

Preclearers Unaware of Shift in Opioid Regulations

BY MARY ELLEN SCHNEIDER
New York Bureau

NEW ORLEANS Get educated about state and federal regulations and policies on the prescription of controlled substances, advised David Joranson, director of the Pain and Policy Studies Group at the University of Wisconsin Paul P. Carbone Comprehensive Cancer Center in Madison.

Mr. Joranson, who spoke at the annual meeting of the American Academy of

Pain Medicine, said that understanding current regulations is critical to avoiding unnecessary fears over the risk of sanctions from prescribing pain medication.

In recent years there has been increasing agreement reached between pain medicine specialists, law enforcement, and regulators. For example, from 2003 to 2006, 19 states either limited or added language to their state's controlled substances prescribing policies to take a more balanced approach—recognizing opioids

are necessary but also pose risks and need to be controlled.

“The state policies are becoming more balanced,” he said.

Importantly, 39 states have adopted a policy aimed at directly addressing physicians' concerns about regulatory scrutiny, he added.

Nearly 10 years ago, the Federation of State Medical Boards made it clear that physicians should recognize that tolerance and physical dependence are the normal

consequences of the sustained use of opioid analgesics and are not synonymous with addiction. As a result, many state medical board guidelines now reflect that statement, Mr. Joranson said.

Last year, at the federal level the Drug Enforcement Administration issued a statement that nearly every prescription issued in the United States is for a legitimate medical purpose and that the amount of dosage units per prescription will never be a basis for investigation for the overwhelming majority of physicians.

Research findings indicated, however, that physicians may not be paying attention to this policy shift. In a study published in the *Journal of Family Practice* in 2001, investigators from the University of California, San Francisco/Stanford Collaborative Research Network surveyed 230 primary care physicians on pain treatment, the use of opioids, and their familiarity with state prescribing and documentation guidelines.

“It can be an uphill battle to get attention to policy,”

by the Medical Board of California in 1994. The guidelines were aimed in part at reducing physicians' fear of regulatory scrutiny. The guidelines were mailed to all licensed physician in the state three times between 1994 and 1996.

Of the 161 physicians who completed the survey, only 39% remembered reading the guidelines 1 year after the third mailing. And 40% of respondents said that fear of legal investigation influenced their opioid prescribing habits.

“It can be an uphill battle to get physicians to pay attention to policy,” Mr. Joranson said.

Despite the growing areas of agreement on proper pain prescriptions, there are still some areas surrounding prescribing of controlled substances that need to be worked out, he said. For example, prescribing opioids to pain patients who may have a substance abuse problem is an area where law enforcement and physicians have the potential to clash. More dialogue is needed between the pain medicine community and DEA on this issue, he said.

In addition, some groups mistakenly believe that physicians and patients are the main source of drug diversion, he said.

And while it's likely that the majority of regulatory and law enforcement actions against physicians are appropriate, there have been exceptions, he said. Some physicians have been charged and later acquitted in court, while others have been convicted only to have their cases overturned later. These cases need to be investigated to figure out what went wrong, he added. ■

COREG CR™ (carvedilol phosphate) Extended-Release Capsules

The following is a brief summary only; see full prescribing information for complete product information.

CONTRAINDICATIONS

COREG CR is contraindicated in patients with bradycardia (A2 cases of death from status asthmaticus have been reported in patients receiving single doses of immediate-release carvedilol) or related bronchospastic conditions, second- or third-degree AV block, sick sinus syndrome or severe bradycardia (unless a permanent pacemaker is in place), or in patients with cardiogenic shock or who have decompensated heart failure requiring the use of intravenous inotropic therapy. Such patients should be first treated from intravenous therapy before initiating COREG CR.

Use of COREG CR in patients with clinically manifest hepatic impairment is not recommended.

COREG CR is contraindicated in patients with hypersensitivity to any component of the product.

WARNINGS

Cessation of Therapy with COREG CR in Patients with coronary artery disease, who are being treated with COREG CR, should be advised against abrupt discontinuation of therapy. Sudden withdrawal of therapy may precipitate myocardial infarction. The last 2 complications may occur with or without preceding exacerbation of the angina pectoris. As with other β -blockers, when discontinuation of COREG CR is planned, the patient should be carefully observed and advised to limit physical activity to a minimum. COREG CR should be discontinued over 1 to 2 weeks whenever possible. If the angina worsens or acute coronary insufficiency develops, it is recommended that COREG CR be promptly reinstated, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue COREG CR therapy abruptly even in patients treated only for hypertension or heart failure (see DOSAGE AND ADMINISTRATION in the full prescribing information).

Peripheral Vascular Disease: β -blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

Anesthesia and Major Surgery: If treatment with COREG CR is to be continued perioperatively, particular care should be taken when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used. See OVERDOSAGE (in the full prescribing information) for information on treatment of bradycardia and hypotension.

Diabetes and Hypoglycemia: In general, β -blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective β -blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned about these possibilities. In heart failure patients, there is a risk of worsening hypoglycemia (see PRECAUTIONS, Effects on Glycemic Control in Type 2 Diabetic Patients).

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

PRECAUTIONS

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

In clinical trials with immediate-release carvedilol, bradycardia was reported in about 2% of hypertensive patients, and 6.5% of myocardial infarction patients with left ventricular dysfunction. Bradycardia was reported in 0.5% of patients receiving COREG CR in a study of heart failure patients and myocardial infarction patients with left ventricular dysfunction. There were no reports of bradycardia in the clinical trial of COREG CR in hypertension. However, if pulse rate drops below 50 beats/min, the dosage of COREG CR should be reduced.

In clinical trials of primarily mild-to-moderate heart failure with immediate-release carvedilol, hypotension and postural hypotension occurred in 9.7% and syncope in 3.4% of patients receiving carvedilol. The incidence of hypotension was higher during the first 50 days of dosing, corresponding to the up-titration period and was a cause for discontinuation of therapy in 0.7% of carvedilol patients, compared to 0.4% of placebo patients. In a long-term, placebo-controlled trial in severe heart failure (COPERNICUS), hypotension and postural hypotension occurred in 15.1% and syncope in 2.9% of heart failure patients receiving carvedilol compared to 6.2% and 2.3% of placebo patients, respectively. These events were a cause for discontinuation of therapy in 1.1% of carvedilol patients, compared to 0.5% of placebo patients.

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

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

To decrease the likelihood of syncope or excessive hypotension, treatment with COREG CR should be initiated with 10 mg once daily for heart failure patients, and at 20 mg once daily for hypertensive patients or survivors of an acute myocardial infarction with left ventricular dysfunction. Dosage should then be increased slowly, according to recommendations in the DOSAGE AND ADMINISTRATION section (see DOSAGE AND ADMINISTRATION in the full prescribing information), and the drug should be taken with food. During initiation of therapy, the patient should be cautioned to avoid situations such as driving or hazardous tasks, where injury could result should syncope occur.

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

Worsening heart failure or fluid retention may occur during up-titration of carvedilol. If such symptoms occur, diuretics should be increased and the dose of COREG CR should not be advanced until clinical stability resumes (see DOSAGE AND ADMINISTRATION in the full prescribing information). Occasionally it is necessary to lower the dose of COREG CR or temporarily discontinue it. Such patients should not receive subsequent treatment of, or a favorable response to, COREG CR. In a placebo-controlled trial of patients with severe heart failure, worsening heart failure during the first 3 months was reported to a similar degree with immediate-release carvedilol and with placebo. When treatment was maintained beyond 3 months, worsening heart failure was reported less frequently in patients treated with carvedilol than with placebo. Worsening heart failure observed during long-term therapy is more likely to be related to the patient's underlying condition.

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

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

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

Effects on Glycemic Control in Type 2 Diabetic Patients: In heart failure patients with diabetes, diabetic therapy may lead to worsening hypoglycemia, which responds to intensification of hypoglycemic therapy. It is recommended that blood glucose be monitored when dosing with COREG CR is initiated, adjusted, or discontinued. Studies designed to examine the effects of carvedilol on glycemic control in patients with diabetes and heart failure have not been conducted.

In a study designed to examine the effects of immediate-release carvedilol on glycemic control in a population with mild-to-moderate hypertension and well-controlled type 2 diabetes mellitus, carvedilol had no adverse effect on glycemic control, based on HbA1c measurements (see CLINICAL TRIALS in the full prescribing information).

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

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema): Patients with bronchospastic disease should, in general, not receive β -blockers. COREG CR may be used with caution, however, in patients with mild, stable, or controlled asthma, or other anti-bronchospastic disease. It is prudent, if COREG CR is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous β -agonists is minimized.

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

Information for Patients: Patients taking COREG CR should be advised of the following:

- They should not interrupt or discontinue using COREG CR without a physician's advice.
- Heart failure patients should consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath.
- They may experience a drop in blood pressure when standing, resulting in dizziness and, rarely, fainting. Patients should be advised to sit or lie down when these symptoms of lowered blood pressure occur.
- Patients experience dizziness or fatigue, they should avoid driving or hazardous tasks.
- They should consult a physician if they experience dizziness or fainting, in case the dosage should be adjusted.
- They should not crush or chew COREG CR capsules.
- They should take COREG CR with food.
- They should separate the administration of COREG CR from alcohol consumption (including prescription and over-the-counter medications that contain ethanol) by at least 2 hours.
- Diabetic patients should report any changes in blood sugar levels to their physician.

• Contact lens wearers may experience decreased lacrimation.

Drug Interactions: (Also see CLINICAL PHARMACOLOGY, Pharmacokinetics/Drug-Drug Interactions in the full prescribing information.)

- Alcohol:** Concomitant administration of COREG CR with alcohol may affect the modified release properties of COREG CR, potentially resulting in a faster rate of release and higher than expected peak and lower than expected trough plasma concentrations of carvedilol phosphate. To avoid the potential for this interaction, the administration of COREG CR with alcohol (including beer, wine, or other alcoholic beverages) should be separated by at least 2 hours. COREG CR should be taken in the morning with food. (See DOSAGE AND ADMINISTRATION in the full prescribing information.)
- Inhibitors of CYP2D6:** Some metabolites of deslorazepam, inhibitors of carvedilol with strong inhibitors of CYP2D6 (such as quinidine, fluoxetine, paroxetine, and propafenone) failed to alter carvedilol levels. These drugs would be expected to increase blood levels of the β -1 antagonist of carvedilol (see CLINICAL PHARMACOLOGY, Pharmacokinetics/Drug-Drug Interactions in the full prescribing information). Retrospective analysis of effects in clinical trials showed that poor CYP2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the α -blocking PIV enantiomer.
- Catecholamine-depleting agents:** Patients taking both agents with β -blocking properties and a drug that can deplete catecholamines (e.g., reserpine and monoamine oxidase inhibitors) should be cautioned against the signs of hypotension and/or severe bradycardia.
- Clonidine:** Concomitant administration of clonidine with agents with β -blocking properties may potentiate blood-pressure- and heart-rate-lowering effects. When concomitant treatment with agents with β -blocking properties and clonidine is to be terminated, the β -blocking agent should be discontinued first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage.
- Cyclopropane:** Modest increases in mean trough cyclopropane concentrations were observed following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30% of patients, the dose of cyclopropane had to be reduced in order to maintain cyclopropane concentrations within the therapeutic range, while in the remainder no adjustment was needed. On the average for the group, the dose of cyclopropane was reduced about 20% in these patients. Due to the potential for increased variability in the dose adjustment required, it is recommended that cyclopropane concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclopropane be adjusted as appropriate.
- Digoxin:** Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Both digoxin and carvedilol slow AV conduction. Therefore, increased monitoring of digoxin is recommended when initiating, adjusting, or discontinuing COREG CR.
- Inducers and inhibitors of hepatic metabolism:** Rifampin reduced plasma concentrations of carvedilol by about 70%. Cimetidine increased AUC by about 30% but caused no change in C_{max} .
- Calcium channel blockers:** Isolated cases of conduction disturbances (rarely with hemodynamic compromise) have been observed when carvedilol is co-administered with diltiazem. As with other agents with β -blocking properties, if COREG CR is to be administered orally with calcium channel blockers of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored.
- Insulin or oral hypoglycemics:** Agents with β -blocking properties may enhance the blood-sugar-reducing effect of insulin and oral hypoglycemics. Therefore, in patients taking insulin or oral hypoglycemics, regular monitoring of blood glucose is recommended.
- Pron Pump Inhibitors:** There is no clinically significant increase in AUC and C_{max} with concomitant administration of carvedilol extended-release capsules with pantoprazole.
- 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 maximum recommended human dose [MRHD]) or mice given up to 200 mg/kg/day (16 times the MRHD) on a mg/m² basis, carvedilol had no carcinogenic effect.
- Carvedilol was negative when tested in a battery of genotoxicity assays, including the Ames and the CHO/Hprt assays for mutagenicity and the in vitro hamster micronucleus and in vivo human lymphocyte cell tests for clastogenicity.
- At doses ≥ 200 mg/kg/day (≥ 23 times the MRHD as mg/m²) carvedilol was toxic to adult rats (reduced weight gain) and was associated with a reduced number of successful matings, prolonged mating time, significantly fewer corpora lutea and implantations per day, 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/m²).
- Pregnancy, Teratogenic Effects:** Pregnancy Category C. Studies performed in pregnant rats and rabbits given carvedilol revealed increased post-implantation loss in rats at doses of 300 mg/kg/day (50 times the MRHD as mg/m²) and in rabbits at doses of 75 mg/kg/day (25 times the MRHD as mg/m²). In the rats, there was also a decrease in fetal body weight at the maternally toxic dose of 300 mg/kg/day (50 times the MRHD as mg/m²). This was accompanied by an elevation in the frequency of fetuses with delayed skeletal development (missing or stunted 13th rib). In rats the no-observed-effect level for developmental toxicity was 60 mg/kg/day (10 times the MRHD as mg/m²) in rabbits it was 15 mg/kg/day (5 times the MRHD as mg/m²). There are no adequate and well-controlled studies in pregnant women. COREG CR should be used during pregnancy only if the potential benefits justifies the potential risk to the fetus.
- Nursing Mothers:** It is not known whether this drug is excreted in human milk. Studies in rats have shown that carvedilol and/or its metabolites (as well as other β -blockers) cross the placental barrier and are excreted in breast milk. There was increased mortality at one week post partum in neonates from rats treated with 60 mg/kg/day (10 times the MRHD as mg/m²) and above during the last trimester through day 22 of lactation. Because many drugs are excreted in human milk because of the potential for serious adverse reactions in nursing infants from β -blockers, especially bradycardia, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. The effects of other β -blocking agents have included neonatal and maternal deaths.
- Pediatric Use:** Safety and efficacy of carvedilol in patients younger than 18 years of age have not been established.
- Geriatric Use:** The clinical studies of carvedilol in patients with hypertension, heart failure, and left ventricular dysfunction following myocardial infarction did not include sufficient numbers of subjects aged 65 years of age and older to determine whether they respond differently from younger patients.
- The following information is available for trials with immediate-release carvedilol. Of 765 patients with heart failure randomized to carvedilol in US clinical trials, 31% (239) were 65 years of age or older, and 7.3% (56) were 75 years of age or older. Of the 1,156 patients randomized to carvedilol in a long-term, placebo-controlled trial in severe heart failure, 47% (541) were 65 years of age or older, 12.6% (146) were 75 years of age or older. Of 1,265 patients randomized to carvedilol in heart failure patients randomized to carvedilol in the CAPRICORN trial, 48% (468) were 65 years of age or older, and 11% (111) were 75 years of age or older. Of the 2,065 myocardial infarction patients in US clinical trials of efficacy or safety who were treated with carvedilol, 21% (436) were 65 years of age or older. Of 2,722 patients receiving immediate-release carvedilol in hypertension clinical trials conducted worldwide, 24% were 65 years of age or older.
- With the exception of dizziness in hypertensive patients (incidence 8.8% in the elderly vs. 6% in younger patients), no overall differences in the safety or effectiveness (see Figures 2 and 4 in the full prescribing information) were observed between the older subjects and younger subjects in each of these populations. Similarly, other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Carvedilol has been evaluated for safety in patients with heart failure (mild, moderate, and severe heart failure), in patients with left ventricular dysfunction following myocardial infarction, and in hypertensive patients. The observed adverse event profile was consistent with the pharmacology of the drug and the health status of the patients in the clinical trials. Adverse events reported for each of these patient populations reflecting the use of either COREG CR or immediate-release carvedilol are provided below. Excluded are adverse events considered too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being

BRIEF SUMMARY

treated or are very common in the treated population. Rates of adverse events were generally similar across demographic subsets (men and women, elderly and non-elderly, blacks and non-blacks). COREG CR has been evaluated for safety in a 4-week (2 weeks of immediate-release carvedilol and 2 weeks of COREG CR) clinical study (n = 167) which included 157 patients with stable mild, moderate, or severe chronic heart failure and 30 patients with left ventricular dysfunction following acute myocardial infarction. The profile of adverse events observed with COREG CR in this small, short-term study was generally similar to that observed with immediate-release carvedilol. Differences in safety would not be expected based on the similarity in plasma levels for COREG CR and immediate-release carvedilol.

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

Carvedilol has been evaluated for safety in heart failure in more than 4,500 patients worldwide of whom more than 2,100 participated in placebo-controlled clinical trials. Approximately 68% of the total treated population in placebo-controlled clinical trials received carvedilol for at least 6 months and 30% received carvedilol for at least 12 months. In the COMPELL trial, 1,511 patients with mild-to-moderate heart failure were treated with carvedilol for up to 5.9 years (mean 4.5 years). Both in US clinical trials in mild-to-moderate heart failure that compared carvedilol in daily doses up to 100 mg (n = 765) to placebo (n = 437), and in a multinational clinical trial in severe heart failure (COPERNICUS) that compared carvedilol in daily doses up to 160 mg (n = 1,156) with placebo (n = 1,123), discontinuation rates for adverse experiences were similar in carvedilol and placebo patients. In placebo-controlled clinical trials, the only cause of discontinuation $\geq 1\%$ and occurring more often on carvedilol was dizziness (1.3% on carvedilol, 0.6% on placebo) in the COPERNICUS trial.

Table 1 shows adverse events reported in patients with mild-to-moderate heart failure enrolled in US placebo-controlled clinical trials, and with severe heart failure enrolled in the COPERNICUS trial. Shown are adverse events that occurred more frequently in drug-treated patients than placebo-treated patients with an incidence of $\geq 3\%$ in patients treated with carvedilol regardless of causality. Median study medication exposure was 6.3 months for both carvedilol and placebo patients in the trials of mild-to-moderate heart failure, and 4.5 months in the trial of severe heart failure patients. The adverse event profile of carvedilol observed in the long-term COMPELL study was generally similar to that observed in the US Heart Failure Trials.

Table 1. Adverse Events (% Discontinuation) Occurring More Frequently With Immediate-Release Carvedilol Than With Placebo in Patients With Mild-to-Moderate Heart Failure Enrolled in US Heart Failure Trials or in Patients With Severe Heart Failure in the COPERNICUS Trial (Incidence $\geq 3\%$ in Patients Treated With Carvedilol, Regardless of Causality)

	Mild-to-Moderate Heart Failure		Severe Heart Failure	
	Carvedilol (n = 765)	Placebo (n = 437)	Carvedilol (n = 1,156)	Placebo (n = 1,123)
Body as a Whole				
Asthenia	7	7	11	9
Fatigue	24	22	4	-
Upper limb increased	4	4	6	-
Edema generalized	3	3	6	5
Edema dependent	4	2	-	-
Cardiovascular				
Bruxism	9	1	10	3
Hypertension	9	3	14	8
SYNCOPE	3	3	6	5
Angina pectoris	3	3	6	5
Central Nervous System				
Dizziness	30	19	24	17
Headache	8	7	7	7
Gastrointestinal				
Diarrhea	12	6	5	3
Nausea	6	6	5	3
Vomiting	6	4	1	2
Metabolic				
Hypoglycemia	12	8	5	3
Weight increase	10	7	12	11
BUN increased	6	5	-	-
Hypercholesterolemia	4	3	1	-
Edema peripheral	2	1	7	6
Musculoskeletal				
Athralgia	6	5	1	1
Respiratory				
Cough increased	8	3	5	4
Rales	4	4	4	2
Vision				
Blurred abnormal	5	2	-	-

Cardiac failure and dyspnea were also reported in these studies, but the rates were equal or greater in patients who received placebo. The following adverse events were reported with a frequency of $\geq 1\%$ but $\leq 3\%$ and more frequently with carvedilol than either the US placebo-controlled trials in patients with mild-to-moderate heart failure, or in patients with severe heart failure in the COPERNICUS trial.

Incidence $\geq 1\%$ to $\leq 3\%$

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

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

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

Control and Peripheral Nervous System: Hypesthesia, vertigo, paresthesia.

Liver and Biliary System: SGPT increased, SGOT increased.

Musculoskeletal: Muscle cramps.

Nausea: Nausea increased.

Weight loss: Hypokalemia, creatinine increased.

Mesenteric Ischemia: Mesenteric ischemia.

Metabolic and Endocrine: Hypokalemia, hypotremia, increased alkaline phosphatase, glycosuria, hypervolemia, diabetes mellitus, GGT increased, weight loss, hypokalemia, creatinine increased.

Mesenteric Ischemia: Muscle cramps.

Neurological: Headache, dizziness, vertigo, paresthesia, hypotension, hypotremia, increased alkaline phosphatase, glycosuria, hypervolemia, diabetes mellitus, GGT increased, weight loss, hypokalemia, creatinine increased.

Psychiatric: Somnolence.

Reproductive, male: Impotence.

Respiratory: Cough increased.

Urinary System: Renal insufficiency, albuminuria, hematuria.

Left Ventricular Dysfunction Following Myocardial Infarction: The following information describes the safety experience in left ventricular dysfunction following acute myocardial infarction.

Carvedilol has been evaluated for safety in survivors of an acute myocardial infarction with left ventricular dysfunction in the CAPRICORN trial which involved 969 patients who received carvedilol and 980 who received placebo. Approximately 75% of the patients received carvedilol for at least 6 months and 55% received carvedilol for at least 12 months.

Patients were treated for an average of 12.9 months with carvedilol and placebo, respectively.

The most common adverse events reported with carvedilol in the CAPRICORN trial were consistent with the profile of the drug in the US heart failure trials and the COPERNICUS trial. The only additional adverse events reported in CAPRICORN $\geq 3\%$ of the patients and more commonly on carvedilol were dyspnea, anemia, and lung edema. The following adverse events, discontinuations were more common in the carvedilol group for postural hypotension (1% vs. 0). The overall incidence of adverse events in US placebo-controlled trials was found to increase with increasing dose of carvedilol. For individual adverse events this could only be distinguished for dizziness, which increased in frequency from 2% to 5% as total daily dose increased from 6.25 mg to 50 mg as single or divided doses.

Hypotension: COREG CR was evaluated for safety in an 8-week double-blind trial in 337 subjects with essential hypertension. The profile of adverse events observed with COREG CR was generally similar to that observed with immediate-release carvedilol. The overall rates of discontinuations due to adverse events were similar between COREG CR and placebo.

The following adverse events occurred more frequently in patients with essential hypertension who were treated with COREG CR, n = 253 (incidence $\geq 1\%$ in patients treated with carvedilol, regardless of causality) during this 8-week trial than in placebo-treated patients (n = 84), respectively: Nasopharyngitis (4% vs. 9%), dizziness (2% vs. 1%), nausea (2% vs. 1%), edema peripheral (2% vs. 1%), nasal congestion (1% vs. 0%), paresthesia (1% vs. 0%), sinus congestion (1% vs. 0%), diarrhea (1% vs. 0%), and insomnia (1% vs. 0%).

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

Carvedilol has been evaluated for safety in hypertension in more than 2,153 patients in US clinical trials and in 2,976 patients in international clinical trials. Approximately 36% of patients had mild to moderate severity. In US controlled clinical trials directly comparing carvedilol monotherapy in doses up to 50 mg (n = 1,142) to placebo (n = 462), 4.9% of carvedilol patients discontinued for adverse events vs. 5.2% of placebo patients. Although there was no overall difference in discontinuation rates, discontinuations were more common in the carvedilol group for postural hypotension (1% vs. 0). The overall incidence of adverse events in US placebo-controlled trials was found to increase with increasing dose of carvedilol. For individual adverse events this could only be distinguished for dizziness, which increased in frequency from 2% to 5% as total daily dose increased from 6.25 mg to 50 mg as single or divided doses.

The following adverse events occurred more frequently in patients with essential hypertension who were treated with COREG CR, n = 253 (incidence $\geq 1\%$ in patients treated with carvedilol, regardless of causality) during this 8-week trial than in placebo-treated patients (n = 84), respectively: Nasopharyngitis (4% vs. 9%),