

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

### RECENT MAJOR CHANGES

Dosage and Administration, Geriatric Use (2.5)

December 2008

### INDICATIONS AND USAGE

COREG CR is an alpha/beta-adrenergic blocking agent indicated for the treatment of:

- Mild to severe chronic heart failure (1.1)
- Left ventricular dysfunction following myocardial infarction in clinically stable patients (1.2)
- Hypertension (1.3)

### DOSAGE AND ADMINISTRATION

Take with food. Do not crush or chew capsules. Individualize dosage and monitor during up-titration. (2)

- Heart failure: Start at 10 mg once daily and increase to 20, 40, and then 80 mg once daily over intervals of at least 2 weeks. Maintain lower doses if higher doses are not tolerated. (2.1)
- Left ventricular dysfunction following myocardial infarction: Start at 20 mg once daily and increase to 40 mg then 80 mg once daily after intervals of 3 to 10 days. A lower starting dose or slower titration may be used. (2.2)
- Hypertension: Start at 20 mg once daily and increase if needed for blood pressure control to 40 mg then 80 mg once daily over intervals of 1 to 2 weeks. (2.3)
- Elderly patients (> 65 years of age): When switching from higher doses of immediate-release carvedilol to COREG CR, a lower starting dose should be considered to reduce the risk of hypotension and syncope.

### DOSAGE FORMS AND STRENGTHS

Capsules: 10, 20, 40, 80 mg (3)

### CONTRAINDICATIONS

- Bronchial asthma or related bronchospastic conditions (4)
- Second- or third-degree AV block (4)
- Sick sinus syndrome (4)
- Severe bradycardia (unless permanent pacemaker in place) (4)
- Patients in cardiogenic shock or decompensated heart failure requiring the use of IV inotropic therapy. (4)
- Severe hepatic impairment (2.4, 4)

- History of serious hypersensitivity reaction (e.g., Stevens-Johnson syndrome, anaphylactic reaction, angioedema) to 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

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

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

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](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: Month Year  
CCR:XXPI

## 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
- 2.5 Geriatric Use

### 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 Nonallergic Bronchospasm
- 5.6 Glycemic Control in Type 2 Diabetes
- 5.7 Peripheral Vascular Disease
- 5.8 Deterioration of Renal Function
- 5.9 Anesthesia and Major Surgery
- 5.10 Thyrotoxicosis
- 5.11 Pheochromocytoma
- 5.12 Prinzmetal's Variant Angina
- 5.13 Risk of Anaphylactic Reaction

### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials 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 Proton Pump Inhibitors

### 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**

17.1 Patient Advice

17.2 FDA-Approved Patient Labeling

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

1

2 **FULL PRESCRIBING INFORMATION**

3 **1 INDICATIONS AND USAGE**

4 **1.1 Heart Failure**

5 COREG CR is indicated for the treatment of mild-to-severe chronic heart failure of  
6 ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitors, and  
7 digitalis, to increase survival and, also, to reduce the risk of hospitalization [*see Clinical Studies*  
8 (*14.1*)].

9 **1.2 Left Ventricular Dysfunction Following Myocardial Infarction**

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

13 **1.3 Hypertension**

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

17 **2 DOSAGE AND ADMINISTRATION**

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

22  
23 **Table 1. Dosing Conversion**

Daily Dose of Immediate-Release Carvedilol Tablets	Daily Dose of COREG CR Capsules*
6.25 mg (3.125 mg twice daily)	10 mg once daily
12.5 mg (6.25 mg twice daily)	20 mg once daily
25 mg (12.5 mg twice daily)	40 mg once daily
50 mg (25 mg twice daily)	80 mg once daily
* When switching from carvedilol 12.5 mg or 25 mg twice daily, a starting dose of COREG CR 20 mg or 40 mg once daily, respectively, may be warranted for elderly patients or those at increased risk of hypotension, dizziness, or syncope. Subsequent titration to higher doses should, as appropriate, be made after an interval of at least 2 weeks.	

24  
25 COREG CR should be taken once daily in the morning with food. COREG CR should be  
26 swallowed as a whole capsule. COREG CR and/or its contents should not be crushed, chewed, or  
27 taken in divided doses.

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

### 33 **2.1 Heart Failure**

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

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

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

50 The dose of COREG CR should be reduced if patients experience bradycardia (heart rate  
51 <55 beats/minute).

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

### 55 **2.2 Left Ventricular Dysfunction Following Myocardial Infarction**

56 DOSAGE MUST BE INDIVIDUALIZED AND MONITORED DURING  
57 UP-TITRATION. Treatment with COREG CR may be started as an inpatient or outpatient and  
58 should be started after the patient is hemodynamically stable and fluid retention has been  
59 minimized. It is recommended that COREG CR be started at 20 mg once daily and increased  
60 after 3 to 10 days, based on tolerability, to 40 mg once daily, then again to the target dose of  
61 80 mg once daily. A lower starting dose may be used (10 mg once daily) and/or the rate of  
62 up-titration may be slowed if clinically indicated (e.g., due to low blood pressure or heart rate, or  
63 fluid retention). Patients should be maintained on lower doses if higher doses are not tolerated.  
64 The recommended dosing regimen need not be altered in patients who received treatment with an  
65 IV or oral  $\beta$ -blocker during the acute phase of the myocardial infarction.

### 66 **2.3 Hypertension**

67 DOSAGE MUST BE INDIVIDUALIZED. The recommended starting dose of  
68 COREG CR is 20 mg once daily. If this dose is tolerated, using standing systolic pressure

69 measured about one hour after dosing as a guide, the dose should be maintained for 7 to 14 days,  
70 and then increased to 40 mg once daily if needed, based on trough blood pressure, again using  
71 standing systolic pressure one hour after dosing as a guide for tolerance. This dose should also be  
72 maintained for 7 to 14 days and can then be adjusted upward to 80 mg once daily if tolerated and  
73 needed. Although not specifically studied, it is anticipated the full antihypertensive effect of  
74 COREG CR would be seen within 7 to 14 days as had been demonstrated with  
75 immediate-release carvedilol. Total daily dose should not exceed 80 mg.

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

## 78 **2.4 Hepatic Impairment**

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

## 81 **2.5 Geriatric Use**

82 When switching elderly patients (65 years of age or older) who are taking the higher  
83 doses of immediate-release carvedilol tablets (12.5 mg or 25 mg twice daily) to COREG CR, a  
84 lower starting dose of COREG CR should be considered to minimize the potential for dizziness,  
85 syncope, or hypotension [*see Dosage and Administration (2)*]. Patients who have switched and  
86 who tolerate COREG CR should, as appropriate, have their dose increased after an interval of at  
87 least 2 weeks [*see Use in Specific Populations (8.5)*].

## 88 **3 DOSAGE FORMS AND STRENGTHS**

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

- 91 • 10 mg – white and green capsule shell printed with GSK COREG CR and 10 mg
- 92 • 20 mg – white and yellow capsule shell printed with GSK COREG CR and 20 mg
- 93 • 40 mg – yellow and green capsule shell printed with GSK COREG CR and 40 mg
- 94 • 80 mg – white capsule shell printed with GSK COREG CR and 80 mg

## 95 **4 CONTRAINDICATIONS**

96 COREG CR is contraindicated in the following conditions:

- 97 • Bronchial asthma or related bronchospastic conditions. Deaths from status asthmaticus have  
98 been reported following single doses of immediate-release carvedilol.
- 99 • Second- or third-degree AV block
- 100 • Sick sinus syndrome
- 101 • Severe bradycardia (unless a permanent pacemaker is in place)
- 102 • Patients with cardiogenic shock or who have decompensated heart failure requiring the use of  
103 intravenous inotropic therapy. Such patients should first be weaned from intravenous therapy  
104 before initiating COREG CR.
- 105 • Patients with severe hepatic impairment

- 106 • Patients with a history of a serious hypersensitivity reaction (e.g., Stevens-Johnson  
107 syndrome, anaphylactic reaction, angioedema) to any component of this medication or other  
108 medications containing carvedilol.

## 109 **5 WARNINGS AND PRECAUTIONS**

110 In clinical trials of COREG CR in patients with hypertension (338 subjects) and in  
111 patients with left ventricular dysfunction following a myocardial infarction or heart failure  
112 (187 subjects), the profile of adverse events observed with carvedilol phosphate was generally  
113 similar to that observed with the administration of immediate-release carvedilol. Therefore, the  
114 information included within this section is based on data from controlled clinical trials with  
115 COREG CR as well as immediate-release carvedilol.

### 116 **5.1 Cessation of Therapy**

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

### 129 **5.2 Bradycardia**

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

### 137 **5.3 Hypotension**

138 In clinical trials of primarily mild-to-moderate heart failure with immediate-release  
139 carvedilol, hypotension and postural hypotension occurred in 9.7% and syncope in 3.4% of  
140 patients receiving carvedilol compared to 3.6% and 2.5% of placebo patients, respectively. The  
141 risk for these events was highest during the first 30 days of dosing, corresponding to the  
142 up-titration period and was a cause for discontinuation of therapy in 0.7% of carvedilol patients,  
143 compared to 0.4% of placebo patients. In a long-term, placebo-controlled trial in severe heart  
144 failure (COPERNICUS), hypotension and postural hypotension occurred in 15.1% and syncope  
145 in 2.9% of heart failure patients receiving carvedilol compared to 8.7% and 2.3% of placebo

146 patients, respectively. These events were a cause for discontinuation of therapy in 1.1% of  
147 carvedilol patients, compared to 0.8% of placebo patients.

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

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

159 In the CAPRICORN study of survivors of an acute myocardial infarction with left  
160 ventricular dysfunction, hypotension or postural hypotension occurred in 20.2% of patients  
161 receiving carvedilol compared to 12.6% of placebo patients. Syncope was reported in 3.9% and  
162 1.9% of patients, respectively. These events were a cause for discontinuation of therapy in 2.5%  
163 of patients receiving carvedilol, compared to 0.2% of placebo patients.

164 Starting with a low dose, administration with food, and gradual up-titration should  
165 decrease the likelihood of syncope or excessive hypotension [*see Dosage and Administration*  
166 *(2.1, 2.2, 2.3)*]. During initiation of therapy, the patient should be cautioned to avoid situations  
167 such as driving or hazardous tasks, where injury could result should syncope occur.

#### 168 **5.4 Heart Failure/Fluid Retention**

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

#### 180 **5.5 Nonallergic Bronchospasm**

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

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

## 191 **5.6 Glycemic Control in Type 2 Diabetes**

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

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

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

## 206 **5.7 Peripheral Vascular Disease**

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

## 209 **5.8 Deterioration of Renal Function**

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

## 217 **5.9 Anesthesia and Major Surgery**

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

## 222 **5.10 Thyrotoxicosis**

223  $\beta$ -adrenergic blockade may mask clinical signs of hyperthyroidism, such as tachycardia.  
224 Abrupt withdrawal of  $\beta$ -blockade may be followed by an exacerbation of the symptoms of  
225 hyperthyroidism or may precipitate thyroid storm.

## 226 **5.11 Pheochromocytoma**

227 In patients with pheochromocytoma, an  $\alpha$ -blocking agent should be initiated prior to the  
228 use of any  $\beta$ -blocking agent. Although carvedilol has both  $\alpha$ - and  $\beta$ -blocking pharmacologic  
229 activities, there has been no experience with its use in this condition. Therefore, caution should  
230 be taken in the administration of carvedilol to patients suspected of having pheochromocytoma.

## 231 **5.12 Prinzmetal's Variant Angina**

232 Agents with non-selective  $\beta$ -blocking activity may provoke chest pain in patients with  
233 Prinzmetal's variant angina. There has been no clinical experience with carvedilol in these  
234 patients although the  $\alpha$ -blocking activity may prevent such symptoms. However, caution should  
235 be taken in the administration of COREG CR to patients suspected of having Prinzmetal's  
236 variant angina.

## 237 **5.13 Risk of Anaphylactic Reaction**

238 While taking  $\beta$ -blockers, patients with a history of severe anaphylactic reaction to a  
239 variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or  
240 therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat  
241 allergic reaction.

## 242 **6 ADVERSE REACTIONS**

### 243 **6.1 Clinical Trials Experience**

244 Carvedilol has been evaluated for safety in patients with heart failure (mild, moderate,  
245 and severe), in patients with left ventricular dysfunction following myocardial infarction, and in  
246 hypertensive patients. The observed adverse event profile was consistent with the pharmacology  
247 of the drug and the health status of the patients in the clinical trials. Adverse events reported for  
248 each of these patient populations reflecting the use of either COREG CR or immediate-release  
249 carvedilol are provided below. Excluded are adverse events considered too general to be  
250 informative, and those not reasonably associated with the use of the drug because they were  
251 associated with the condition being treated or are very common in the treated population. Rates  
252 of adverse events were generally similar across demographic subsets (men and women, elderly  
253 and non-elderly, blacks and non-blacks). COREG CR has been evaluated for safety in a 4-week  
254 (2 weeks of immediate-release carvedilol and 2 weeks of COREG CR) clinical study (n = 187)  
255 which included 157 patients with stable mild, moderate, or severe chronic heart failure and 30  
256 patients with left ventricular dysfunction following acute myocardial infarction. The profile of  
257 adverse events observed with COREG CR in this small, short-term study was generally similar  
258 to that observed with immediate-release carvedilol. Differences in safety would not be expected  
259 based on the similarity in plasma levels for COREG CR and immediate-release carvedilol.

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

262 Carvedilol has been evaluated for safety in heart failure in more than 4,500 patients  
263 worldwide of whom more than 2,100 participated in placebo-controlled clinical trials.  
264 Approximately 60% of the total treated population in placebo-controlled clinical trials received  
265 carvedilol for at least 6 months and 30% received carvedilol for at least 12 months. In the

266 COMET trial, 1,511 patients with mild-to-moderate heart failure were treated with carvedilol for  
267 up to 5.9 years (mean 4.8 years). Both in US clinical trials in mild-to-moderate heart failure that  
268 compared carvedilol in daily doses up to 100 mg (n = 765) to placebo (n = 437), and in a  
269 multinational clinical trial in severe heart failure (COPERNICUS) that compared carvedilol in  
270 daily doses up to 50 mg (n = 1,156) with placebo (n = 1,133), discontinuation rates for adverse  
271 experiences were similar in carvedilol and placebo patients. In placebo-controlled clinical trials,  
272 the only cause of discontinuation >1%, and occurring more often on carvedilol was dizziness  
273 (1.3% on carvedilol, 0.6% on placebo in the COPERNICUS trial).

274 Table 2 shows adverse events reported in patients with mild-to-moderate heart failure  
275 enrolled in US placebo-controlled clinical trials, and with severe heart failure enrolled in the  
276 COPERNICUS trial. Shown are adverse events that occurred more frequently in drug-treated  
277 patients than placebo-treated patients with an incidence of >3% in patients treated with  
278 carvedilol regardless of causality. Median study medication exposure was 6.3 months for both  
279 carvedilol and placebo patients in the trials of mild-to-moderate heart failure, and 10.4 months in  
280 the trial of severe heart failure patients. The adverse event profile of carvedilol observed in the  
281 long-term COMET study was generally similar to that observed in the US Heart Failure Trials.  
282

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

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

288  
 289 Cardiac failure and dyspnea were also reported in these studies, but the rates were equal  
 290 or greater in patients who received placebo.

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

294 **Incidence >1% to ≤3%**

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

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

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

299 *Gastrointestinal:* Melena, periodontitis.

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

301 *Metabolic and Nutritional:* Hyperuricemia, hypoglycemia, hyponatremia, increased  
302 alkaline phosphatase, glycosuria, hypervolemia, diabetes mellitus, GGT increased, weight loss,  
303 hyperkalemia, creatinine increased.

304 *Musculoskeletal:* Muscle cramps.

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

306 *Psychiatric:* Somnolence.

307 *Reproductive, male:* Impotence.

308 *Special Senses:* Blurred vision.

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

310 **Left Ventricular Dysfunction Following Myocardial Infarction:** The following  
311 information describes the safety experience in left ventricular dysfunction following acute  
312 myocardial infarction with immediate-release carvedilol.

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

318 The most common adverse events reported with carvedilol in the CAPRICORN trial were  
319 consistent with the profile of the drug in the US heart failure trials and the COPERNICUS trial.  
320 The only additional adverse events reported in CAPRICORN in >3% of the patients and more  
321 commonly on carvedilol were dyspnea, anemia, and lung edema. The following adverse events  
322 were reported with a frequency of >1% but ≤3% and more frequently with carvedilol: Flu  
323 syndrome, cerebrovascular accident, peripheral vascular disorder, hypotonia, depression,  
324 gastrointestinal pain, arthritis, and gout. The overall rates of discontinuations due to adverse  
325 events were similar in both groups of patients. In this database, the only cause of discontinuation  
326 >1%, and occurring more often on carvedilol was hypotension (1.5% on carvedilol, 0.2% on  
327 placebo).

328 **Hypertension:** COREG CR was evaluated for safety in an 8-week double-blind trial in  
329 337 subjects with essential hypertension. The profile of adverse events observed with  
330 COREG CR was generally similar to that observed with immediate-release carvedilol. The

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

333

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

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

337

338 The following information describes the safety experience in hypertension with  
339 immediate-release carvedilol.

340 Carvedilol has been evaluated for safety in hypertension in more than 2,193 patients in  
341 US clinical trials and in 2,976 patients in international clinical trials. Approximately 36% of the  
342 total treated population received carvedilol for at least 6 months. In general, carvedilol was well  
343 tolerated at doses up to 50 mg daily. Most adverse events reported during carvedilol therapy  
344 were of mild to moderate severity. In US controlled clinical trials directly comparing carvedilol  
345 monotherapy in doses up to 50 mg (n = 1,142) to placebo (n = 462), 4.9% of carvedilol patients  
346 discontinued for adverse events versus 5.2% of placebo patients. Although there was no overall  
347 difference in discontinuation rates, discontinuations were more common in the carvedilol group  
348 for postural hypotension (1% versus 0). The overall incidence of adverse events in US  
349 placebo-controlled trials was found to increase with increasing dose of carvedilol. For individual  
350 adverse events this could only be distinguished for dizziness, which increased in frequency from  
351 2% to 5% as total daily dose increased from 6.25 mg to 50 mg as single or divided doses.

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

355

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

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

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

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

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

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

*Cardiovascular:* Peripheral ischemia, tachycardia.

*Central and Peripheral Nervous System:* Hypokinesia.

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

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

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

*Reproductive, male:* Decreased libido.

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

*Special Senses:* Tinnitus.

*Urinary System:* Micturition frequency increased.

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

*Metabolic and Nutritional:* Hypokalemia, hypertriglyceridemia.

382 *Hematologic:* Anemia, leukopenia.

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

## 388 **6.2 Laboratory Abnormalities**

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

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

## 402 **6.3 Postmarketing Experience**

403 The following adverse reactions have been identified during post-approval use of  
404 COREG<sup>®</sup> or COREG CR. Because these reactions are reported voluntarily from a population of  
405 uncertain size, it is not always possible to reliably estimate their frequency or establish a causal  
406 relationship to drug exposure.

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

# 415 **7 DRUG INTERACTIONS**

## 416 **7.1 CYP2D6 Inhibitors and Poor Metabolizers**

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

421 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from  
422 vasodilating effects of the higher concentrations of the  $\alpha$ -blocking R(+) enantiomer.

## 423 **7.2 Hypotensive Agents**

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

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

## 432 **7.3 Cyclosporine**

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

## 441 **7.4 Digitalis Glycosides**

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

## 447 **7.5 Inducers/Inhibitors of Hepatic Metabolism**

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

## 451 **7.6 Amiodarone**

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

## 459 **7.7 Calcium Channel Blockers**

460 Conduction disturbance (rarely with hemodynamic compromise) has been observed when  
461 carvedilol is co-administered with diltiazem. As with other agents with  $\beta$ -blocking properties, if

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

#### 464 **7.8 Insulin or Oral Hypoglycemics**

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

#### 468 **7.9 Proton Pump Inhibitors**

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

### 471 **8 USE IN SPECIFIC POPULATIONS**

#### 472 **8.1 Pregnancy**

473 Pregnancy Category C. Studies performed in pregnant rats and rabbits given carvedilol  
474 revealed increased post-implantation loss in rats at doses of 300 mg/kg/day (50 times the  
475 maximum recommended human dose [MRHD] as  $\text{mg}/\text{m}^2$ ) and in rabbits at doses of  
476 75 mg/kg/day (25 times the MRHD as  $\text{mg}/\text{m}^2$ ). In the rats, there was also a decrease in fetal body  
477 weight at the maternally toxic dose of 300 mg/kg/day (50 times the MRHD as  $\text{mg}/\text{m}^2$ ), which  
478 was accompanied by an elevation in the frequency of fetuses with delayed skeletal development  
479 (missing or stunted 13th rib). In rats the no-observed-effect level for developmental toxicity was  
480 60 mg/kg/day (10 times the MRHD as  $\text{mg}/\text{m}^2$ ); in rabbits it was 15 mg/kg/day (5 times the  
481 MRHD as  $\text{mg}/\text{m}^2$ ). There are no adequate and well-controlled studies in pregnant women.  
482 COREG CR should be used during pregnancy only if the potential benefit justifies the potential  
483 risk to the fetus.

#### 484 **8.3 Nursing Mothers**

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

#### 494 **8.4 Pediatric Use**

495 Effectiveness of carvedilol in patients younger than 18 years of age has not been  
496 established.

497 In a double-blind trial, 161 children (mean age 6 years, range 2 months to 17 years; 45%  
498 younger than 2 years old) with chronic heart failure [NYHA class II-IV, left ventricular ejection  
499 fraction <40% for children with a systemic left ventricle (LV), and moderate-severe ventricular  
500 dysfunction qualitatively by echo for those with a systemic ventricle that was not an LV] who  
501 were receiving standard background treatment were randomized to placebo or to 2 dose levels of

502 carvedilol. These dose levels produced placebo-corrected heart rate reduction of 4-6 heart beats  
503 per minute, indicative of  $\beta$ -blockade activity. Exposure appeared to be lower in pediatric subjects  
504 than adults. After 8 months of follow-up, there was no significant effect of treatment on clinical  
505 outcomes. Adverse reactions in this trial that occurred in greater than 10% of patients treated  
506 with immediate-release carvedilol and at twice the rate of placebo-treated patients included chest  
507 pain (17% versus 6%), dizziness (13% versus 2%), and dyspnea (11% versus 0%).

## 508 **8.5 Geriatric Use**

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

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

521 The following information is available for trials with immediate-release carvedilol. Of the  
522 765 patients with heart failure randomized to carvedilol in US clinical trials, 31% (235) were  
523 65 years of age or older, and 7.3% (56) were 75 years of age or older. Of the 1,156 patients  
524 randomized to carvedilol in a long-term, placebo-controlled trial in severe heart failure, 47%  
525 (547) were 65 years of age or older, and 15% (174) were 75 years of age or older. Of  
526 3,025 patients receiving carvedilol in heart failure trials worldwide, 42% were 65 years of age or  
527 older. Of the 975 myocardial infarction patients randomized to carvedilol in the CAPRICORN  
528 trial, 48% (468) were 65 years of age or older, and 11% (111) were 75 years of age or older. Of  
529 the 2,065 hypertensive patients in US clinical trials of efficacy or safety who were treated with  
530 carvedilol, 21% (436) were 65 years of age or older. Of 3,722 patients receiving immediate-  
531 release carvedilol in hypertension clinical trials conducted worldwide, 24% were 65 years of age  
532 or older.

533 With the exception of dizziness in hypertensive patients (incidence 8.8% in the elderly  
534 versus 6% in younger patients), no overall differences in the safety or effectiveness (see Figures  
535 2 and 4) were observed between the older subjects and younger subjects in each of these  
536 populations. Similarly, other reported clinical experience has not identified differences in  
537 responses between the elderly and younger subjects, but greater sensitivity of some older  
538 individuals cannot be ruled out.

539 **10 OVERDOSAGE**

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

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

546 *for excessive bradycardia:* atropine, 2 mg IV.

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

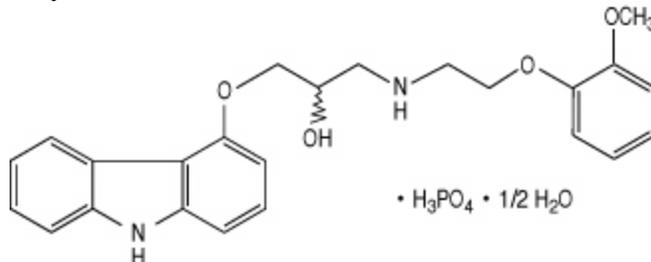
550 If peripheral vasodilation dominates, it may be necessary to administer adrenaline or  
551 noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant  
552 bradycardia, pacemaker therapy should be performed. For bronchospasm,  $\beta$ -sympathomimetics  
553 (as aerosol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

555 NOTE: In the event of severe intoxication where there are symptoms of shock, treatment  
556 with antidotes must be continued for a sufficiently long period of time consistent with the 7- to  
557 10-hour half-life of carvedilol.

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

562 **11 DESCRIPTION**

563 Carvedilol phosphate is a nonselective  $\beta$ -adrenergic blocking agent with  $\alpha_1$ -blocking  
564 activity. It is (2*RS*)-1-(9*H*-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol  
565 phosphate salt (1:1) hemihydrate. It is a racemic mixture with the following structure:



566 Carvedilol phosphate is a white to almost-white solid with a molecular weight of 513.5  
567 (406.5 carvedilol free base) and a molecular formula of  $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_4 \cdot \text{H}_3\text{PO}_4 \cdot \frac{1}{2} \text{H}_2\text{O}$ .

569 COREG CR is available for once-a-day administration as controlled-release oral capsules  
570 containing 10, 20, 40, or 80 mg carvedilol phosphate. COREG CR hard gelatin capsules are  
571 filled with carvedilol phosphate immediate-release and controlled-release microparticles that are  
572 drug-layered and then coated with methacrylic acid copolymers. Inactive ingredients include

573 crospovidone, hydrogenated castor oil, hydrogenated vegetable oil, magnesium stearate,  
574 methacrylic acid copolymers, microcrystalline cellulose, and povidone.

## 575 **12 CLINICAL PHARMACOLOGY**

### 576 **12.1 Mechanism of Action**

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

### 580 **12.2 Pharmacodynamics**

#### 581 Heart Failure and Left Ventricular Dysfunction Following Myocardial Infarction:

582 The basis for the beneficial effects of carvedilol in patients with heart failure and in patients with  
583 left ventricular dysfunction following an acute myocardial infarction is not known. The  
584 concentration-response relationship for  $\beta_1$ -blockade following administration of COREG CR is  
585 equivalent ( $\pm 20\%$ ) to immediate-release carvedilol tablets.

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

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

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

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

602 In a randomized, double-blind, placebo-controlled trial, the  $\beta_1$ -blocking effect of  
603 COREG CR, as measured by heart rate response to submaximal bicycle ergometry, was shown to  
604 be equivalent to that observed with immediate-release carvedilol at steady state in adult patients  
605 with essential hypertension.

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

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

613 **12.3 Pharmacokinetics**

614 Absorption: Carvedilol is rapidly and extensively absorbed following oral administration  
615 of immediate-release carvedilol tablets, with an absolute bioavailability of approximately 25% to  
616 35% due to a significant degree of first-pass metabolism. COREG CR extended-release capsules  
617 have approximately 85% of the bioavailability of immediate-release carvedilol tablets. For  
618 corresponding dosages [*see Dosage and Administration (2)*], the exposure (AUC, C<sub>max</sub>, trough  
619 concentration) of carvedilol as COREG CR extended-release capsules is equivalent to those of  
620 immediate-release carvedilol tablets when both are administered with food. The absorption of  
621 carvedilol from COREG CR is slower and more prolonged compared to the immediate-release  
622 carvedilol tablet with peak concentrations achieved approximately 5 hours after administration.  
623 Plasma concentrations of carvedilol increase in a dose-proportional manner over the dosage  
624 range of COREG CR 10 to 80 mg. Within-subject and between-subject variability for AUC and  
625 C<sub>max</sub> is similar for COREG CR and immediate-release carvedilol.

626 Effect of Food: Administration of COREG CR with a high-fat meal resulted in  
627 increases (~20%) in AUC and C<sub>max</sub> compared to COREG CR administered with a standard meal.  
628 Decreases in AUC (27%) and C<sub>max</sub> (43%) were observed when COREG CR was administered in  
629 the fasted state compared to administration after a standard meal. COREG CR should be taken  
630 with food.

631 In a study with adult subjects, sprinkling the contents of the COREG CR capsule on  
632 applesauce did not appear to have a significant effect on overall exposure (AUC) compared to  
633 administration of the intact capsule following a standard meal but did result in a decrease in C<sub>max</sub>  
634 (18%).

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

639 Metabolism and Excretion: Carvedilol is extensively metabolized. Following oral  
640 administration of radiolabelled carvedilol to healthy volunteers, carvedilol accounted for only  
641 about 7% of the total radioactivity in plasma as measured by AUC. Less than 2% of the dose was  
642 excreted unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation  
643 and glucuronidation. The oxidative metabolites are further metabolized by conjugation via  
644 glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile  
645 into the feces. Demethylation and hydroxylation at the phenol ring produce 3 active metabolites  
646 with  $\beta$ -receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl metabolite  
647 is approximately 13 times more potent than carvedilol for  $\beta$ -blockade.

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

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

653 administration of COREG CR in healthy subjects. Apparent clearance is 90 L/h and 213 L/h for  
654 R(+)- and S(-)-carvedilol, respectively.

655 The primary P450 enzymes responsible for the metabolism of both R(+) and  
656 S(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent  
657 CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4' - and  
658 5'-hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be  
659 of primary importance in the O-methylation pathway of S(-)-carvedilol.

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

#### 667 **12.4 Specific Populations**

668 Heart Failure: Following administration of immediate-release carvedilol tablets,  
669 steady-state plasma concentrations of carvedilol and its enantiomers increased proportionally  
670 over the dose range in patients with heart failure. Compared to healthy subjects, heart failure  
671 patients had increased mean AUC and  $C_{max}$  values for carvedilol and its enantiomers, with up to  
672 50% to 100% higher values observed in 6 patients with NYHA class IV heart failure. The mean  
673 apparent terminal elimination half-life for carvedilol was similar to that observed in healthy  
674 subjects.

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

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

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

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

689 Renal Impairment: No studies have been performed with COREG CR in patients with  
690 renal impairment. Although carvedilol is metabolized primarily by the liver, plasma  
691 concentrations of carvedilol have been reported to be increased in patients with renal impairment  
692 after dosing with immediate-release carvedilol. Based on mean AUC data, approximately 40% to  
693 50% higher plasma concentrations of carvedilol were observed in hypertensive patients with

694 moderate to severe renal impairment compared to a control group of hypertensive patients with  
695 normal renal function. However, the ranges of AUC values were similar for both groups.  
696 Changes in mean peak plasma levels were less pronounced, approximately 12% to 26% higher in  
697 patients with impaired renal function.

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

## 700 **12.5 Drug-Drug Interactions**

701 Since carvedilol undergoes substantial oxidative metabolism, the metabolism and  
702 pharmacokinetics of carvedilol may be affected by induction or inhibition of cytochrome P450  
703 enzymes.

704 The following drug interaction studies were performed with immediate-release carvedilol  
705 tablets.

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

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

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

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

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

723 Rifampin: In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin  
724 (600 mg daily for 12 days) decreased the AUC and  $C_{max}$  of carvedilol by about 70% [see Drug  
725 Interactions (7.5)].

726 Torsemide: In a study of 12 healthy subjects, combined oral administration of carvedilol  
727 25 mg once daily and torsemide 5 mg once daily for 5 days did not result in any significant  
728 differences in their pharmacokinetics compared with administration of the drugs alone.

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

732 **13 NONCLINICAL TOXICOLOGY**

733 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

745 **14 CLINICAL STUDIES**

746 Support for the use of COREG CR extended-release capsules for the treatment of mild-  
747 to-severe heart failure and for patients with left ventricular dysfunction following myocardial  
748 infarction is based on the equivalence of pharmacokinetic and pharmacodynamic (β<sub>1</sub>-blockade)  
749 parameters between COREG CR and immediate-release carvedilol [*see Clinical Pharmacology*  
750 (*12.2, 12.3*)].

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

753 **14.1 Heart Failure**

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

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

759 Four US multicenter, double-blind, placebo-controlled studies enrolled 1,094 patients  
760 (696 randomized to carvedilol) with NYHA class II-III heart failure and ejection fraction ≤0.35.  
761 The vast majority were on digitalis, diuretics, and an ACE inhibitor at study entry. Patients were  
762 assigned to the studies based upon exercise ability. An Australia-New Zealand double-blind,  
763 placebo-controlled study enrolled 415 patients (half randomized to immediate-release carvedilol)  
764 with less severe heart failure. All protocols excluded patients expected to undergo cardiac  
765 transplantation during the 7.5 to 15 months of double-blind follow-up. All randomized patients  
766 had tolerated a 2-week course on immediate-release carvedilol 6.25 mg twice daily.

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

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

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

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

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

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

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

791 *Mortality:* Death was not a pre-specified end point in any study, but was analyzed in all  
792 studies. Overall, in these 4 US trials, mortality was reduced, nominally significantly so in  
793 2 studies.

794 The COMET Trial: In this double-blind trial, 3,029 patients with NYHA class II-IV  
795 heart failure (left ventricular ejection fraction  $\leq 35\%$ ) were randomized to receive either  
796 carvedilol (target dose: 25 mg twice daily) or immediate-release metoprolol tartrate (target dose:  
797 50 mg twice daily). The mean age of the patients was approximately 62 years, 80% were males,  
798 and the mean left ventricular ejection fraction at baseline was 26%. Approximately 96% of the  
799 patients had NYHA class II or III heart failure. Concomitant treatment included diuretics (99%),  
800 ACE inhibitors (91%), digitalis (59%), aldosterone antagonists (11%), and "statin" lipid-  
801 lowering agents (21%). The mean duration of follow-up was 4.8 years. The mean dose of  
802 carvedilol was 42 mg per day.

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

812

813 **Table 5. Results of COMET**

End point	Carvedilol N = 1,511	Metoprolol N = 1,518	Hazard ratio	(95% CI)
All-cause mortality	34%	40%	0.83	0.74 – 0.93
Mortality + all hospitalization	74%	76%	0.94	0.86 – 1.02
Cardiovascular death	30%	35%	0.80	0.70 – 0.90
Sudden death	14%	17%	0.81	0.68 – 0.97
Death due to circulatory failure	11%	13%	0.83	0.67 – 1.02
Death due to stroke	0.9%	2.5%	0.33	0.18 – 0.62

814  
815 It is not known whether this formulation of metoprolol at any dose or this low dose of  
816 metoprolol in any formulation has any effect on survival or hospitalization in patients with heart  
817 failure. Thus, this trial extends the time over which carvedilol manifests benefits on survival in  
818 heart failure, but it is not evidence that carvedilol improves outcome over the formulation of  
819 metoprolol (TOPROL-XL<sup>®</sup>) with benefits in heart failure.

820 **Severe Heart Failure (COPERNICUS):** In a double-blind study, 2,289 patients with  
821 heart failure at rest or with minimal exertion and left ventricular ejection fraction <25% (mean  
822 20%), despite digitalis (66%), diuretics (99%), and ACE inhibitors (89%) were randomized to  
823 placebo or carvedilol. Carvedilol was titrated from a starting dose of 3.125 mg twice daily to the  
824 maximum tolerated dose or up to 25 mg twice daily over a minimum of 6 weeks. Most subjects  
825 achieved the target dose of 25 mg. The study was conducted in Eastern and Western Europe, the  
826 United States, Israel, and Canada. Similar numbers of subjects per group (about 100) withdrew  
827 during the titration period.

828 The primary end point of the trial was all-cause mortality, but cause-specific mortality  
829 and the risk of death or hospitalization (total, cardiovascular [CV], or heart failure [HF]) were  
830 also examined. The developing trial data were followed by a data monitoring committee, and  
831 mortality analyses were adjusted for these multiple looks. The trial was stopped after a median  
832 follow-up of 10 months because of an observed 35% reduction in mortality (from 19.7% per  
833 patient year on placebo to 12.8% on carvedilol, hazard ratio 0.65, 95% CI 0.52 – 0.81,  
834 p = 0.0014, adjusted) (see Figure 1). The results of COPERNICUS are shown in Table 6.  
835

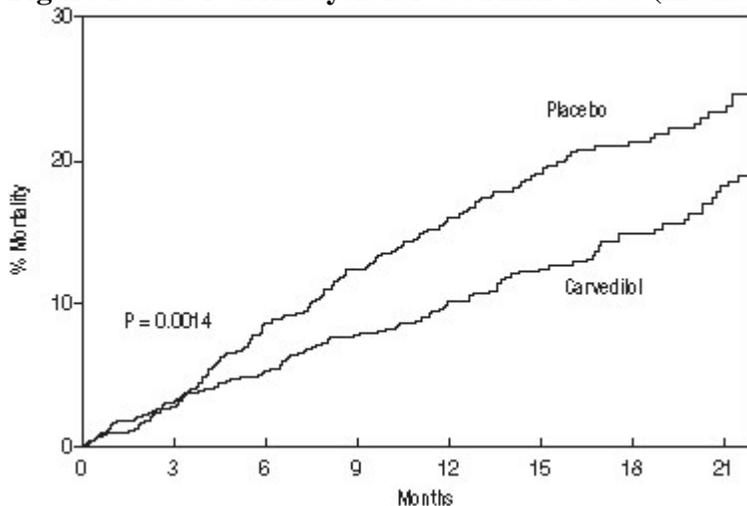
836 **Table 6. Results of COPERNICUS Trial in Patients With Severe Heart Failure**

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

837 Cardiovascular = CV; Heart failure = HF

838

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



840

841

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

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

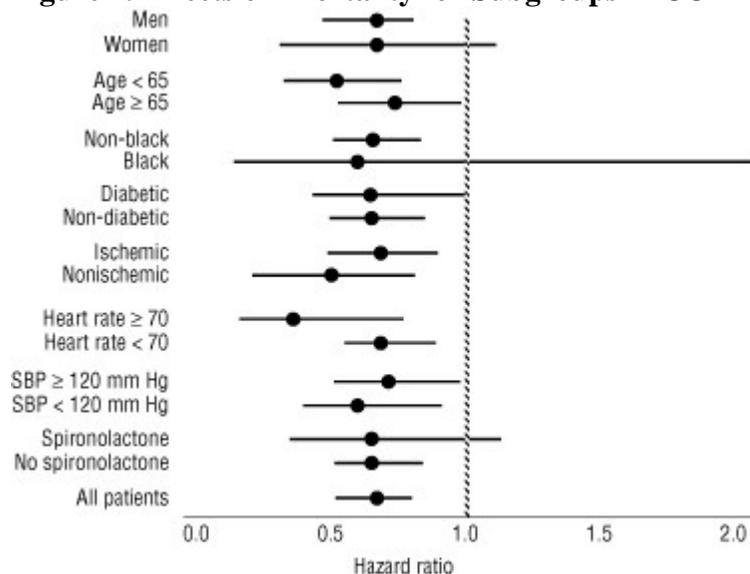
849 The protocol also specified that hospitalizations would be assessed. Fewer patients on  
850 immediate-release carvedilol than on placebo were hospitalized for any reason (372 versus 432,  
851  $p = 0.0029$ ), for cardiovascular reasons (246 versus 314,  $p = 0.0003$ ), or for worsening heart  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

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

856 women, elderly and non-elderly, blacks and non-blacks, and diabetics and non-diabetics (see  
857 Figure 2).

858

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



860

861

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

#### 865 **14.2 Left Ventricular Dysfunction Following Myocardial Infarction**

866 CAPRICORN was a double-blind study comparing carvedilol and placebo in 1,959  
867 patients with a recent myocardial infarction (within 21 days) and left ventricular ejection fraction  
868 of  $\leq 40\%$ , with (47%) or without symptoms of heart failure. Patients given carvedilol received  
869 6.25 mg twice daily, titrated as tolerated to 25 mg twice daily. Patients had to have a systolic  
870 blood pressure  $>90$  mm Hg, a sitting heart rate  $>60$  beats/minute, and no contraindication to  
871  $\beta$ -blocker use. Treatment of the index infarction included aspirin (85%), IV or oral  $\beta$ -blockers  
872 (37%), nitrates (73%), heparin (64%), thrombolytics (40%), and acute angioplasty (12%).  
873 Background treatment included ACE inhibitors or angiotensin receptor blockers (97%),  
874 anticoagulants (20%), lipid-lowering agents (23%), and diuretics (34%). Baseline population  
875 characteristics included an average age of 63 years, 74% male, 95% Caucasian, mean blood  
876 pressure 121/74 mm Hg, 22% with diabetes, and 54% with a history of hypertension. Mean  
877 dosage achieved of carvedilol was 20 mg twice daily; mean duration of follow-up was  
878 15 months.

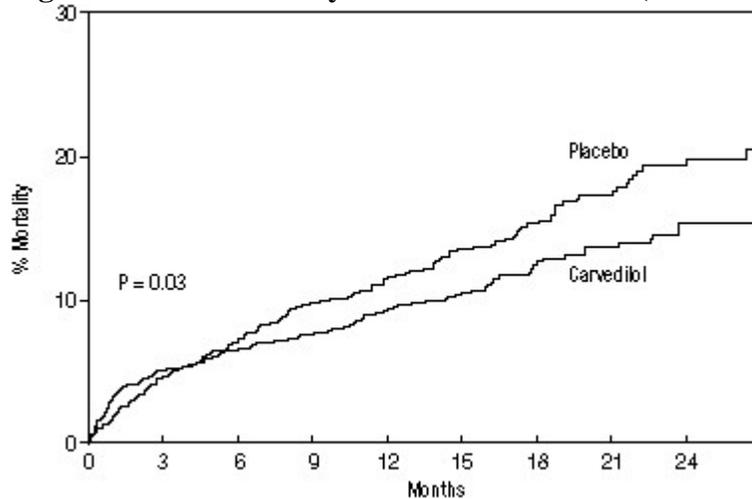
879 All-cause mortality was 15% in the placebo group and 12% in the carvedilol group,  
880 indicating a 23% risk reduction in patients treated with carvedilol (95% CI 2% to 40%,  $p = 0.03$ ),  
881 as shown in Figure 3. The effects on mortality in various subgroups are shown in Figure 4.  
882 Nearly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

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

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

890

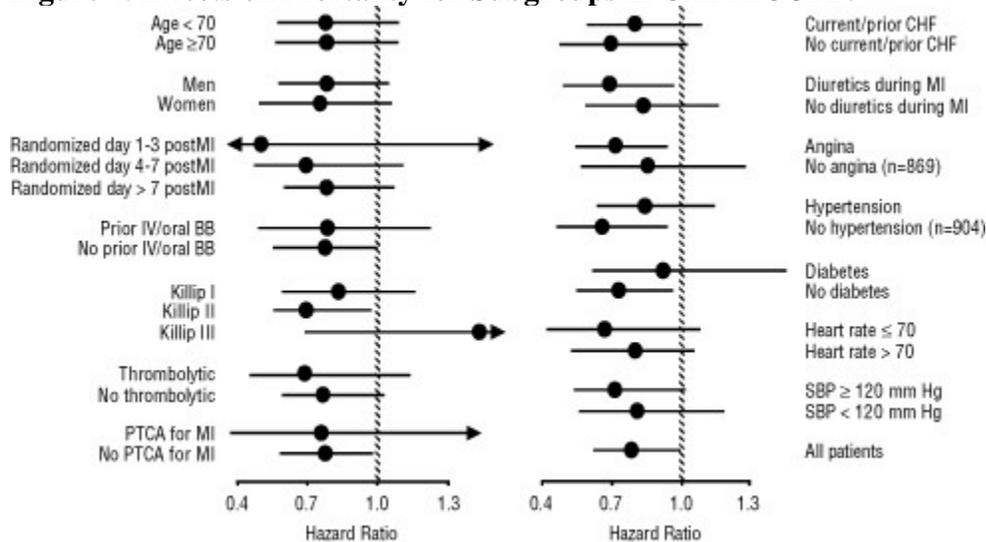
891 **Figure 3. Survival Analysis for CAPRICORN (intent-to-treat)**



892

893

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



895

896

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

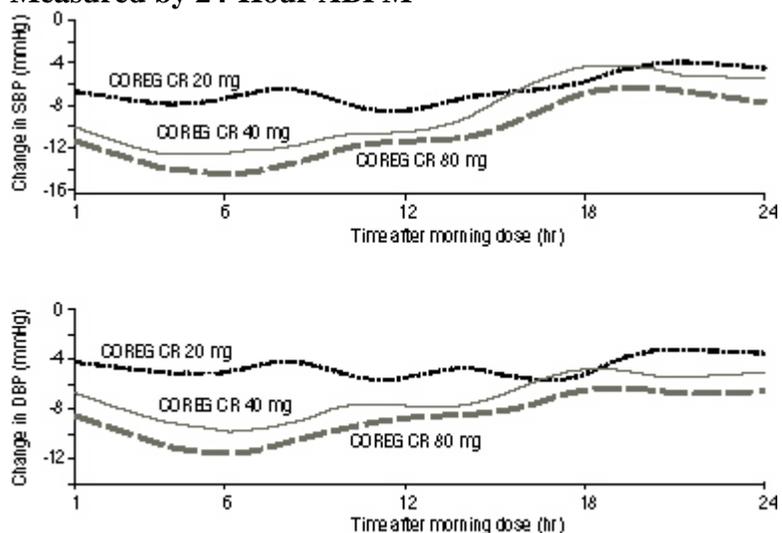
901 **14.3 Hypertension**

902 A double-blind, randomized, placebo-controlled, 8-week trial evaluated the blood  
903 pressure lowering effects of COREG CR 20 mg, 40 mg, and 80 mg once daily in 338 patients  
904 with essential hypertension (sitting diastolic blood pressure [DBP]  $\geq 90$  and  $\leq 109$  mm Hg). Of  
905 337 evaluable patients, a total of 273 patients (81%) completed the study. Of the 64 (19%)  
906 patients withdrawn from the study, 10 (3%) were due to adverse events, 10 (3%) were due to  
907 lack of efficacy; the remaining 44 (13%) withdrew for other reasons. The mean age of the  
908 patients was approximately 53 years, 66% were male, and the mean sitting systolic blood  
909 pressure (SBP) and DBP at baseline were 150 mm Hg and 99 mm Hg, respectively. Dose  
910 titration occurred at 2-week intervals.

911 Statistically significant reductions in blood pressure as measured by 24-hour ambulatory  
912 blood pressure monitoring (ABPM) were observed with each dose of COREG CR compared to  
913 placebo. Placebo-subtracted mean changes from baseline in mean SBP/DBP were  
914 -6.1/-4.0 mm Hg, -9.4/-7.6 mm Hg, and -11.8/-9.2 mm Hg for COREG CR 20 mg, 40 mg, and  
915 80 mg, respectively. Placebo-subtracted mean changes from baseline in mean trough (average of  
916 hours 20-24) SBP/DBP were -3.3/-2.8 mm Hg, -4.9/-5.2 mm Hg, and -8.4/-7.4 mm Hg for  
917 COREG CR 20 mg, 40 mg, and 80 mg, respectively. The placebo-corrected trough to peak  
918 (3-7 hr) ratio was approximately 0.6 for COREG CR 80 mg. In this study, assessments of  
919 24-hour ABPM monitoring demonstrated statistically significant blood pressure reductions with  
920 COREG CR throughout the dosing period (Figure 5).

921

922 **Figure 5. Changes from Baseline in Systolic Blood Pressure and Diastolic Blood Pressure**  
923 **Measured by 24-Hour ABPM**



924

925

926

927

928

Lines smoothed using locally weighted regression smoothing methodology.

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

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

#### 935 **14.4 Hypertension With Type 2 Diabetes Mellitus**

936 In a double-blind study (GEMINI), carvedilol, added to an ACE inhibitor or angiotensin  
937 receptor blocker, was evaluated in a population with mild-to-moderate hypertension and well-  
938 controlled type 2 diabetes mellitus. The mean HbA1c at baseline was 7.2%. COREG was titrated  
939 to a mean dose of 17.5 mg twice daily and maintained for 5 months. COREG had no adverse  
940 effect on glycemic control, based on HbA1c measurements (mean change from baseline of  
941 0.02%, 95% CI -0.06 to 0.10, p = NS) [see *Warnings and Precautions (5.6)*].

## 942 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

- 944 • 10 mg – white and green capsule shell printed with GSK COREG CR and 10 mg
- 945 • 20 mg – white and yellow capsule shell printed with GSK COREG CR and 20 mg
- 946 • 40 mg – yellow and green capsule shell printed with GSK COREG CR and 40 mg
- 947 • 80 mg – white capsule shell printed with GSK COREG CR and 80 mg
- 948
- 949 • 10 mg 30's: NDC 0007-3370-13
- 950 • 10 mg 90's: NDC 0007-3370-59
- 951 • 20 mg 30's: NDC 0007-3371-13
- 952 • 20 mg 90's: NDC 0007-3371-59
- 953 • 40 mg 30's: NDC 0007-3372-13
- 954 • 40 mg 90's: NDC 0007-3372-59
- 955 • 80 mg 30's: NDC 0007-3373-13
- 956 • 80 mg 90's: NDC 0007-3373-59

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

## 959 **17 PATIENT COUNSELING INFORMATION**

960 See FDA-Approved Patient Labeling (17.2).

### 961 **17.1 Patient Advice**

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

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

- 966 • Patients may experience a drop in blood pressure when standing, resulting in dizziness and,  
967 rarely, fainting. Patients should sit or lie down when these symptoms of lowered blood  
968 pressure occur.
- 969 • If experiencing dizziness or fatigue, patients should avoid driving or hazardous tasks.
- 970 • Patients should consult a physician if they experience dizziness or faintness, in case the  
971 dosage should be adjusted.
- 972 • Patients should not crush or chew COREG CR capsules.
- 973 • Patients should take COREG CR with food.
- 974 • Diabetic patients should report any changes in blood sugar levels to their physician.
- 975 • Contact lens wearers may experience decreased lacrimation.

976 **17.2 FDA-Approved Patient Labeling**

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

979

980 COREG CR and COREG are registered trademarks of GlaxoSmithKline.

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

982



983

984 GlaxoSmithKline

985 Research Triangle Park, NC 27709

986 ©Year, GlaxoSmithKline. All rights reserved.

987

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

989 -----  
990 **PATIENT INFORMATION LEAFLET**

991 **COREG CR<sup>®</sup> (Co-REG)**

992 **(carvedilol phosphate) Extended-release Capsules**

993  
994 Read the Patient Information that comes with COREG CR before you start taking it and each  
995 time you get a refill. There may be new information. This information does not take the place of  
996 talking with your doctor about your medical condition or your treatment. If you have any  
997 questions about COREG CR, ask your doctor or pharmacist.

998  
999 **What is the most important information I should know about COREG CR?**

1000 **It is important for you to take your medicine every day as directed by your doctor. If you**  
1001 **stop taking COREG CR suddenly, you could have chest pain and a heart attack. If your**  
1002 **doctor decides that you should stop taking COREG CR, your doctor may slowly lower**  
1003 **your dose over time before stopping it completely.**

1004  
1005 **What is COREG CR?**

1006 COREG CR is a prescription medicine that belongs to a group of medicines called “beta-  
1007 blockers”. COREG CR is used, often with other medicines, for the following conditions:

- 1008 • to treat patients with high blood pressure (hypertension)  
1009 • to treat patients who had a heart attack that worsened how well the heart pumps  
1010 • to treat patients with certain types of heart failure

1011  
1012 COREG CR is not approved for use in children under 18 years of age.

1013  
1014 **Who should not take COREG CR?**

1015 Do not take COREG CR if you:

- 1016 • have severe heart failure and require certain intravenous medicines that help support  
1017 circulation.  
1018 • have asthma or other breathing problems.  
1019 • have a slow heartbeat or certain conditions that cause your heart to skip a beat (irregular  
1020 heartbeat).  
1021 • have liver problems.  
1022 • are allergic to any of the ingredients in COREG CR. *See “What are the ingredients in*  
1023 *COREG CR?”*

1024  
1025 **What should I tell my doctor before taking COREG CR?**

1026 Tell your doctor about all of your medical conditions, including if you:

- 1027 • have asthma or other lung problems (such as bronchitis or emphysema).

- 1028 • have problems with blood flow in your feet and legs (peripheral vascular disease).
- 1029 COREG CR can make some of your symptoms worse.
- 1030 • have diabetes.
- 1031 • have thyroid problems.
- 1032 • have a condition called pheochromocytoma.
- 1033 • have had severe allergic reactions.
- 1034 • are scheduled for surgery and will be given anesthetic agents.
- 1035 • are pregnant or trying to become pregnant. It is not known if COREG CR is safe for your
- 1036 unborn baby. You and your doctor should talk about the best way to control your high blood
- 1037 pressure during pregnancy.
- 1038 • are breastfeeding. It is not known if COREG CR passes into your breast milk. You should
- 1039 not breastfeed while using COREG CR.

1040

1041 **Tell your doctor about all of the medicines you take** including prescription and non-  
1042 prescription medicines, vitamins, and herbal supplements. COREG CR and certain other  
1043 medicines can affect each other and cause serious side effects. COREG CR may affect the way  
1044 other medicines work. Also, other medicines may affect how well COREG CR works.

1045

1046 Know the medicines you take. Keep a list of your medicines and show it to your doctor and  
1047 pharmacist before you start a new medicine.

1048

#### 1049 **How should I take COREG CR?**

- 1050 • Take COREG CR exactly as prescribed. Take COREG CR **one** time each day with food. **It is**  
1051 **important that you take COREG CR only one time each day.** To lessen possible side  
1052 effects, your doctor might begin with a low dose and then slowly increase the dose.
- 1053 • Swallow COREG CR capsules whole. Do not chew or crush COREG CR capsules.
- 1054 • If you have trouble swallowing COREG CR whole:
  - 1055 • The capsule may be carefully opened and the beads sprinkled over a spoonful of
  - 1056 applesauce which should be eaten right away. The applesauce should not be warm.
  - 1057 • Do not sprinkle beads on foods other than applesauce.
- 1058 • **Do not stop taking COREG CR and do not change the amount of COREG CR you take**  
1059 **without talking to your doctor.**
- 1060 • If you miss a dose of COREG CR, take your dose as soon as you remember, unless it is time  
1061 to take your next dose. Take your next dose at the usual time. Do not take 2 doses at the same  
1062 time.
- 1063 • If you take too much COREG CR, call your doctor or poison control center right away.

1064

#### 1065 **What should I avoid while taking COREG CR?**

1066 COREG CR can cause you to feel dizzy, tired, or faint. Do not drive a car, use machinery, or do  
1067 anything that needs you to be alert if you have these symptoms.

1068

1069 **What are possible side effects of COREG CR?**

1070 Serious side effects of COREG CR include:

- 1071 • **chest pain and heart attack if you suddenly stop taking COREG CR.** See “What is the  
1072 *most important information I should know about COREG CR?*”
- 1073 • **slow heart beat.**
- 1074 • **low blood pressure (which may cause dizziness or fainting when you stand up).** If these  
1075 happen, sit or lie down, and tell your doctor right away.
- 1076 • **worsening heart failure.** Tell your doctor right away if you have signs and symptoms that  
1077 your heart failure may be worse, such as weight gain or increased shortness of breath.
- 1078 • **changes in your blood sugar. If you have diabetes, tell your doctor if you have any**  
1079 **changes in your blood sugar levels.**
- 1080 • masking (hiding) the symptoms of low blood sugar, especially a fast heartbeat.
- 1081 • **new or worsening symptoms of peripheral vascular disease.**
- 1082 • leg pain that happens when you walk, but goes away when you rest
- 1083 • no feeling (numbness) in your legs or feet while you are resting
- 1084 • cold legs or feet
- 1085 • masking the symptoms of hyperthyroidism (overactive thyroid), such as a fast heartbeat.
- 1086 • **worsening of severe allergic reactions.** Medicines to treat a severe allergic reaction may not  
1087 work as well while you are taking COREG CR.
- 1088 • **rare but serious allergic reactions** (including hives or swelling of the face, lips, tongue,  
1089 and/or throat that may cause difficulty in breathing or swallowing) have happened in patients  
1090 who were on COREG or COREG CR. These reactions can be life-threatening. In some cases,  
1091 these reactions happened in patients who had been on COREG before taking COREG CR.

1092

1093 Common side effects of COREG CR include shortness of breath, weight gain, diarrhea, and  
1094 tiredness. If you wear contact lenses, you may have fewer tears or dry eyes that can become  
1095 bothersome.

1096

1097 Call your doctor if you have any side effects that bother you or don't go away.

1098

1099 **How should I store COREG CR?**

1100 Store COREG CR at less than 86°F (30°C).

1101 Safely throw away COREG CR that is out of date or no longer needed.

1102 **Keep COREG CR and all medicines out of the reach of children.**

1103

1104 **General information about COREG CR**

1105 Medicines are sometimes prescribed for conditions other than those described in patient  
1106 information leaflets. Do not use COREG CR for a condition for which it was not prescribed. Do  
1107 not give COREG CR to other people, even if they have the same symptoms you have. It may  
1108 harm them.

1109

1110 This leaflet summarizes the most important information about COREG CR. If you would like  
1111 more information, talk with your doctor. You can ask your doctor or pharmacist for information  
1112 about COREG CR that is written for healthcare professionals. You can also find out more about  
1113 COREG CR by visiting the website [www.COREGCR.com](http://www.COREGCR.com) or calling 1-888-825-5249. This call  
1114 is free.

1115

1116 **What are the ingredients in COREG CR?**

1117 Active ingredient: carvedilol phosphate

1118 Inactive ingredients: crospovidone, hydrogenated castor oil, hydrogenated vegetable oil,  
1119 magnesium stearate, methacrylic acid copolymers, microcrystalline cellulose, and povidone

1120 COREG CR capsules come in the following strengths: 10 mg, 20 mg, 40 mg, 80 mg.

1121

1122 COREG CR and COREG are registered trademarks of GlaxoSmithKline.

1123



1124

1125 GlaxoSmithKline

1126 Research Triangle Park, NC 27709

1127 ©Year, GlaxoSmithKline. All rights reserved.

1128

1129 Month Year

1130 CCR:XPIL