lowering agents (23%), and diuretics  
 792 (34%). Baseline population characteristics included an average age of 63 years, 74% male, 95%  
 793 Caucasian, mean blood pressure 121/74 mm Hg, 22% with diabetes, and 54% with a history of  
 794 hypertension. Mean dosage achieved of carvedilol was 20 mg twice daily; mean duration of  
 795 follow-up was 15 months.

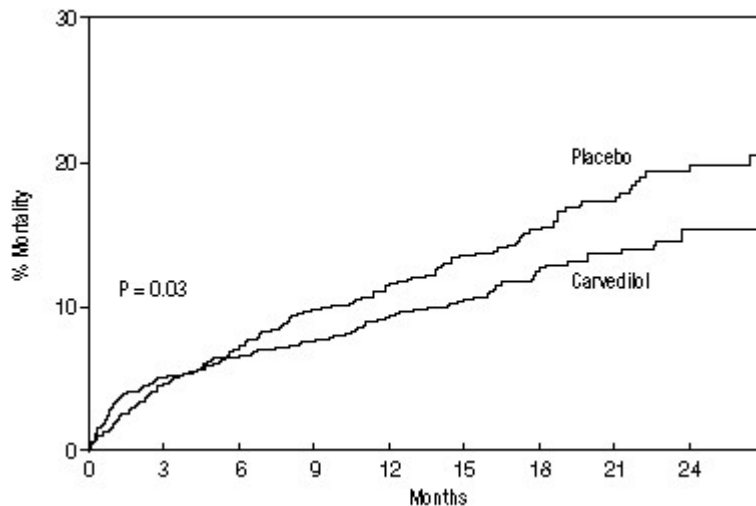
796 All-cause mortality was 15% in the placebo group and 12% in the carvedilol group, indicating a  
 797 23% risk reduction in subjects treated with carvedilol (95% CI: 2% to 40%,  $P = 0.03$ ), as shown  
 798 in Figure 3. The effects on mortality in various subgroups are shown in Figure 4. Nearly all  
 799 deaths were cardiovascular (which were reduced by 25% by carvedilol), and most of these deaths

800 were sudden or related to pump failure (both types of death were reduced by carvedilol). Another  
 801 trial end point, total mortality and all-cause hospitalization, did not show a significant  
 802 improvement.

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

807

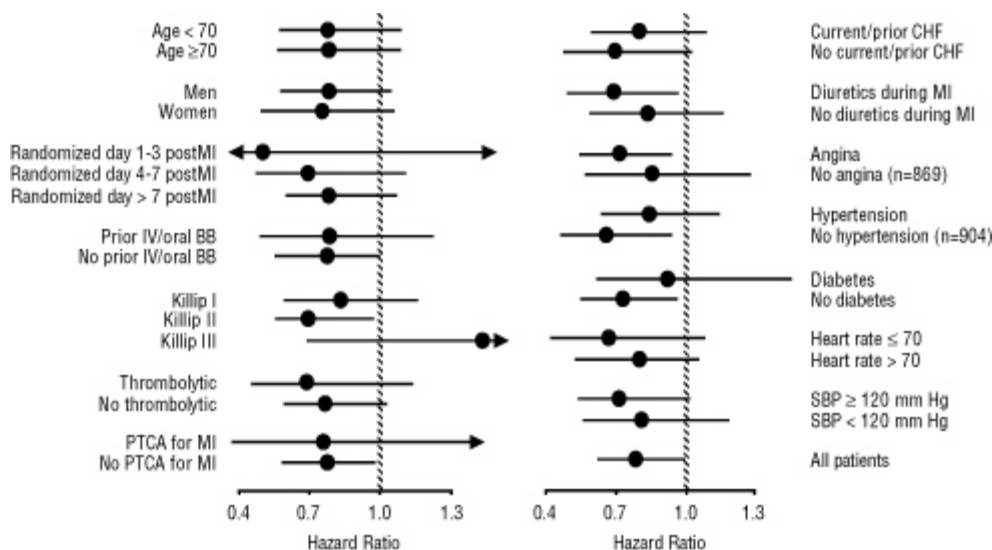
808 **Figure 3. Survival Analysis for CAPRICORN (Intent-to-Treat)**



809

810

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



812

813

814 **14.3 Hypertension**

815 COREG was studied in 2 placebo-controlled trials that utilized twice-daily dosing, at total daily  
816 doses of 12.5 to 50 mg. In these and other trials, the starting dose did not exceed 12.5 mg. At  
817 50 mg per day, COREG reduced sitting trough (12-hour) blood pressure by about 9/5.5 mm Hg;  
818 at 25 mg per day the effect was about 7.5/3.5 mm Hg. Comparisons of trough-to-peak blood  
819 pressure showed a trough-to-peak ratio for blood pressure response of about 65%. Heart rate fell  
820 by about 7.5 beats per minute at 50 mg per day. In general, as is true for other  $\beta$ -blockers,  
821 responses were smaller in black than non-black subjects. There were no age- or gender-related  
822 differences in response.

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

826 **14.4 Hypertension with Type 2 Diabetes Mellitus**

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

833 **16 HOW SUPPLIED/STORAGE AND HANDLING**

834 The white, oval, film-coated tablets are available in the following strengths:

- 835 • 3.125 mg – engraved with “39” and “SB”
- 836 • 6.25 mg – engraved with “4140” and “SB”
- 837 • 12.5 mg – engraved with “4141” and “SB”
- 838 • 25 mg – engraved with “4142” and “SB”

839 The 6.25-mg, 12.5-mg, and 25-mg tablets are TILTAB tablets.

- 840• 3.125 mg bottles of 100: NDC 0007-4139-20
- 841• 6.25 mg bottles of 100: NDC 0007-4140-20
- 842• 12.5 mg bottles of 100: NDC 0007-4141-20
- 843• 25 mg bottles of 100: NDC 0007-4142-20

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

845 **17 PATIENT COUNSELING INFORMATION**

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

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

860

861 COREG, COREG CR, and TILTAB are registered trademarks of the GSK group of companies.

862 TOPROL-XL is a trademark of its respective owner and is not a trademark of the GSK group of  
863 companies. The maker of this brand is not affiliated with and does not endorse the GSK group of  
864 companies or its products.

865

866



867

868

869

870

871

872

873

GlaxoSmithKline  
Research Triangle Park, NC 27709

©20xx, the GSK group of companies. All rights reserved.

CRG:XXPI

874 PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

875 -----

876

877

## PATIENT INFORMATION

878

### COREG<sup>®</sup> (Co-REG)

879

carvedilol tablets

880

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

885

#### 886 **What is COREG?**

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

- 889 • to treat patients with certain types of heart failure
- 890 • to treat patients who had a heart attack that worsened how well the heart  
891 pumps
- 892 • to treat patients with high blood pressure (hypertension)

893

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

895

#### 896 **Who should not take COREG?**

897 Do not take COREG if you:

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

906

#### 907 **What should I tell my doctor before taking COREG?**

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

- 909 • have asthma or other lung problems (such as bronchitis or emphysema).
- 910 • have problems with blood flow in your feet and legs (peripheral vascular  
911 disease). COREG can make some of your symptoms worse.
- 912 • have diabetes.
- 913 • have thyroid problems.

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

928

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

931

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

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

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

951



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

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

956  
957 **What are possible side effects of COREG?**

- 958 • **Low blood pressure (which may cause dizziness or fainting when you**  
959 **stand up).** If these happen, sit or lie down right away and tell your doctor.  
960 • **Tiredness.** If you feel tired or dizzy you should not drive, use machinery, or do  
961 anything that needs you to be alert.  
962 • **Slow heartbeat.**  
963 • **Changes in your blood sugar. If you have diabetes, tell your doctor if**  
964 **you have any changes in your blood sugar levels.**  
965 • COREG may hide some of the symptoms of low blood sugar, especially a fast  
966 heartbeat.  
967 • COREG may mask the symptoms of hyperthyroidism (overactive thyroid).  
968 • **Worsening of severe allergic reactions.**  
969 • Rare but serious allergic reactions (including hives or swelling of the face, lips,  
970 tongue, and/or throat that may cause difficulty in breathing or swallowing) have  
971 happened in patients who were on COREG. These reactions can be life-  
972 threatening.

973  
974 Other side effects of COREG include shortness of breath, weight gain, diarrhea, and  
975 fewer tears or dry eyes that become bothersome if you wear contact lenses.

976  
977 Call your doctor if you have any side effects that bother you or don't go away.

978  
979 Call your doctor for medical advice about side effects. You may report side effects  
980 to FDA at 1-800-FDA-1088.

981  
982 **How should I store COREG?**

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

986  
987 **General Information about COREG**

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

992  
993 This leaflet summarizes the most important information about COREG. If you would  
994 like more information, talk with your doctor. You can ask your doctor or pharmacist  
995 for information about COREG that is written for healthcare professionals. You can  
996 also find out more about COREG by visiting the website [www.COREG.com](http://www.COREG.com) or calling  
997 1-888-825-5249. This call is free.

998

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

1000 Active Ingredient: carvedilol.

1001

1002 Inactive Ingredients: colloidal silicon dioxide, crospovidone, hypromellose, lactose,  
1003 magnesium stearate, polyethylene glycol, polysorbate 80, povidone, sucrose, and  
1004 titanium dioxide.

1005

1006 Carvedilol tablets come in the following strengths: 3.125 mg, 6.25 mg, 12.5 mg,  
1007 25 mg.

1008

1009 **What is high blood pressure (hypertension)?**

1010 Blood pressure is the force of blood in your blood vessels when your heart beats  
1011 and when your heart rests. You have high blood pressure when the force is too  
1012 much. High blood pressure makes the heart work harder to pump blood through the  
1013 body and causes damage to blood vessels. COREG can help your blood vessels  
1014 relax so your blood pressure is lower. Medicines that lower blood pressure may  
1015 lower your chance of having a stroke or heart attack.

1016

1017 COREG is a registered trademark of the GSK group of companies.

1018

1019

1020 Manufactured for



1021

1022 GlaxoSmithKline

1023 Research Triangle Park, NC 27709

1024

1025 ©201x, the GSK group of companies. All rights reserved.

1026

1027 XX/201x

1028 CRG: xPIL