

Ranolazine Doesn't Need BP Reduction to Work

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SNOWMASS, COLO. A year-old drug believed to inhibit ischemia through a novel mechanism may prove useful for angina patients whose symptoms are not relieved by revascularization or other agents. Dr. C. Richard Conti said at a conference sponsored by the Society for Cardiovascular Angiography and Interventions.

Ranolazine, approved in early 2006, is

thought to block the late sodium current that results from a decreased oxygen supply to the heart, thereby reducing the sodium-dependent calcium overload that acts as a key player in the development of ischemia, explained Dr. Conti at the meeting, which was cosponsored by the American Academy of Cardiology.

It is the first major advance in antianginal therapy since calcium channel blockers, he noted.

Ranolazine's unusual mechanism trans-

lates into important clinical information, because its antianginal and anti-ischemic effects do not depend on reductions in heart rate or blood pressure.

"All of the other drugs do," said Dr. Conti, eminent scholar and professor of cardiology at the University of Florida, Gainesville.

In clinical trials, patients experienced mild changes in mean heart rate (less than 2 beats/min) and systolic blood pressure (less than 3 mm Hg). In patients with

severe renal impairment, ranolazine did increase blood pressure by 10-15 mm Hg, so "you need to be careful" and monitor blood pressure regularly.

Dr. Conti said the "important trial that everyone knows about" was the Combination Assessment of Ranolazine in Stable Angina (CARISA), in which ranolazine significantly improved exercise duration and angina onset at trough and peak dose, as well as reducing angina frequency by 36% and nitroglycerine use by 43%.

The more recent, less well known Efficacy of Ranolazine in Chronic Angina (ERICA) trial was launched at the behest of the FDA and conducted mostly in Eastern European countries.

Among 565 subjects who had a mean of more than 6 angina attacks per week at baseline, angina frequency was reduced to 3.3 attacks per week in those randomly assigned to receive 1,000 mg twice daily of ranolazine, compared with 4.3 in those receiving placebo, a 23% reduction in frequency over placebo. Patients in both groups received 10 mg of amlodipine daily and sublingual nitrates as needed.

The ERICA trial also found a 25% reduction in nitroglycerine use among ranolazine users, compared with those receiving placebo.

Dr. Conti pointed out that a dose-related increase in QT intervals has been observed in patients taking ranolazine: "Not way up, but they go up."

In the ERICA trial, the mean change in QT intervals, in milliseconds, was -2.3 in patients taking placebo, 1.9 in patients taking 500 mg twice-daily ranolazine, and 5.4 in those taking 1,000 mg twice-daily ranolazine, with standard deviations of 15.6, 20.6, and 14.7, respectively.

"I suspect that if you go to 1,500 or 2,000 mg twice daily, it'll even go further," he said, adding that he does not believe doses higher than 1,000 mg twice daily should be used.

No incidents of torsades de pointes-type arrhythmias have been reported in patients taking ranolazine, but the grave complication that has been associated with other drugs that prolong the QT interval, and the same could occur with ranolazine.

Dr. Conti reserves the agent for patients who have not achieved adequate symptom control with other drugs, and he obtains baseline and follow-up electrocardiograms.

"How often? I think it's a matter of clinical judgment," he said.

Another important point is that ranolazine is metabolized by CYP3A, contraindicating its use with other drugs that are potent or moderately potent inhibitors of that enzyme, including diltiazem, verapamil, ketoconazole and other azole antifungals, macrolide antibiotics, HIV protease inhibitors, and grapefruit products.

For the same reason, doses of simvastatin, digoxin, and drugs that are mainly metabolized by CYP2D6 may need to be reduced if given to patients also taking ranolazine, said Dr. Conti.

Dr. Conti disclosed that he serves on the speakers' bureau for CV Therapeutics, maker of ranolazine, marketed under the name Ranexa.

CORE CR™ (carvedilol phosphate) Extended-Release Capsules

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

CONTRAINDICATIONS

CORE CR is contraindicated in patients with bronchial asthma (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 cardiac shock or who have decompensated heart failure requiring the use of intravenous inotropic therapy. Such patients should be first weaned from intravenous therapy before initiating CORE CR.

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

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

WARNINGS

Cessation of Therapy with CORE CR: Patients with coronary artery disease, who are being treated with CORE 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 β -blockers. The least 2 complications may occur with or without preceding exacerbation of the angina pectoris. As with other β -blockers, when discontinuation of CORE CR is planned, the patients should be carefully monitored and advised to limit physical activity to a minimum. CORE CR should be discontinued over 1 to 2 weeks whenever possible. If the angina worsens or acute coronary insufficiency develops, it is recommended that CORE CR be discontinued at least 2 months before starting another anty-ischemic therapy. Because severe angina may be unresponsive, it may be prudent not to discontinue CORE 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 CORE CR is to be continued preoperatively, 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. Nonspecific 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 thyrotoxicosis, such as tachycardia. Abrupt withdrawal of β -blockade may be followed by an exacerbation of the symptoms of thyrotoxicosis or may precipitate thyrotoxic storm.

PRECAUTIONS

General: In clinical trials of CORE 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 CORE CR as well as immediate-release carvedilol.

In clinical trials with immediate-release carvedilol, hypertension was reported in about 2% of hypertensive patients, 3% of heart failure patients, and 6.5% of myocardial infarction patients with left ventricular dysfunction. Bradycardia was reported in 0.5% of patients receiving CORE 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 CORE CR in hypertension. However, if pulse rate drops below 55 beats/minute, the dosage of CORE CR should be reduced.

In clinical trials of primarily mild-to-moderate heart failure with immediate-release carvedilol, hypertension and postural hypertension occurred in 9.7% and syncope in 3.4% of patients receiving carvedilol compared to 3.6% and 2.5% 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 (CORE CR), hypertension and postural hypertension occurred in 15.1% and syncope in 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 0.8% of placebo patients.

In the clinical trial of CORE CR in hypertensive patients, syncope was reported in 0.3% of patients receiving CORE CR compared to 0% of patients receiving placebo. There were no reports of postural hypertension in this trial. Postural hypertension occurred in 1.8% 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 hypertension occurred in 20.2% of patients receiving carvedilol compared to 12.9% 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 1.2% of placebo patients.

To decrease the likelihood of syncope or excessive hypotension, treatment with CORE CR should be initiated with 10 mg once daily for heart failure patients, and at 20 mg once daily for hypertensive patients and 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 CORE 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 CORE CR should not be advanced until clinically stable (see DOSAGE AND ADMINISTRATION in the full prescribing information). Occasionally it is necessary to lower the dose of CORE CR or temporarily discontinue it. Such episodes do not preclude subsequent successful titration, or a favorable response to CORE CR. In a placebo-controlled trial of patients with severe heart failure, worsening heart failure was reported to a similar degree with immediate-release carvedilol and placebo. When treatment with immediate-release carvedilol was discontinued, the clinical course was similar to that of placebo. Worsening heart failure observed during long-term therapy is more likely to be related to the patients' underlying disease than to treatment with carvedilol.

In patients with phlebotomy, an ex-Blocker agent should be initiated prior to the use of any β -blocking agent. Although carvedilol has both α_1 - and β -blocking pharmacologic activities, it has been an 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 ex-Blocker activity may prevent such symptoms. However, caution should be taken in the administration of CORE 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 hyperglycemia, which responds to intensification of hypoglycemic therapy. It is recommended that blood glucose be monitored when dosing with CORE 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 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 reaction.

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema): Patients with bronchospastic disease should, in general, not receive β -blockers. 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 in that they did not require oral or inhaled medication to treat their bronchospastic disease. In such patients, it is recommended that CORE 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 of carvedilol.

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

- They should not interrupt or discontinue using CORE 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 and increasing shortness of breath.
- They may experience adverse effects of hypotension when standing, such as dizziness, lightheadedness, fainting, fatigue, or weakness. Patients should be cautioned 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 crush or chew CORE CR capsules.
- They should take CORE CR with food.
- They should separate the administration of CORE 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 difficulty in removing their lenses.

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

Alcohol: Concomitant administration of CORE CR with alcohol may affect the modified release properties of CORE 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 CORE CR with alcohol (including beverages and over-the-counter medications that contain alcohol) should be separated by at least 2 hours. CORE CR should be taken in the morning with food. (See DOSAGE AND ADMINISTRATION in the full prescribing information.)

Inhibitors of CYP2D6: poor metabolizers of cisprindolol. Interactions of carvedilol with strong inhibitors of CYP2D6 (such as quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would be expected to increase blood levels of the R(-) enantiomer 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 α_1 -blocking R(-) 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 for signs of hypotension and 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.

Cyclosporine: Modest increases in mean trough cyclosporine 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 cyclosporine had to be reduced in order to maintain cyclosporine concentrations within the therapeutic range, while in the remainder no adjustment was needed. On the average for the group, the dose of cyclosporine was reduced about 20% in these patients. Due to wide interindividual variability in the dose adjustment required, it is recommended that cyclosporine concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporine 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 or discontinuing CORE 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 disturbance (rarely with hemodynamic compromise) have been observed when carvedilol is co-administered with diltiazem. As with other agents with β -blocking properties, if CORE 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.

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

Contraception, Menstruation, 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/m² basis) or in 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/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/m²) 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/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 (12 times the MRHD as mg/m²). In the rats, there was also a decrease in fetal body weight at the maternal dose of 300 mg/kg/day (50 times the MRHD as mg/m²) and a decrease 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 (2.5 times the MRHD as mg/m²). There is no adequate and well-controlled studies in pregnant women. CORE CR should be used during pregnancy only if the potential benefits justify the potential risks to the fetus.

Nursing Mothers: It is not known whether CORE CR 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. It 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) or 300 mg/kg/day (50 times the MRHD as mg/m²) and in their pups at 22 days of age. It has not been established.

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 65 years of age or older to determine whether they respond differently 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 US clinical trials, 31% (235) were 65 years of age or older, and 7.2% (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% (547) were 65 years of age or older, and 11% (127) were 75 years of age or older. Of the 975 myocardial infarction 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 2,053 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 3,722 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 elderly and younger 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, and 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 CORE CR or immediate-release carvedilol are provided below. Excluded are adverse events considered to 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). CORE CR has been evaluated for safety in a 4-week (2 weeks of immediate-release carvedilol and 2 weeks of CORE CR) clinical study (n = 187) which included 150 patients with mild-to-moderate, or severe chronic heart failure and 30 patients with left ventricular dysfunction following acute myocardial infarction. The profile of adverse events observed with CORE 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 CORE 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 60% 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 5.3 years (mean 4.8 years). Both in US clinical trials in mild-to-moderate heart failure that compared carvedilol to daily doses up to 100 mg (n = 765) to placebo (n = 437) and in a multinational clinical trial in severe heart failure (CORENICUS) 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 >1%, and occurring more often on carvedilol was dizziness (1.3% on carvedilol, 0.6% on placebo in the CORENICUS 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 CORENICUS 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 in the 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 (All Occurrences) 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 CORENICUS 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 = 1,133)
Body as a Whole				
Asthenia	7	7	11	9
Fatigue	24	22	-	-
Dignon level increased	5	4	2	1
Edema dependent	4	2	5	5
Edema independent	4	2	5	5
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	5
Gastrointestinal				
Diarrhea	12	6	5	3
Nausea	9	5	4	3
Vomiting	6	4	1	2
Metabolic				
Hypoglycemia	12	8	5	3
Weight increase	10	7	12	11
BUN increased	6	5	-	-
BUN decreased	4	3	-	-
Hypochlosterolemia	4	3	1	1
Edema peripheral	2	1	7	6
Musculoskeletal				
Arthralgia	6	5	1	1
Respiratory				
Cough increased	8	9	5	4
Cough decreased	4	4	4	2
Vision				
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 CORENICUS 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: Hyposthesia, vertigo, paraesthesia.

Gastrointestinal: Melena, periodontitis.

Liver and Biliary System: SGPT increased, SGOT increased.

Metabolic and Nutritional: Hypocarnemia, hypoglycemia, hypoproteinemia, increased alkaline phosphatase, glycosuria, hypervolemia, diabetes mellitus, GGT increased, weight loss, hyperkalemia, creatinine increased.

Musculoskeletal: Muscle cramps.

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

Psychiatric: Somnolence.

Special Senses: Blurred vision.

Urnary 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 12.9 months and