

# Aspirin, NSAIDs Risky for Colorectal Ca Prevention

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Routine use of aspirin or non-steroidal anti-inflammatory drugs should not be recommended as preventive therapy for colorectal cancer in patients at average risk for the disease, according to a statement released by the U.S. Preventive Services Task Force.

The caution against prophylactic use of these agents applies to asymptomatic

adults, including those with a family history of colon cancer, but not to patients with a personal history of colon cancer or polyps, familial adenomatous polyposis, or hereditary nonpolyposis colon cancer syndromes, the statement specified (Ann. Intern. Med. 2007;146:361-4).

The USPSTF issued its recommendation based on literature reviews conducted by the Agency for Healthcare Research and Quality (AHRQ). These reviews evaluated the role of aspirin, NSAIDs, and cy-

clo-oxygenase-2 (COX-2) inhibitors for the primary prevention of colorectal cancer and colorectal adenoma. On the basis of the relevant literature published between 1996 and 2006, the USPSTF determined that “the harms outweigh the benefits of aspirin and NSAID use for the prevention of colorectal cancer.”

The literature reviews showed that aspirin, COX-2 inhibitors, and NSAIDs reduce the incidence of colonic adenomas and that aspirin and NSAIDs reduce the in-

cidence of colorectal cancer. However, these drugs were associated with adverse gastrointestinal outcomes and, in the case of COX-2 inhibitors, with important cardiovascular events.

But the USPSTF also said that clinicians should continue to discuss aspirin chemoprophylaxis in patients who are at increased risk for coronary heart disease, because there is “good evidence” that low-dose (less than 100 mg) aspirin therapy can reduce the risk of heart disease. ■

## Fatalism Tied to Lower Colorectal Screening Rates

HOUSTON — Barriers to early detection of colorectal cancer among underserved patients include limited access to care and fatalism beliefs about a cancer diagnosis, Aimee James, Ph.D., reported at the annual meeting of the American Society of Preventive Oncology.

“Fatalist views and myths were prevalent” in a focus-group study of 18 underserved patients. Such misconceptions included “the risk of ‘going under the knife,’ and dangers of exposing cancer to air,” said Dr. James, of the department of pre-



**‘Fatalist views and myths were prevalent’ in a focus-group study of 18 underserved patients.**

DR. JAMES

ventive medicine and public health, University of Kansas, Kansas City.

She and her associates interviewed patients at a federally funded community health center who volunteered to participate in focus group sessions. Most were unemployed, and 71% were uninsured. The study was funded by the American Cancer Society.

“Many said they knew nothing about colorectal cancer or expressed confusion about GI anatomy or what the tests might entail,” Dr. James said in an interview.

In regard to access to care, the main issues were not being able afford follow-up, not knowing where to go, or not having confidence in the care they would receive. Other barriers to early detection were negative attitudes about survival. “Some told us that surgery can cause cancer to spread, and they do believe that. The health care provider needs to address these belief systems,” Dr. James said.

Participants said that early detection improved outcomes, yet many doubted the effectiveness of treatment. As one patient put it, “When it’s time for you to go, I don’t care how many surgeries they do, how many pap smears you get, or how many times they scrape you clean, it’s time to go.”

—Carole Bullock

### BRIEF SUMMARY

#### 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 bronchial asthma (2 cases of death from status asthmaticus have been reported in patients receiving single doses of immediate-release carvedilol or related bronchodilators), 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 experienced 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: Patients with coronary artery disease, who are being treated with COREG CR, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with  $\beta$ -blockers. The last 2 complications may occur with or without preceding exacerbation of the angina pectoris. As with other  $\beta$ -blockers, the abrupt discontinuation of COREG CR in patients 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 unsuspected, 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:**  $\beta$ -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,  $\beta$ -blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonspecific  $\beta$ -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 Diabetic Control in Type 2 Diabetic Patients).

**Thyrotocosis:**  $\beta$ -adrenergic blockade may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of  $\beta$ -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, 9% of heart failure 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 receiving COREG CR in hypertension. However, if pulse rate drops below 50 beats/minute, the dosage of COREG CR should be reduced.

In clinical trials of primarily mild-to-moderate heart failure with immediate-release carvedilol, hypertension and postural hypotension occurred in 8.7% and 3.4% of patients receiving carvedilol, respectively, in this trial. Postural hypotension occurred in 12.8% of placebo patients, respectively. The risk for these events was highest during the first 30 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 (CAPRICORN), hypertension and postural hypotension occurred in 15.1% and 2.9% of heart failure patients receiving carvedilol compared to 8.7% and 2.3% of placebo patients, respectively. These events were a cause for discontinuation of therapy in 1.1% of carvedilol patients, compared to 0.6% 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 1.2% and 0.1% of hypertensive patients receiving immediate-release carvedilol, primarily following the initial dose or at the time of dose increase and was a cause for discontinuation of therapy in 1% of patients.

In the CAPRICORN study of survivors of an acute myocardial infarction with left ventricular dysfunction, hypertension or postural hypotension occurred in 20.2% of patients receiving carvedilol compared to 12.8% of placebo patients receiving immediate-release carvedilol, 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 daily for hypertensive patients with left ventricular dysfunction. Dose should 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), acute heart failure, advanced renal 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 such 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 episodes do not preclude subsequent successful titration of or a favorable response to COREG CR. In a placebo-controlled trial in 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 disease than to treatment with carvedilol.

In patients with pheochromocytoma, an  $\alpha$ -blocker agent should be initiated prior to the use of any  $\beta$ -blocker agent. Although carvedilol has both  $\alpha$ - and  $\beta$ -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  $\beta$ -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  $\alpha$ -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, carvedilol 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, Hypertensive Patients with Type 2 Diabetes Mellitus (GEMINI) in the full prescribing information).

**Risk of Anaphylactic Reaction:** While taking  $\beta$ -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 reaction.

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

In clinical trials 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 dosage 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 carvedilol therapy 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 sit or lie down when these symptoms of lowered blood pressure occur.
- If patients experience dizziness or fatigue, they should avoid driving or hazardous tasks.
- They should consult a physician if they experience dizziness or faintness, in case the dosage should be adjusted.
- They should not cough or be troubled by colds.
- They should take COREG CR with food.
- They should separate the use 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, Pharmacokinetic Drug-Drug Interactions in the full prescribing information.)

**Alcohol:** Concurrent 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 beverages that contain ethanol) 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:** Poor metabolizers of debrisoquine (inactivated by CYP2D6 [such as quinidine, fluoxetine, paroxetine, and propafenone]) have not been studied, but these drugs would be expected to increase the plasma concentration of carvedilol (see CLINICAL PHARMACOLOGY in the full prescribing information). Retrospective analysis of side effects in clinical trials showed that poor 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the  $\alpha$ -blocking P1 antagonist.

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

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

**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, there was also a decrease in total body weight at the maternally toxic dose (200 mg/kg/day) (50 times the MRHD as mg/m<sup>2</sup>), which was accompanied by an elevation in the frequency of fetuses with delayed skeletal development (missing or reduced 13th rib). In rats the no-observed-effect level for developmental toxicity was 60 mg/kg/day (10 times the MRHD as mg/m<sup>2</sup>) in rabbits it was 15 mg/kg/day (5 times the MRHD as mg/m<sup>2</sup>). There are no adequate and well-controlled studies in pregnant women. COREG CR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**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<sub>max</sub>.

**Calcium channel blockers:** Isolated cases of conduction disturbance (rarely with hemodynamic compromise) have been observed when carvedilol is co-administered with diltiazem. As with other agents with  $\beta$ -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  $\beta$ -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.

**Potassium Inhibitors:** There is no clinically meaningful increase in AUC and C<sub>max</sub> with concomitant administration of carvedilol extended-release capsules with pantoprazole.

**Cardiogenic, Metabolic, 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]) when compared on a mg/m<sup>2</sup> or a mg/kg basis (10 times the MRHD as mg/m<sup>2</sup>), carvedilol had no cardiogenic or metabolic effect.

Inhibitors of Fertility: 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 genotoxicity.

At doses  $\geq 200$  mg/kg/day ( $\geq 2$  times the MRHD as mg/m<sup>2</sup>) carvedilol was toxic to adult rats (reduction in body weight gain) and was associated with a reduced number of successful matings, prolonged mating time, significant delay in corpora lutea and implantation gain, 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<sup>2</sup>).

**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 200 mg/kg/day (10 times the MRHD as mg/m<sup>2</sup>) in rabbits at doses of 75 mg/kg/day (12 times the MRHD as mg/m<sup>2</sup>). In the rats, there was also a decrease in fetal body weight at the maternally toxic dose (200 mg/kg/day) (50 times the MRHD as mg/m<sup>2</sup>), which was accompanied by an elevation in the frequency of fetuses with delayed skeletal development (missing or reduced 13th rib). In rats the no-observed-effect level for developmental toxicity was 60 mg/kg/day (10 times the MRHD as mg/m<sup>2</sup>) in rabbits it was 15 mg/kg/day (5 times the MRHD as mg/m<sup>2</sup>). There are no adequate and well-controlled studies in pregnant women. COREG CR should be used during pregnancy only if the potential benefit 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  $\beta$ -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/m<sup>2</sup>) and above during the last trimester through day 22 of lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from  $\beta$ -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  $\alpha$ - and  $\beta$ -blocking agents have included pupal and neonatal distress.

**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 or older to determine whether they differ from younger patients.

The following information is available for trials with immediate-release carvedilol. Of the 765 patients with heart failure randomized to carvedilol in 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% (474) were 65 years of age or older, and 11.7% (116) were 75 years of age or older. In the CAPRICORN study of survivors of heart failure patients randomized to carvedilol in heart failure trials, 48% (468) were 65 years of age or older, and 11% (111) were 75 years of age or older. Of the 2,065 hypertensive 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, 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

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 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 65% 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 COMET trial, 1,511 patients with mild-to-moderate heart failure were treated with carvedilol for up to 5.9 years (mean 4.8 years). Both in US clinical trials in mild-to-moderate heart failure that compared carvedilol in daily doses up to 100 mg (n = 769) to placebo (n = 437), and in a multinational clinical trial in severe heart failure (CAPRICORN) that compared carvedilol in daily doses up to 50 mg (n = 1,156) with placebo (n = 1,133), 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 CAPRICORN 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 CAPRICORN 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 10.4 months for trial of severe heart failure patients. The adverse event profile of carvedilol observed in the long-term COMET study was generally similar to that observed in the US Heart Failure Trials.

**Table 1. Adverse Events (Regardless of Causality) Occurring More Frequently With Immediate-Release Carvedilol Than With Placebo in Patients With Mild-to-Moderate Heart Failure, Regardless of Causality**

	Mild-to-Moderate Heart Failure		Severe Heart Failure	
	Carvedilol (n = 765)	Placebo (n = 437)	Carvedilol (n = 1,156)	Placebo (n = 1,133)
<b>Body as a Whole</b>				
Asthma	7	7	11	9
Fatigue	24	22	7	1
Dizziness level increased	4	4	2	1
Edema generalized	5	5	6	5
Edema dependent	4	2	-	-
<b>Cardiovascular</b>				
Bradycardia	9	1	10	3
Hypertension	9	3	14	8
Postural hypotension	2	2	3	5
Angina pectoris	2	3	4	4
<b>Central Nervous System</b>				
Dizziness	32	19	24	17
Nausea	6	5	5	5
<b>Gastrointestinal</b>				
Diarrhea	12	6	5	3
Nausea	9	5	4	3
Vomiting	6	4	1	2
<b>Metabolic</b>				
Hypoglycemia	12	8	5	3
Weight increase	10	7	12	11
BUN increased	6	5	-	-
Na increased	6	5	-	-
<b>Neoplasms</b>				
Hypochlosterolemia	4	3	1	1
Edema peripheral	2	1	7	6
<b>Musculoskeletal</b>				
Athralgia	6	5	1	1
<b>Respiratory</b>				
Cough increased	8	3	5	4
Rhinitis	4	4	4	2
<b>Vision</b>				
Vision 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  $< 3\%$  and more frequently with carvedilol in either the US placebo-controlled trials in patients with mild-to-moderate heart failure, or in patients with severe heart failure in the CAPRICORN trial.

#### Incidence $\geq 1\%$ to $< 3\%$

**Body as a Whole:** Allergy, malaise, hypotolemia, fever, leg edema.  
**Cardiovascular:** Fluid overload, postural hypotension, aggravated angina pectoris, AV block, palpitation, hypertension.  
**Central and Peripheral Nervous System:** Hypesthesia, vertigo, paresthesia.  
**Diabetes and Nutrition:** Hypoglycemia, hypoglycemia, hypotremia, increased alkaline phosphatase, glycosuria, hypervolemia, diabetes mellitus, GGT increased, weight loss, hypokalemia, creatinine increased.  
**Musculoskeletal:** Muscle cramps.  
**Platelet, Bleeding and Clotting:** Prothrombin decreased, purpura, thrombocytopenia.  
**Psychiatric:** Somnolence.  
**Reproductive, male:** Impotence.  
**Special Senses:** Blurred vision.  
**Urology 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 with immediate-release carvedilol.

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 53% received carvedilol for at least 12 months. Patients were treated for an average of 12.8 months and 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 CAPRICORN trial. The only additional adverse events reported to CAPRICORN  $\geq 3\%$  of the patients and more commonly on carvedilol were dyspnea, anemia, and lung edema. The following adverse events were reported with a frequency of  $\geq 1\%$  but  $< 3\%$  and more frequently with carvedilol: flu syndrome, cardiovascular accident, peripheral vascular disorder, hypotonia, depression, gastrointestinal pain, arthritis, and gout. The overall rates of discontinuations due to adverse events were similar in both groups of patients. In this database, ischemia (2% vs. 1%), diarrhea (2% vs. 1%), thrombocytopenia (1% vs. 1%), hypotension (1% vs. 1%), and dizziness (1% vs. 1%) were the most frequent.

**Hypertension:** 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.

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