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 --------------------
Warnings and Precautions, Intraoperative Floppy Iris   Month Year
Syndrome (5.14)

----------------------------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. (2.5)

-------------------- 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 carvedilol or any of the components of COREG CR. (4)

---------------------- WARNINGS AND PRECAUTIONS ----------------
- Acute exacerbation of coronary artery disease upon cessation of therapy: Do not abruptly discontinue. (5.1)
- Bradycardia, hypotension, worsening heart failure/fluid retention may occur. Reduce the dose as needed. (5.2, 5.3, 5.4)
- Non-allergic bronchospasm (e.g., chronic bronchitis and emphysema): Avoid β-blockers. (4) However, if deemed necessary, use with caution and at lowest effective dose. (5.5)
- Diabetes: Monitor glucose as β-blockers may mask symptoms of hypoglycemia or worsen hyperglycemia. (5.6)

------------------------------ ADVERSE REACTIONS -----------------------
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 (≥10%): Dizziness, fatigue, hypotension, diarrhea, hyperglycemia, asthenia, bradycardia, weight increase
- Hypertension (≥5%): Dizziness

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-------------------------------DRUG INTERACTIONS-----------------------
- CYP P450 2D6 enzyme inhibitors may increase and rifampin may decrease carvedilol levels. (7.1, 7.5)
- Hypotensive agents (e.g., reserpine, MAO inhibitors, clonidine) may increase the risk of hypotension and/or severe bradycardia. (7.2)
- Cyclosporine or digoxin levels may increase. (7.3, 7.4)
- Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. (7.4)
- Amiodarone may increase carvedilol levels resulting in further slowing of the heart rate or cardiac conduction. (7.6)
- Verapamil- or diltiazem-type calcium channel blockers may affect ECG and/or blood pressure. (7.7)
- Insulin and oral hypoglycemics action may be enhanced. (7.8)

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

Revised: Month Year

1

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

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 ≤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   <u>Alternative Administration:</u> 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 β-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 (25 mg twice daily) to COREG CR, a lower
84 starting dose (40 mg) of COREG CR is recommended 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 carvedilol or any of the components of
108 COREG CR.

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 reinstituted, 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 β-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 β-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, β-blockers may mask some of the manifestations of hypoglycemia,
193   particularly tachycardia. Nonselective β-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   β-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   β-adrenergic blockade may mask clinical signs of hyperthyroidism, such as tachycardia.
224   Abrupt withdrawal of β-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 α-blocking agent should be initiated prior to the
228 use of any β-blocking agent. Although carvedilol has both α- and β-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 β-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 α-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 β-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 **5.14 Intraoperative Floppy Iris Syndrome**

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

252 **6 ADVERSE REACTIONS**

253 **6.1 Clinical Trials Experience**

254 Carvedilol has been evaluated for safety in patients with heart failure (mild, moderate,
255 and severe), in patients with left ventricular dysfunction following myocardial infarction, and in
256 hypertensive patients. The observed adverse event profile was consistent with the pharmacology
257 of the drug and the health status of the patients in the clinical trials. Adverse events reported for
258 each of these patient populations reflecting the use of either COREG CR or immediate-release
259 carvedilol are provided below. Excluded are adverse events considered too general to be
260 informative, and those not reasonably associated with the use of the drug because they were
261 associated with the condition being treated or are very common in the treated population. Rates
262 of adverse events were generally similar across demographic subsets (men and women, elderly
263 and non-elderly, blacks and non-blacks). COREG CR has been evaluated for safety in a 4-week
264 (2 weeks of immediate-release carvedilol and 2 weeks of COREG CR) clinical study (n = 187)
265 which included 157 patients with stable mild, moderate, or severe chronic heart failure and 30

266   patients with left ventricular dysfunction following acute myocardial infarction. The profile of
267   adverse events observed with COREG CR in this small, short-term study was generally similar
268   to that observed with immediate-release carvedilol. Differences in safety would not be expected
269   based on the similarity in plasma levels for COREG CR and immediate-release carvedilol.
270   <u>Heart Failure:</u> The following information describes the safety experience in heart failure
271   with immediate-release carvedilol.
272   Carvedilol has been evaluated for safety in heart failure in more than 4,500 patients
273   worldwide of whom more than 2,100 participated in placebo-controlled clinical trials.
274   Approximately 60% of the total treated population in placebo-controlled clinical trials received
275   carvedilol for at least 6 months and 30% received carvedilol for at least 12 months. In the
276   COMET trial, 1,511 patients with mild-to-moderate heart failure were treated with carvedilol for
277   up to 5.9 years (mean 4.8 years). Both in US clinical trials in mild-to-moderate heart failure that
278   compared carvedilol in daily doses up to 100 mg (n = 765) to placebo (n = 437), and in a
279   multinational clinical trial in severe heart failure (COPERNICUS) that compared carvedilol in
280   daily doses up to 50 mg (n = 1,156) with placebo (n = 1,133), discontinuation rates for adverse
281   experiences were similar in carvedilol and placebo patients. In placebo-controlled clinical trials,
282   the only cause of discontinuation >1%, and occurring more often on carvedilol was dizziness
283   (1.3% on carvedilol, 0.6% on placebo in the COPERNICUS trial).
284   Table 2 shows adverse events reported in patients with mild-to-moderate heart failure
285   enrolled in US placebo-controlled clinical trials, and with severe heart failure enrolled in the
286   COPERNICUS trial. Shown are adverse events that occurred more frequently in drug-treated
287   patients than placebo-treated patients with an incidence of >3% in patients treated with
288   carvedilol regardless of causality. Median study medication exposure was 6.3 months for both
289   carvedilol and placebo patients in the trials of mild-to-moderate heart failure, and 10.4 months in
290   the trial of severe heart failure patients. The adverse event profile of carvedilol observed in the
291   long-term COMET study was generally similar to that observed in the US Heart Failure Trials.
292

293 **Table 2. Adverse Events (%) Occurring More Frequently With Immediate-Release**
294 **Carvedilol Than With Placebo in Patients With Mild-to-Moderate Heart Failure (HF)**
295 **Enrolled in US Heart Failure Trials or in Patients With Severe Heart Failure in the**
296 **COPERNICUS Trial (Incidence >3% in Patients Treated With Carvedilol, Regardless of**
297 **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	—	—

298

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

301   The following adverse events were reported with a frequency of >1% but ≤3% and more
302 frequently with carvedilol in either the US placebo-controlled trials in patients with
303 mild-to-moderate heart failure, or in patients with severe heart failure in the COPERNICUS trial.
304   **Incidence >1% to ≤3%**
305   *Body as a Whole:* Allergy, malaise, hypovolemia, fever, leg edema.
306   *Cardiovascular:* Fluid overload, postural hypotension, aggravated angina pectoris, AV
307 block, palpitation, hypertension.
308   *Central and Peripheral Nervous System:* Hypesthesia, vertigo, paresthesia.
309   *Gastrointestinal:* Melena, periodontitis.
310   *Liver and Biliary System:* SGPT increased, SGOT increased.
311   *Metabolic and Nutritional:* Hyperuricemia, hypoglycemia, hyponatremia, increased
312 alkaline phosphatase, glycosuria, hypervolemia, diabetes mellitus, GGT increased, weight loss,
313 hyperkalemia, creatinine increased.
314   *Musculoskeletal:* Muscle cramps.
315   *Platelet, Bleeding and Clotting:* Prothrombin decreased, purpura, thrombocytopenia.
316   *Psychiatric:* Somnolence.
317   *Reproductive, male:* Impotence.
318   *Special Senses:* Blurred vision.
319   *Urinary System:* Renal insufficiency, albuminuria, hematuria.
320   <u>Left Ventricular Dysfunction Following Myocardial Infarction:</u> The following
321 information describes the safety experience in left ventricular dysfunction following acute
322 myocardial infarction with immediate-release carvedilol.
323   Carvedilol has been evaluated for safety in survivors of an acute myocardial infarction
324 with left ventricular dysfunction in the CAPRICORN trial which involved 969 patients who
325 received carvedilol and 980 who received placebo. Approximately 75% of the patients received
326 carvedilol for at least 6 months and 53% received carvedilol for at least 12 months. Patients were
327 treated for an average of 12.9 months and 12.8 months with carvedilol and placebo, respectively.
328   The most common adverse events reported with carvedilol in the CAPRICORN trial were
329 consistent with the profile of the drug in the US heart failure trials and the COPERNICUS trial.
330 The only additional adverse events reported in CAPRICORN in >3% of the patients and more
331 commonly on carvedilol were dyspnea, anemia, and lung edema. The following adverse events
332 were reported with a frequency of >1% but ≤3% and more frequently with carvedilol: Flu
333 syndrome, cerebrovascular accident, peripheral vascular disorder, hypotonia, depression,
334 gastrointestinal pain, arthritis, and gout. The overall rates of discontinuations due to adverse
335 events were similar in both groups of patients. In this database, the only cause of discontinuation
336 >1%, and occurring more often on carvedilol was hypotension (1.5% on carvedilol, 0.2% on
337 placebo).
338   <u>Hypertension:</u> COREG CR was evaluated for safety in an 8-week double-blind trial in
339 337 subjects with essential hypertension. The profile of adverse events observed with
340 COREG CR was generally similar to that observed with immediate-release carvedilol. The

341 overall rates of discontinuations due to adverse events were similar between COREG CR and
342 placebo.
343
344 **Table 3. Adverse Events (%) Occurring More Frequently With COREG CR Than With**
345 **Placebo in Patients With Hypertension (Incidence ≥1% in Patients Treated With**
346 **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

347
348　　　　The following information describes the safety experience in hypertension with
349 immediate-release carvedilol.
350　　　　Carvedilol has been evaluated for safety in hypertension in more than 2,193 patients in
351 US clinical trials and in 2,976 patients in international clinical trials. Approximately 36% of the
352 total treated population received carvedilol for at least 6 months. In general, carvedilol was well
353 tolerated at doses up to 50 mg daily. Most adverse events reported during carvedilol therapy
354 were of mild to moderate severity. In US controlled clinical trials directly comparing carvedilol
355 monotherapy in doses up to 50 mg (n = 1,142) to placebo (n = 462), 4.9% of carvedilol patients
356 discontinued for adverse events versus 5.2% of placebo patients. Although there was no overall
357 difference in discontinuation rates, discontinuations were more common in the carvedilol group
358 for postural hypotension (1% versus 0). The overall incidence of adverse events in US
359 placebo-controlled trials was found to increase with increasing dose of carvedilol. For individual
360 adverse events this could only be distinguished for dizziness, which increased in frequency from
361 2% to 5% as total daily dose increased from 6.25 mg to 50 mg as single or divided doses.
362　　　　Table 4 shows adverse events in US placebo-controlled clinical trials for hypertension
363 that occurred with an incidence of ≥1% regardless of causality, and that were more frequent in
364 drug-treated patients than placebo-treated patients.
365

Table 4. Adverse Events (% Occurrence) in US Placebo-Controlled Hypertension Trials With Immediate-Release Carvedilol (Incidence ≥1% in Patients Treated With Carvedilol, 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 ≤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.

392   *Hematologic:* Anemia, leukopenia.

393   The following events were reported in ≤0.1% of patients and are potentially important:

394 Complete AV block, bundle branch block, myocardial ischemia, cerebrovascular disorder,

395 convulsions, migraine, neuralgia, paresis, anaphylactoid reaction, alopecia, exfoliative

396 dermatitis, amnesia, GI hemorrhage, bronchospasm, pulmonary edema, decreased hearing,

397 respiratory alkalosis, increased BUN, decreased HDL, pancytopenia, and atypical lymphocytes.

398 **6.2   Laboratory Abnormalities**

399   Reversible elevations in serum transaminases (ALT or AST) have been observed during

400 treatment with carvedilol. Rates of transaminase elevations (2- to 3-times the upper limit of

401 normal) observed during controlled clinical trials have generally been similar between patients

402 treated with carvedilol and those treated with placebo. However, transaminase elevations,

403 confirmed by rechallenge, have been observed with carvedilol. In a long-term, placebo-

404 controlled trial in severe heart failure, patients treated with carvedilol had lower values for

405 hepatic transaminases than patients treated with placebo, possibly because carvedilol-induced

406 improvements in cardiac function led to less hepatic congestion and/or improved hepatic blood

407 flow.

408   Carvedilol therapy has not been associated with clinically significant changes in serum

409 potassium, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen,

410 or creatinine. No clinically relevant changes were noted in fasting serum glucose in hypertensive

411 patients; fasting serum glucose was not evaluated in the heart failure clinical trials.

412 **6.3   Postmarketing Experience**

413   The following adverse reactions have been identified during post-approval use of

414 COREG® or COREG CR. Because these reactions are reported voluntarily from a population of

415 uncertain size, it is not always possible to reliably estimate their frequency or establish a causal

416 relationship to drug exposure.

417   Reports of aplastic anemia and severe skin reactions (Stevens-Johnson syndrome, toxic

418 epidermal necrolysis, and erythema multiforme) have been rare and received only when

419 carvedilol was administered concomitantly with other medications associated with such

420 reactions. Rare reports of hypersensitivity reactions (e.g., anaphylactic reaction, angioedema, and

421 urticaria) have been received for COREG and COREG CR, including cases occurring after the

422 initiation of COREG CR in patients previously treated with COREG. Urinary incontinence in

423 women (which resolved upon discontinuation of the medication) and interstitial pneumonitis

424 have been reported rarely.

425 **7   DRUG INTERACTIONS**

426 **7.1   CYP2D6 Inhibitors and Poor Metabolizers**

427   Interactions of carvedilol with potent inhibitors of CYP2D6 isoenzyme (such as

428 quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would

429 be expected to increase blood levels of the R(+) enantiomer of carvedilol *[see Clinical*

430 *Pharmacology (12.3)].* Retrospective analysis of side effects in clinical trials showed that poor

431   2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from

432   vasodilating effects of the higher concentrations of the α-blocking R(+) enantiomer.

433   **7.2   Hypotensive Agents**

434   Patients taking both agents with β-blocking properties and a drug that can deplete

435   catecholamines (e.g., reserpine and monoamine oxidase inhibitors) should be observed closely

436   for signs of hypotension and/or severe bradycardia.

437   Concomitant administration of clonidine with agents with β-blocking properties may

438   potentiate blood-pressure- and heart-rate-lowering effects. When concomitant treatment with

439   agents with β-blocking properties and clonidine is to be terminated, the β-blocking agent should

440   be discontinued first. Clonidine therapy can then be discontinued several days later by gradually

441   decreasing the dosage.

442   **7.3   Cyclosporine**

443   Modest increases in mean trough cyclosporine concentrations were observed following

444   initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular

445   rejection. In about 30% of patients, the dose of cyclosporine had to be reduced in order to

446   maintain cyclosporine concentrations within the therapeutic range, while in the remainder no

447   adjustment was needed. On the average for the group, the dose of cyclosporine was reduced

448   about 20% in these patients. Due to wide interindividual variability in the dose adjustment

449   required, it is recommended that cyclosporine concentrations be monitored closely after initiation

450   of carvedilol therapy and that the dose of cyclosporine be adjusted as appropriate.

451   **7.4   Digitalis Glycosides**

452   Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease

453   heart rate. Concomitant use can increase the risk of bradycardia. Digoxin concentrations are

454   increased by about 15% when digoxin and carvedilol are administered concomitantly. Therefore,

455   increased monitoring of digoxin is recommended when initiating, adjusting, or discontinuing

456   COREG CR *[see Clinical Pharmacology (12.5)]*.

457   **7.5   Inducers/Inhibitors of Hepatic Metabolism**

458   Rifampin reduced plasma concentrations of carvedilol by about 70% *[see Clinical*

459   *Pharmacology (12.5)]*. Cimetidine increased area under the curve (AUC) by about 30% but

460   caused no change in C_{max} *[see Clinical Pharmacology (12.5)]*.

461   **7.6   Amiodarone**

462   Amiodarone, and its metabolite desethyl amiodarone, inhibitors of CYP2C9 and P-

463   glycoprotein, increased concentrations of the S(-) enantiomer of carvedilol by at least 2-fold *[see*

464   *Clinical Pharmacology (12.5)]*. The concomitant administration of amiodarone or other CYP2C9

465   inhibitors such as fluconazole with COREG CR may enhance the β-blocking properties of

466   carvedilol resulting in further slowing of the heart rate or cardiac conduction. Patients should be

467   observed for signs of bradycardia or heart block, particularly when one agent is added to pre-

468   existing treatment with the other.

469   **7.7   Calcium Channel Blockers**

470   Conduction disturbance (rarely with hemodynamic compromise) has been observed when

471   carvedilol is co-administered with diltiazem. As with other agents with β-blocking properties, if

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

474 **7.8   Insulin or Oral Hypoglycemics**

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

478 **7.9   Proton Pump Inhibitors**

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

481 **8   USE IN SPECIFIC POPULATIONS**

482 **8.1   Pregnancy**

483   Pregnancy Category C. Studies performed in pregnant rats and rabbits given carvedilol
484 revealed increased post-implantation loss in rats at doses of 300 mg/kg/day (50 times the
485 maximum recommended human dose [MRHD] as mg/m^2) and in rabbits at doses of
486 75 mg/kg/day (25 times the MRHD as mg/m^2). In the rats, there was also a decrease in fetal body
487 weight at the maternally toxic dose of 300 mg/kg/day (50 times the MRHD as mg/m^2), which
488 was accompanied by an elevation in the frequency of fetuses with delayed skeletal development
489 (missing or stunted 13th rib). In rats the no-observed-effect level for developmental toxicity was
490 60 mg/kg/day (10 times the MRHD as mg/m^2); in rabbits it was 15 mg/kg/day (5 times the
491 MRHD as mg/m^2). There are no adequate and well-controlled studies in pregnant women.
492 COREG CR should be used during pregnancy only if the potential benefit justifies the potential
493 risk to the fetus.

494 **8.3   Nursing Mothers**

495   It is not known whether this drug is excreted in human milk. Studies in rats have shown
496 that carvedilol and/or its metabolites (as well as other β-blockers) cross the placental barrier and
497 are excreted in breast milk. There was increased mortality at one week post partum in neonates
498 from rats treated with 60 mg/kg/day (10 times the MRHD as mg/m^2) and above during the last
499 trimester through day 22 of lactation. Because many drugs are excreted in human milk and
500 because of the potential for serious adverse reactions in nursing infants from β-blockers,
501 especially bradycardia, a decision should be made whether to discontinue nursing or to
502 discontinue the drug, taking into account the importance of the drug to the mother. The effects of
503 other α- and β-blocking agents have included perinatal and neonatal distress.

504 **8.4   Pediatric Use**

505   Effectiveness of carvedilol in patients younger than 18 years of age has not been
506 established.
507   In a double-blind trial, 161 children (mean age 6 years, range 2 months to 17 years; 45%
508 younger than 2 years old) with chronic heart failure [NYHA class II-IV, left ventricular ejection
509 fraction <40% for children with a systemic left ventricle (LV), and moderate-severe ventricular
510 dysfunction qualitatively by echo for those with a systemic ventricle that was not an LV] who
511 were receiving standard background treatment were randomized to placebo or to 2 dose levels of

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

518   **8.5   Geriatric Use**

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

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

531   The following information is available for trials with immediate-release carvedilol. Of the
532   765 patients with heart failure randomized to carvedilol in US clinical trials, 31% (235) were
533   65 years of age or older, and 7.3% (56) were 75 years of age or older. Of the 1,156 patients
534   randomized to carvedilol in a long-term, placebo-controlled trial in severe heart failure, 47%
535   (547) were 65 years of age or older, and 15% (174) were 75 years of age or older. Of
536   3,025 patients receiving carvedilol in heart failure trials worldwide, 42% were 65 years of age or
537   older. Of the 975 myocardial infarction patients randomized to carvedilol in the CAPRICORN
538   trial, 48% (468) were 65 years of age or older, and 11% (111) were 75 years of age or older. Of
539   the 2,065 hypertensive patients in US clinical trials of efficacy or safety who were treated with
540   carvedilol, 21% (436) were 65 years of age or older. Of 3,722 patients receiving immediate-
541   release carvedilol in hypertension clinical trials conducted worldwide, 24% were 65 years of age
542   or older.

543   With the exception of dizziness in hypertensive patients (incidence 8.8% in the elderly
544   versus 6% in younger patients), no overall differences in the safety or effectiveness (see Figures
545   2 and 4) were observed between the older subjects and younger subjects in each of these
546   populations. Similarly, other reported clinical experience has not identified differences in
547   responses between the elderly and younger subjects, but greater sensitivity of some older
548   individuals cannot be ruled out.

549 **10   OVERDOSAGE**

550   Overdosage may cause severe hypotension, bradycardia, cardiac insufficiency,
551 cardiogenic shock, and cardiac arrest. Respiratory problems, bronchospasms, vomiting, lapses of
552 consciousness, and generalized seizures may also occur.
553   The patient should be placed in a supine position and, where necessary, kept under
554 observation and treated under intensive-care conditions. Gastric lavage or pharmacologically
555 induced emesis may be used shortly after ingestion. The following agents may be administered:
556   *for excessive bradycardia:* atropine, 2 mg IV.
557   *to support cardiovascular function:* glucagon, 5 to 10 mg IV rapidly over 30 seconds,
558 followed by a continuous infusion of 5 mg/hour; sympathomimetics (dobutamine, isoprenaline,
559 adrenaline) at doses according to body weight and effect.
560   If peripheral vasodilation dominates, it may be necessary to administer adrenaline or
561 noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant
562 bradycardia, pacemaker therapy should be performed. For bronchospasm, β-sympathomimetics
563 (as aerosol or IV) or aminophylline IV should be given. In the event of seizures, slow IV
564 injection of diazepam or clonazepam is recommended.
565   NOTE: In the event of severe intoxication where there are symptoms of shock, treatment
566 with antidotes must be continued for a sufficiently long period of time consistent with the 7- to
567 10-hour half-life of carvedilol.
568   There is no experience of overdosage with COREG CR. Cases of overdosage with
569 carvedilol alone or in combination with other drugs have been reported. Quantities ingested in
570 some cases exceeded 1,000 milligrams. Symptoms experienced included low blood pressure and
571 heart rate. Standard supportive treatment was provided and individuals recovered.

572 **11   DESCRIPTION**

573   Carvedilol phosphate is a nonselective β-adrenergic blocking agent with α_1-blocking
574 activity. It is (2*RS*)-1-(9*H*-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol
575 phosphate salt (1:1) hemihydrate. It is a racemic mixture with the following structure:
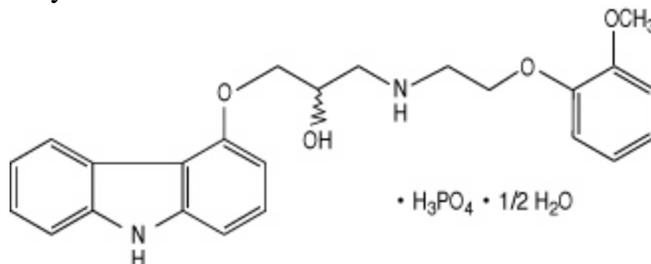
576
577   Carvedilol phosphate is a white to almost-white solid with a molecular weight of 513.5
578 (406.5 carvedilol free base) and a molecular formula of $C_{24}H_{26}N_2O_4 \bullet H_3PO_4 \bullet 1/2\ H_2O$.
579   COREG CR is available for once-a-day administration as controlled-release oral capsules
580 containing 10, 20, 40, or 80 mg carvedilol phosphate. COREG CR hard gelatin capsules are
581 filled with carvedilol phosphate immediate-release and controlled-release microparticles that are
582 drug-layered and then coated with methacrylic acid copolymers. Inactive ingredients include

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

585 **12   CLINICAL PHARMACOLOGY**
586 **12.1   Mechanism of Action**
587   Carvedilol is a racemic mixture in which nonselective β-adrenoreceptor blocking activity
588 is present in the S(-) enantiomer and α_1-adrenergic blocking activity is present in both R(+) and
589 S(-) enantiomers at equal potency. Carvedilol has no intrinsic sympathomimetic activity.
590 **12.2   Pharmacodynamics**
591   <u>Heart Failure and Left Ventricular Dysfunction Following Myocardial Infarction:</u>
592 The basis for the beneficial effects of carvedilol in patients with heart failure and in patients with
593 left ventricular dysfunction following an acute myocardial infarction is not known. The
594 concentration-response relationship for β_1-blockade following administration of COREG CR is
595 equivalent (±20%) to immediate-release carvedilol tablets.
596   <u>Hypertension:</u> The mechanism by which β-blockade produces an antihypertensive effect
597 has not been established.
598   β-adrenoreceptor blocking activity has been demonstrated in animal and human studies
599 showing that carvedilol (1) reduces cardiac output in normal subjects; (2) reduces exercise-
600 and/or isoproterenol-induced tachycardia; and (3) reduces reflex orthostatic tachycardia.
601 Significant β-adrenoreceptor blocking effect is usually seen within 1 hour of drug administration.
602   α_1-adrenoreceptor blocking activity has been demonstrated in human and animal studies,
603 showing that carvedilol (1) attenuates the pressor effects of phenylephrine; (2) causes
604 vasodilation; and (3) reduces peripheral vascular resistance. These effects contribute to the
605 reduction of blood pressure and usually are seen within 30 minutes of drug administration.
606   Due to the α_1-receptor blocking activity of carvedilol, blood pressure is lowered more in
607 the standing than in the supine position, and symptoms of postural hypotension (1.8%), including
608 rare instances of syncope, can occur. Following oral administration, when postural hypotension
609 has occurred, it has been transient and is uncommon when immediate-release carvedilol is
610 administered with food at the recommended starting dose and titration increments are closely
611 followed *[see Dosage and Administration (2)]*.
612   In a randomized, double-blind, placebo-controlled trial, the β_1-blocking effect of
613 COREG CR, as measured by heart rate response to submaximal bicycle ergometry, was shown to
614 be equivalent to that observed with immediate-release carvedilol at steady state in adult patients
615 with essential hypertension.
616   In hypertensive patients with normal renal function, therapeutic doses of carvedilol
617 decreased renal vascular resistance with no change in glomerular filtration rate or renal plasma
618 flow. Changes in excretion of sodium, potassium, uric acid, and phosphorus in hypertensive
619 patients with normal renal function were similar after carvedilol and placebo.
620   Carvedilol has little effect on plasma catecholamines, plasma aldosterone, or electrolyte
621 levels, but it does significantly reduce plasma renin activity when given for at least 4 weeks. It
622 also increases levels of atrial natriuretic peptide.

12.3 Pharmacokinetics

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

Effect of Food: Administration of COREG CR with a high-fat meal resulted in increases (~20%) in AUC and C_{max} compared to COREG CR administered with a standard meal. Decreases in AUC (27%) and C_{max} (43%) were observed when COREG CR was administered in the fasted state compared to administration after a standard meal. COREG CR should be taken with food.

In a study with adult subjects, sprinkling the contents of the COREG CR capsule on applesauce did not appear to have a significant effect on overall exposure (AUC) compared to administration of the intact capsule following a standard meal but did result in a decrease in C_{max} (18%).

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

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

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

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

663   administration of COREG CR in healthy subjects. Apparent clearance is 90 L/h and 213 L/h for
664   R(+)- and S(-)-carvedilol, respectively.
665   The primary P450 enzymes responsible for the metabolism of both R(+) and
666   S(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent
667   CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and
668   5'-hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be
669   of primary importance in the O-methylation pathway of S(-)-carvedilol.
670   Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of
671   debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma
672   concentrations of R(+)-carvedilol compared to extensive metabolizers. In contrast, plasma levels
673   of S(-)-carvedilol are increased only about 20% to 25% in poor metabolizers, indicating this
674   enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol. The
675   pharmacokinetics of carvedilol do not appear to be different in poor metabolizers of
676   S-mephenytoin (patients deficient in cytochrome P450 2C19).
677   **12.4   Specific Populations**
678   Heart Failure: Following administration of immediate-release carvedilol tablets,
679   steady-state plasma concentrations of carvedilol and its enantiomers increased proportionally
680   over the dose range in patients with heart failure. Compared to healthy subjects, heart failure
681   patients had increased mean AUC and C_{max} values for carvedilol and its enantiomers, with up to
682   50% to 100% higher values observed in 6 patients with NYHA class IV heart failure. The mean
683   apparent terminal elimination half-life for carvedilol was similar to that observed in healthy
684   subjects.
685   For corresponding dose levels *[see Dosage and Administration (2)]*, the steady-state
686   pharmacokinetics of carvedilol (AUC, C_{max}, trough concentrations) observed after administration
687   of COREG CR to chronic heart failure patients (mild, moderate, and severe) were similar to
688   those observed after administration of immediate-release carvedilol tablets.
689   Hypertension: For corresponding dose levels *[see Dosage and Administration (2)]*, the
690   pharmacokinetics (AUC, C_{max}, and trough concentrations) observed with administration of
691   COREG CR were equivalent (±20%) to those observed with immediate-release carvedilol tablets
692   following repeat dosing in patients with essential hypertension.
693   Geriatric: Plasma levels of carvedilol average about 50% higher in the elderly compared
694   to young subjects after administration of immediate-release carvedilol.
695   Hepatic Impairment: No studies have been performed with COREG CR in patients with
696   hepatic impairment. Compared to healthy subjects, patients with severe liver impairment
697   (cirrhosis) exhibit a 4- to 7-fold increase in carvedilol levels. Carvedilol is contraindicated in
698   patients with severe liver impairment.
699   Renal Impairment: No studies have been performed with COREG CR in patients with
700   renal impairment. Although carvedilol is metabolized primarily by the liver, plasma
701   concentrations of carvedilol have been reported to be increased in patients with renal impairment
702   after dosing with immediate-release carvedilol. Based on mean AUC data, approximately 40% to
703   50% higher plasma concentrations of carvedilol were observed in hypertensive patients with

704 moderate to severe renal impairment compared to a control group of hypertensive patients with
705 normal renal function. However, the ranges of AUC values were similar for both groups.
706 Changes in mean peak plasma levels were less pronounced, approximately 12% to 26% higher in
707 patients with impaired renal function.
708 Consistent with its high degree of plasma protein binding, carvedilol does not appear to
709 be cleared significantly by hemodialysis.
710 **12.5   Drug-Drug Interactions**
711 Since carvedilol undergoes substantial oxidative metabolism, the metabolism and
712 pharmacokinetics of carvedilol may be affected by induction or inhibition of cytochrome P450
713 enzymes.
714 The following drug interaction studies were performed with immediate-release carvedilol
715 tablets.
716 Amiodarone: In a pharmacokinetic study conducted in 106 Japanese patients with heart
717 failure, coadministration of small loading and maintenance doses of amiodarone with carvedilol
718 resulted in at least a 2-fold increase in the steady-state trough concentrations of S(-)-carvedilol
719 *[see Drug Interactions (7.6)]*.
720 Cimetidine: In a pharmacokinetic study conducted in 10 healthy male subjects,
721 cimetidine (1,000 mg/day) increased the steady-state AUC of carvedilol by 30% with no change
722 in C_{max} *[see Drug Interactions (7.5)]*.
723 Digoxin: Following concomitant administration of carvedilol (25 mg once daily) and
724 digoxin (0.25 mg once daily) for 14 days, steady-state AUC and trough concentrations of digoxin
725 were increased by 14% and 16%, respectively, in 12 hypertensive patients *[see Drug
726 Interactions (7.4)]*.
727 Glyburide: In 12 healthy subjects, combined administration of carvedilol (25 mg once
728 daily) and a single dose of glyburide did not result in a clinically relevant pharmacokinetic
729 interaction for either compound.
730 Hydrochlorothiazide: A single oral dose of carvedilol 25 mg did not alter the
731 pharmacokinetics of a single oral dose of hydrochlorothiazide 25 mg in 12 patients with
732 hypertension. Likewise, hydrochlorothiazide had no effect on the pharmacokinetics of carvedilol.
733 Rifampin: In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin
734 (600 mg daily for 12 days) decreased the AUC and C_{max} of carvedilol by about 70% *[see Drug
735 Interactions (7.5)]*.
736 Torsemide: In a study of 12 healthy subjects, combined oral administration of carvedilol
737 25 mg once daily and torsemide 5 mg once daily for 5 days did not result in any significant
738 differences in their pharmacokinetics compared with administration of the drugs alone.
739 Warfarin: Carvedilol (12.5 mg twice daily) did not have an effect on the steady-state
740 prothrombin time ratios and did not alter the pharmacokinetics of R(+)- and S(-)-warfarin
741 following concomitant administration with warfarin in 9 healthy volunteers.

13   NONCLINICAL TOXICOLOGY

13.1   Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

14   CLINICAL STUDIES

Support for the use of COREG CR extended-release capsules for the treatment of mild-to-severe heart failure and for patients with left ventricular dysfunction following myocardial infarction is based on the equivalence of pharmacokinetic and pharmacodynamic (β_1-blockade) parameters between COREG CR and immediate-release carvedilol *[see Clinical Pharmacology (12.2, 12.3)]*.

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

14.1   Heart Failure

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

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

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

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

782   cardiovascular hospitalizations. In situations where the primary end points of a trial do not show
783   a significant benefit of treatment, assignment of significance values to the other results is
784   complex, and such values need to be interpreted cautiously.
785   The results of the US and Australia-New Zealand trials were as follows:
786   *Slowing Progression of Heart Failure:* One US multicenter study (366 subjects) had as
787   its primary end point the sum of cardiovascular mortality, cardiovascular hospitalization, and
788   sustained increase in heart failure medications. Heart failure progression was reduced, during an
789   average follow-up of 7 months, by 48% (p = 0.008).
790   In the Australia-New Zealand study, death and total hospitalizations were reduced by
791   about 25% over 18 to 24 months. In the 3 largest US studies, death and total hospitalizations
792   were reduced by 19%, 39%, and 49%, nominally statistically significant in the last 2 studies. The
793   Australia-New Zealand results were statistically borderline.
794   *Functional Measures:* None of the multicenter studies had NYHA classification as a
795   primary end point, but all such studies had it as a secondary end point. There was at least a trend
796   toward improvement in NYHA class in all studies. Exercise tolerance was the primary end point
797   in 3 studies; in none was a statistically significant effect found.
798   *Subjective Measures:* Health-related quality of life, as measured with a standard
799   questionnaire (a primary end point in 1 study), was unaffected by carvedilol. However, patients'
800   and investigators' global assessments showed significant improvement in most studies.
801   *Mortality:* Death was not a pre-specified end point in any study, but was analyzed in all
802   studies. Overall, in these 4 US trials, mortality was reduced, nominally significantly so in
803   2 studies.
804   <u>The COMET Trial:</u> In this double-blind trial, 3,029 patients with NYHA class II-IV
805   heart failure (left ventricular ejection fraction ≤35%) were randomized to receive either
806   carvedilol (target dose: 25 mg twice daily) or immediate-release metoprolol tartrate (target dose:
807   50 mg twice daily). The mean age of the patients was approximately 62 years, 80% were males,
808   and the mean left ventricular ejection fraction at baseline was 26%. Approximately 96% of the
809   patients had NYHA class II or III heart failure. Concomitant treatment included diuretics (99%),
810   ACE inhibitors (91%), digitalis (59%), aldosterone antagonists (11%), and "statin" lipid-
811   lowering agents (21%). The mean duration of follow-up was 4.8 years. The mean dose of
812   carvedilol was 42 mg per day.
813   The study had 2 primary end points: all-cause mortality and the composite of death plus
814   hospitalization for any reason. The results of COMET are presented in Table 5 below. All-cause
815   mortality carried most of the statistical weight and was the primary determinant of the study size.
816   All-cause mortality was 34% in the patients treated with carvedilol and was 40% in the
817   immediate-release metoprolol group (p = 0.0017; hazard ratio = 0.83, 95% CI 0.74–0.93). The
818   effect on mortality was primarily due to a reduction in cardiovascular death. The difference
819   between the 2 groups with respect to the composite end point was not significant (p = 0.122).
820   The estimated mean survival was 8.0 years with carvedilol and 6.6 years with immediate-release
821   metoprolol.
822

823 **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

824

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

830 <u>Severe Heart Failure (COPERNICUS):</u> In a double-blind study, 2,289 patients with
831 heart failure at rest or with minimal exertion and left ventricular ejection fraction <25% (mean
832 20%), despite digitalis (66%), diuretics (99%), and ACE inhibitors (89%) were randomized to
833 placebo or carvedilol. Carvedilol was titrated from a starting dose of 3.125 mg twice daily to the
834 maximum tolerated dose or up to 25 mg twice daily over a minimum of 6 weeks. Most subjects
835 achieved the target dose of 25 mg. The study was conducted in Eastern and Western Europe, the
836 United States, Israel, and Canada. Similar numbers of subjects per group (about 100) withdrew
837 during the titration period.

838 The primary end point of the trial was all-cause mortality, but cause-specific mortality
839 and the risk of death or hospitalization (total, cardiovascular [CV], or heart failure [HF]) were
840 also examined. The developing trial data were followed by a data monitoring committee, and
841 mortality analyses were adjusted for these multiple looks. The trial was stopped after a median
842 follow-up of 10 months because of an observed 35% reduction in mortality (from 19.7% per
843 patient year on placebo to 12.8% on carvedilol, hazard ratio 0.65, 95% CI 0.52 – 0.81,
844 $p = 0.0014$, adjusted) (see Figure 1). The results of COPERNICUS are shown in Table 6.

845

846 **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

847 Cardiovascular = CV; Heart failure = HF

848

849 **Figure 1. Survival Analysis for COPERNICUS (intent-to-treat)**
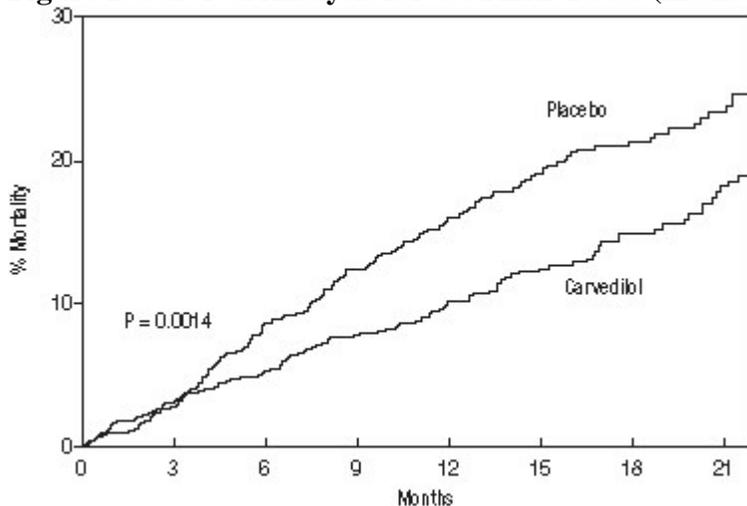
850
851
852   The effect on mortality was principally the result of a reduction in the rate of sudden
853 death among patients without worsening heart failure.
854   Patients' global assessments, in which carvedilol-treated patients were compared to
855 placebo, were based on pre-specified, periodic patient self-assessments regarding whether
856 clinical status post-treatment showed improvement, worsening, or no change compared to
857 baseline. Patients treated with carvedilol showed significant improvements in global assessments
858 compared with those treated with placebo in COPERNICUS.
859   The protocol also specified that hospitalizations would be assessed. Fewer patients on
860 immediate-release carvedilol than on placebo were hospitalized for any reason (372 versus 432,
861 p = 0.0029), for cardiovascular reasons (246 versus 314, p = 0.0003), or for worsening heart
862 failure (198 versus 268, p = 0.0001).
863   Immediate-release carvedilol had a consistent and beneficial effect on all-cause mortality
864 as well as the combined end points of all-cause mortality plus hospitalization (total, CV, or for
865 heart failure) in the overall study population and in all subgroups examined, including men and

866   women, elderly and non-elderly, blacks and non-blacks, and diabetics and non-diabetics (see

867   Figure 2).

868

869   **Figure 2. Effects on Mortality for Subgroups in COPERNICUS**
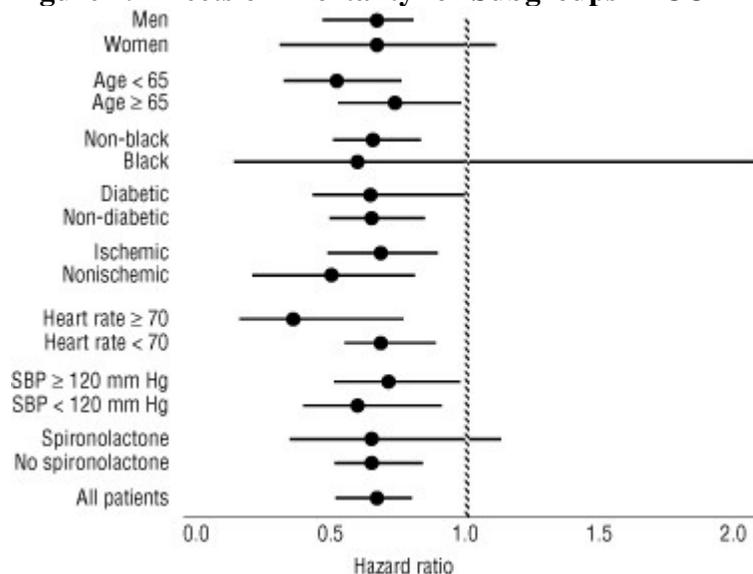
870

871

872   Although the clinical trials used twice-daily dosing, clinical pharmacologic and

873   pharmacokinetic data provide a reasonable basis for concluding that once-daily dosing with

874   COREG CR should be adequate in the treatment of heart failure.

875   **14.2   Left Ventricular Dysfunction Following Myocardial Infarction**

876   CAPRICORN was a double-blind study comparing carvedilol and placebo in 1,959

877   patients with a recent myocardial infarction (within 21 days) and left ventricular ejection fraction

878   of ≤40%, with (47%) or without symptoms of heart failure. Patients given carvedilol received

879   6.25 mg twice daily, titrated as tolerated to 25 mg twice daily. Patients had to have a systolic

880   blood pressure >90 mm Hg, a sitting heart rate >60 beats/minute, and no contraindication to

881   β-blocker use. Treatment of the index infarction included aspirin (85%), IV or oral β-blockers

882   (37%), nitrates (73%), heparin (64%), thrombolytics (40%), and acute angioplasty (12%).

883   Background treatment included ACE inhibitors or angiotensin receptor blockers (97%),

884   anticoagulants (20%), lipid-lowering agents (23%), and diuretics (34%). Baseline population

885   characteristics included an average age of 63 years, 74% male, 95% Caucasian, mean blood

886   pressure 121/74 mm Hg, 22% with diabetes, and 54% with a history of hypertension. Mean

887   dosage achieved of carvedilol was 20 mg twice daily; mean duration of follow-up was

888   15 months.

889   All-cause mortality was 15% in the placebo group and 12% in the carvedilol group,

890   indicating a 23% risk reduction in patients treated with carvedilol (95% CI 2% to 40%, p = 0.03),

891   as shown in Figure 3. The effects on mortality in various subgroups are shown in Figure 4.

892   Nearly all deaths were cardiovascular (which were reduced by 25% by carvedilol), and most of

893   these deaths were sudden or related to pump failure (both types of death were reduced by

894   carvedilol). Another study end point, total mortality and all-cause hospitalization, did not show a
895   significant improvement.
896   There was also a significant 40% reduction in fatal or non-fatal myocardial infarction
897   observed in the group treated with carvedilol (95% CI 11% to 60%, p = 0.01). A similar
898   reduction in the risk of myocardial infarction was also observed in a meta-analysis of placebo-
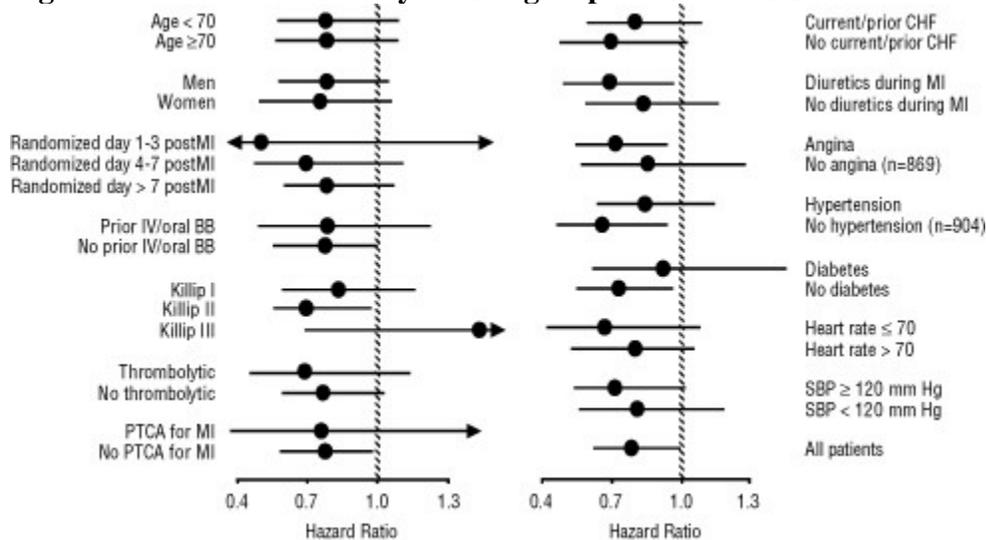899   controlled trials of carvedilol in heart failure.
900
901   **Figure 3. Survival Analysis for CAPRICORN (intent-to-treat)**
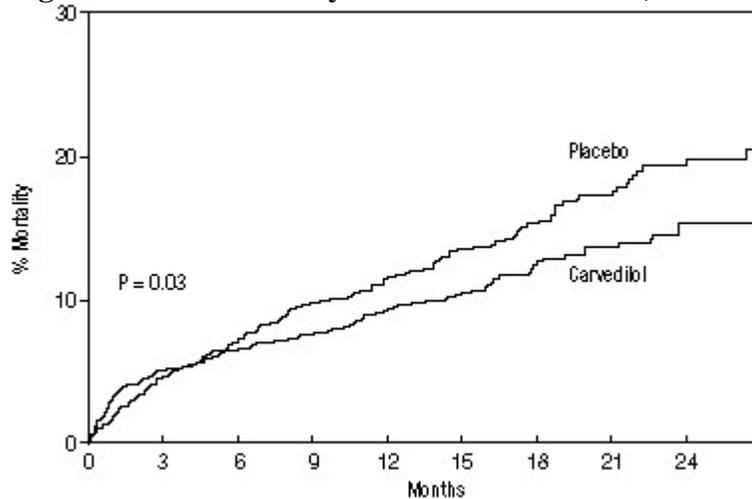
902
903
904   **Figure 4. Effects on Mortality for Subgroups in CAPRICORN**

905
906
907   Although the clinical trials used twice-daily dosing, clinical pharmacologic and
908   pharmacokinetic data provide a reasonable basis for concluding that once-daily dosing with
909   COREG CR should be adequate in the treatment of left ventricular dysfunction following
910   myocardial infarction.

14.3 Hypertension

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

Statistically significant reductions in blood pressure as measured by 24-hour ambulatory blood pressure monitoring (ABPM) were observed with each dose of COREG CR compared to placebo. Placebo-subtracted mean changes from baseline in mean SBP/DBP were -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 80 mg, respectively. Placebo-subtracted mean changes from baseline in mean trough (average of 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 COREG CR 20 mg, 40 mg, and 80 mg, respectively. The placebo-corrected trough to peak (3-7 hr) ratio was approximately 0.6 for COREG CR 80 mg. In this study, assessments of 24-hour ABPM monitoring demonstrated statistically significant blood pressure reductions with COREG CR throughout the dosing period (Figure 5).

Figure 5. Changes from Baseline in Systolic Blood Pressure and Diastolic Blood Pressure Measured by 24-Hour ABPM
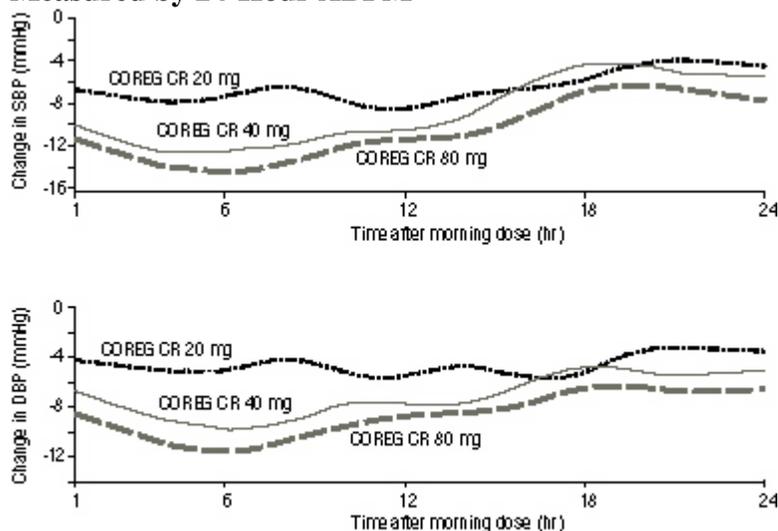
Lines smoothed using locally weighted regression smoothing methodology.

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

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

945 **14.4 Hypertension With Type 2 Diabetes Mellitus**

946 In a double-blind study (GEMINI), carvedilol, added to an ACE inhibitor or angiotensin
947 receptor blocker, was evaluated in a population with mild-to-moderate hypertension and well-
948 controlled type 2 diabetes mellitus. The mean HbA1c at baseline was 7.2%. COREG was titrated
949 to a mean dose of 17.5 mg twice daily and maintained for 5 months. COREG had no adverse
950 effect on glycemic control, based on HbA1c measurements (mean change from baseline of
951 0.02%, 95% CI -0.06 to 0.10, p = NS) *[see Warnings and Precautions (5.6)]*.

952 **16   HOW SUPPLIED/STORAGE AND HANDLING**

953 The hard gelatin capsules are available in the following strengths:
954 • 10 mg – white and green capsule shell printed with GSK COREG CR and 10 mg
955 • 20 mg – white and yellow capsule shell printed with GSK COREG CR and 20 mg
956 • 40 mg – yellow and green capsule shell printed with GSK COREG CR and 40 mg
957 • 80 mg – white capsule shell printed with GSK COREG CR and 80 mg
958
959 • 10 mg 30's: NDC 0007-3370-13
960 • 10 mg 90's: NDC 0007-3370-59
961 • 20 mg 30's: NDC 0007-3371-13
962 • 20 mg 90's: NDC 0007-3371-59
963 • 40 mg 30's: NDC 0007-3372-13
964 • 40 mg 90's: NDC 0007-3372-59
965 • 80 mg 30's: NDC 0007-3373-13
966 • 80 mg 90's: NDC 0007-3373-59

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

969 **17   PATIENT COUNSELING INFORMATION**

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

971 **17.1 Patient Advice**

972 Patients taking COREG CR should be advised of the following:
973 • Patients should not interrupt or discontinue using COREG CR without a physician's advice.
974 • Patients with heart failure should consult their physician if they experience signs or
975 symptoms of worsening heart failure such as weight gain or increasing shortness of breath.

976 • Patients may experience a drop in blood pressure when standing, resulting in dizziness and,
977   rarely, fainting. Patients should sit or lie down when these symptoms of lowered blood
978   pressure occur.
979 • If experiencing dizziness or fatigue, patients should avoid driving or hazardous tasks.
980 • Patients should consult a physician if they experience dizziness or faintness, in case the
981   dosage should be adjusted.
982 • Patients should not crush or chew COREG CR capsules.
983 • Patients should take COREG CR with food.
984 • Diabetic patients should report any changes in blood sugar levels to their physician.
985 • Contact lens wearers may experience decreased lacrimation.

986 **17.2   FDA-Approved Patient Labeling**

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

989

990 COREG CR and COREG are registered trademarks of GlaxoSmithKline.
991 TOPROL-XL is a registered trademark of the AstraZeneca group of companies.
992

993
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997
998 Month Year
999 CCR:XXPI

PATIENT INFORMATION LEAFLET

COREG CR® (Co-REG)

(carvedilol phosphate) Extended-release Capsules

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

What is the most important information I should know about COREG CR?
It is important for you to take your medicine every day as directed by your doctor. If you stop taking COREG CR suddenly, you could have chest pain and a heart attack. If your doctor decides that you should stop taking COREG CR, your doctor may slowly lower your dose over time before stopping it completely.

What is COREG CR?
COREG CR is a prescription medicine that belongs to a group of medicines called "beta-blockers". COREG CR is used, often with other medicines, for the following conditions:
- to treat patients with high blood pressure (hypertension)
- to treat patients who had a heart attack that worsened how well the heart pumps
- to treat patients with certain types of heart failure

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

Who should not take COREG CR?
Do not take COREG CR if you:
- have severe heart failure and require certain intravenous medicines that help support circulation.
- have asthma or other breathing problems.
- have a slow heartbeat or certain conditions that cause your heart to skip a beat (irregular heartbeat).
- have liver problems.
- are allergic to any of the ingredients in COREG CR. *See "What are the ingredients in COREG CR?"*

What should I tell my doctor before taking COREG CR?
Tell your doctor about all of your medical conditions, including if you:
- have asthma or other lung problems (such as bronchitis or emphysema).

1040 • have problems with blood flow in your feet and legs (peripheral vascular disease).
1041 COREG CR can make some of your symptoms worse.
1042 • have diabetes.
1043 • have thyroid problems.
1044 • have a condition called pheochromocytoma.
1045 • have had severe allergic reactions.
1046 • are scheduled for surgery and will be given anesthetic agents.
1047 • are scheduled for cataract surgery and have taken or are currently taking COREG CR.
1048 • are pregnant or trying to become pregnant. It is not known if COREG CR is safe for your
1049 unborn baby. You and your doctor should talk about the best way to control your high blood
1050 pressure during pregnancy.
1051 • are breastfeeding. It is not known if COREG CR passes into your breast milk. You should
1052 not breastfeed while using COREG CR.
1053
1054 **Tell your doctor about all of the medicines you take** including prescription and non-
1055 prescription medicines, vitamins, and herbal supplements. COREG CR and certain other
1056 medicines can affect each other and cause serious side effects. COREG CR may affect the way
1057 other medicines work. Also, other medicines may affect how well COREG CR works.
1058
1059 Know the medicines you take. Keep a list of your medicines and show it to your doctor and
1060 pharmacist before you start a new medicine.
1061
1062 **How should I take COREG CR?**
1063 • Take COREG CR exactly as prescribed. Take COREG CR **one** time each day with food. **It is**
1064 **important that you take COREG CR only one time each day.** To lessen possible side
1065 effects, your doctor might begin with a low dose and then slowly increase the dose.
1066 • Swallow COREG CR capsules whole. Do not chew or crush COREG CR capsules.
1067 • If you have trouble swallowing COREG CR whole:
1068 • The capsule may be carefully opened and the beads sprinkled over a spoonful of
1069 applesauce which should be eaten right away. The applesauce should not be warm.
1070 • Do not sprinkle beads on foods other than applesauce.
1071 • **Do not stop taking COREG CR and do not change the amount of COREG CR you take**
1072 **without talking to your doctor.**
1073 • If you miss a dose of COREG CR, take your dose as soon as you remember, unless it is time
1074 to take your next dose. Take your next dose at the usual time. Do not take 2 doses at the same
1075 time.
1076 • If you take too much COREG CR, call your doctor or poison control center right away.
1077
1078 **What should I avoid while taking COREG CR?**
1079 COREG CR can cause you to feel dizzy, tired, or faint. Do not drive a car, use machinery, or do
1080 anything that needs you to be alert if you have these symptoms.

1081

What are possible side effects of COREG CR?

Serious side effects of COREG CR include:

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

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

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

How should I store COREG CR?

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

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

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

General information about COREG CR

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

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1123 This leaflet summarizes the most important information about COREG CR. If you would like
1124 more information, talk with your doctor. You can ask your doctor or pharmacist for information
1125 about COREG CR that is written for healthcare professionals. You can also find out more about
1126 COREG CR by visiting the website www.COREGCR.com or calling 1-888-825-5249. This call
1127 is free.
1128

1129 **What are the ingredients in COREG CR?**
1130 Active ingredient: carvedilol phosphate
1131 Inactive ingredients: crospovidone, hydrogenated castor oil, hydrogenated vegetable oil,
1132 magnesium stearate, methacrylic acid copolymers, microcrystalline cellulose, and povidone
1133 COREG CR capsules come in the following strengths: 10 mg, 20 mg, 40 mg, 80 mg.
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