HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Carvedilol Phosphate Extended-release Capsules safely and effectively. See full prescribing information for Carvedilol Phosphate Extended-release Capsules.

Carvedilol Phosphate Extended-release Capsules
Initial U.S. Approval: 1995

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, Major Surgery (5.9)	October 2010
Warnings and Precautions, Intraoperative Floppy Iris Syndrome (5.14)	January 2011

----------INDICATIONS AND USAGE----------

Carvedilol Phosphate Extended-release Capsules are an alpha/beta-adrenergic blocking agent indicated for the treatment of:

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

---------- DOSAGE AND ADMINISTRATION ----------

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

- Heart failure: Start at 10 mg once daily and increase to 20, 40, and then 80 mg once daily over intervals of at least 2 weeks. Maintain lower doses if higher doses are not tolerated. (2.1)
- Left ventricular dysfunction following myocardial infarction: Start at 20 mg once daily and increase to 40 mg then 80 mg once daily after intervals of 3 to 10 days. A lower starting dose or slower titration may be used. (2.2)
- Hypertension: Start at 20 mg once daily and increase if needed for blood pressure control to 40 mg then 80 mg once daily over intervals of 1 to 2 weeks. (2.3)
- Elderly patients (> 65 years of age): When switching from higher doses of immediate-release carvedilol tablets to Carvedilol Phosphate Extended-release Capsules, a lower starting dose should be considered to reduce the risk of hypotension and syncope. (2.5)

---------- DOSAGE FORMS AND STRENGTHS ----------

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

----------CONTRAINDICATIONS----------

- Bronchial asthma or related bronchospastic conditions (4)
- Second- or third-degree AV block (4)
- Sick sinus syndrome (4)
- Severe bradycardia (unless permanent pacemaker in place) (4)
- Patients in cardiogenic shock or decompensated heart failure requiring the use of IV inotropic therapy. (4)
- Severe hepatic impairment (2.4, 4)
- History of serious hypersensitivity reaction (e.g., Stevens-Johnson syndrome, anaphylactic reaction, angioedema) to carvedilol or any of the components of Carvedilol Phosphate Extended-release Capsules. (4)

---------- WARNINGS AND PRECAUTIONS ----------

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

---------- ADVERSE REACTIONS ----------

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Apotex Corp. at 1-800-667-4708 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

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

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

Revised: July 2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Heart Failure

Carvedilol Phosphate Extended-release Capsules are indicated for the treatment of mild-to-severe chronic heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitors, and digitalis, to increase survival and, also, to reduce the risk of hospitalization *[see Clinical Studies (14.1)]*.

1.2 Left Ventricular Dysfunction Following Myocardial Infarction

Carvedilol Phosphate Extended-release Capsules are indicated to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of ≤40% (with or without symptomatic heart failure) *[see Clinical Studies (14.2)]*.

1.3 Hypertension

Carvedilol Phosphate Extended-release Capsules are indicated for the management of essential hypertension *[see Clinical Studies (14.3, 14.4)]*. They can be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics *[see Drug Interactions (7.2)]*.

2 DOSAGE AND ADMINISTRATION

Carvedilol Phosphate Extended-release Capsules are intended for once-daily administration. Patients controlled with immediate-release carvedilol tablets alone or in combination with other medications may be switched to Carvedilol Phosphate Extended-release Capsules based on the total daily doses shown in Table 1.

Table 1. Dosing Conversion

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

Carvedilol Phosphate Extended-release Capsules should be taken once daily in the morning with food. Carvedilol Phosphate Extended-release should be swallowed as a whole capsule. A Carvedilol Phosphate Extended-release Capsule and/or its contents should not be crushed, chewed, or taken in divided doses.

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

2.1 Heart Failure

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

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

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

The dose of Carvedilol Phosphate Extended-release Capsules should be reduced if patients experience bradycardia (heart rate <55 beats/minute).

Episodes of dizziness or fluid retention during initiation of Carvedilol Phosphate Extended-release Capsules can generally be managed without discontinuation of treatment and do not preclude subsequent successful titration of, or a favorable response to, Carvedilol Phosphate Extended-release Capsules.

2.2 Left Ventricular Dysfunction Following Myocardial Infarction

DOSAGE MUST BE INDIVIDUALIZED AND MONITORED DURING UP-TITRATION. Treatment with Carvedilol Phosphate Extended-release Capsules may be started as an inpatient or outpatient and should be started after the patient is hemodynamically stable and fluid retention has been minimized. It is recommended that Carvedilol Phosphate Extended-release Capsules be started at 20 mg once daily and increased after 3 to 10 days, based on tolerability, to 40 mg once daily, then again to the target dose of 80 mg once daily. A lower

starting dose may be used (10 mg once daily) and/or the rate of up-titration may be slowed if clinically indicated (e.g., due to low blood pressure or heart rate, or fluid retention). Patients should be maintained on lower doses if higher doses are not tolerated. The recommended dosing regimen need not be altered in patients who received treatment with an IV or oral β-blocker during the acute phase of the myocardial infarction.

2.3 Hypertension

DOSAGE MUST BE INDIVIDUALIZED. The recommended starting dose of Carvedilol Phosphate Extended-release Capsules is 20 mg once daily. If this dose is tolerated, using standing systolic pressure measured about one hour after dosing as a guide, the dose should be maintained for 7 to 14 days, and then increased to 40 mg once daily if needed, based on trough blood pressure, again using standing systolic pressure one hour after dosing as a guide for tolerance. This dose should also be maintained for 7 to 14 days and can then be adjusted upward to 80 mg once daily if tolerated and needed. Although not specifically studied, it is anticipated the full antihypertensive effect of Carvedilol Phosphate Extended-release Capsules would be seen within 7 to 14 days as had been demonstrated with immediate-release carvedilol. Total daily dose should not exceed 80 mg.

Concomitant administration with a diuretic can be expected to produce additive effects and exaggerate the orthostatic component of Carvedilol Phosphate Extended-release action.

2.4 Hepatic Impairment

Carvedilol Phosphate Extended-release Capsules should not be given to patients with severe hepatic impairment *[see Contraindications (4)]*.

2.5 Geriatric Use

When switching elderly patients (65 years of age or older) who are taking the higher doses of immediate-release carvedilol tablets (25 mg twice daily) to Carvedilol Phosphate Extended-release Capsules, a lower starting dose (40 mg) of Carvedilol Phosphate Extended-release Capsules is recommended to minimize the potential for dizziness, syncope, or hypotension *[see Dosage and Administration (2)]*. Patients who have switched and who tolerate Carvedilol Phosphate Extended-release Capsules should, as appropriate, have their dose increased after an interval of at least 2 weeks *[see Use in Specific Populations (8.5)]*.

3 DOSAGE FORMS AND STRENGTHS

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

- 10 mg – white and green capsule shell printed with GSK COREG CR and 10 mg
- 20 mg – white and yellow capsule shell printed with GSK COREG CR and 20 mg
- 40 mg – yellow and green capsule shell printed with GSK COREG CR and 40 mg
- 80 mg – white capsule shell printed with GSK COREG CR and 80 mg

4 CONTRAINDICATIONS

Carvedilol Phosphate Extended-release Capsules are contraindicated in the following conditions:

- Bronchial asthma or related bronchospastic conditions. Deaths from status asthmaticus have been reported following single doses of immediate-release carvedilol.
- Second- or third-degree AV block
- Sick sinus syndrome
- Severe bradycardia (unless a permanent pacemaker is in place)
- Patients with cardiogenic shock or who have decompensated heart failure requiring the use of intravenous inotropic therapy. Such patients should first be weaned from intravenous therapy before initiating Carvedilol Phosphate Extended-release Capsules.
- Patients with severe hepatic impairment
- Patients with a history of a serious hypersensitivity reaction (e.g., Stevens-Johnson syndrome, anaphylactic reaction, angioedema) to carvedilol or any of the components of Carvedilol Phosphate Extended-release Capsules.

5 WARNINGS AND PRECAUTIONS

In clinical trials of Carvedilol Phosphate Extended-release Capsules 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 Carvedilol Phosphate Extended-release Capsules as well as immediate-release carvedilol tablets.

5.1 Cessation of Therapy

Patients with coronary artery disease, who are being treated with Carvedilol Phosphate Extended-release Capsules, 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 last 2 complications may occur with or without preceding exacerbation of the angina pectoris. As with other β-blockers, when discontinuation of Carvedilol Phosphate Extended-release Capsules is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. Carvedilol Phosphate Extended-release Capsules should be discontinued over 1 to 2 weeks whenever possible. If the angina worsens or acute coronary insufficiency develops, it is recommended that Carvedilol Phosphate Extended-release Capsules be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue therapy with Carvedilol Phosphate Extended-release Capsules abruptly even in patients treated only for hypertension or heart failure.

5.2 Bradycardia

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

Carvedilol Phosphate Extended-release Capsules 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 Carvedilol Phosphate Extended-release Capsules in hypertension. However, if pulse rate drops below 55 beats/minute, the dosage of Carvedilol Phosphate Extended-release Capsules should be reduced.

5.3 Hypotension

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 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 (COPERNICUS), hypotension and postural hypotension 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 a trial comparing heart failure patients switched to Carvedilol Phosphate Extended-release Capsules or maintained on immediate-release carvedilol tablets, there was a 2-fold increase in the combined incidence of hypotension, syncope or dizziness in elderly patients (> 65 years) switched from the highest dose of immediate-release carvedilol (25 mg twice daily) to Carvedilol Phosphate Extended-release 80 mg once daily *[see Dosage and Administration (2), Use in Specific Populations (8.5)]*.

In the clinical trial of Carvedilol Phosphate Extended-release Capsules in hypertensive patients, syncope was reported in 0.3% of patients receiving Carvedilol Phosphate Extended-release Capsules 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 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, 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.

Starting with a low dose, administration with food, and gradual up-titration should decrease the likelihood of syncope or excessive hypotension *[see Dosage and Administration (2.1, 2.2, 2.3)]*. 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.

5.4 Heart Failure/Fluid Retention

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 Carvedilol Phosphate Extended-release Capsules should not be advanced until clinical stability resumes *[see Dosage*

and Administration (2)]. Occasionally it is necessary to lower the dose of Carvedilol Phosphate Extended-release Capsules or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of, or a favorable response to, Carvedilol Phosphate Extended-release Capsules. 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 patients' underlying disease than to treatment with carvedilol.

5.5 Nonallergic Bronchospasm

Patients with bronchospastic disease (e.g., chronic bronchitis and emphysema) should, in general, not receive β-blockers. Carvedilol Phosphate Extended-release Capsules may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if Carvedilol Phosphate Extended-release Capsules are 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 Carvedilol Phosphate Extended-release Capsules 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.

5.6 Glycemic Control in Type 2 Diabetes

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 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 Carvedilol Phosphate Extended-release Capsules 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 Studies (14.4)]*.

5.7 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.

5.8 Deterioration of Renal Function

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 Carvedilol Phosphate Extended-release and the drug discontinued or dosage reduced if worsening of renal function occurs.

5.9 Major Surgery

Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

5.10 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.

5.11 Pheochromocytoma

In patients with pheochromocytoma, an α-blocking 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.

5.12 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 Carvedilol Phosphate Extended-release Capsules to patients suspected of having Prinzmetal's variant angina.

5.13 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.

5.14 Intraoperative Floppy Iris Syndrome

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in some patients treated with alpha-1 blockers (Carvedilol Phosphate Extended-release Capsules are an alpha/beta blocker). This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phacoemulsification incisions. The patient's ophthalmologist should be prepared for possible modifications to the surgical technique, such as utilization of iris

hooks, iris dilator rings, or viscoelastic substances. There does not appear to be a benefit of stopping alpha-1 blocker therapy prior to cataract surgery.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Carvedilol has been evaluated for safety in patients with heart failure (mild, moderate, and severe), 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 Carvedilol Phosphate Extended-release Capsules or immediate-release carvedilol tablets 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). Carvedilol Phosphate Extended-release has been evaluated for safety in a 4-week (2 weeks of immediate-release carvedilol tablets and 2 weeks of Carvedilol Phosphate Extended-release Capsules) clinical study (n = 187) 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 Carvedilol Phosphate Extended-release Capsules in this small, short-term study was generally similar to that observed with immediate-release carvedilol tablets. Differences in safety would not be expected based on the similarity in plasma levels for Carvedilol Phosphate Extended-release 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 5.9 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 = 765) to placebo (n = 437), and in a multinational clinical trial in severe heart failure (COPERNICUS) 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 COPERNICUS trial).

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

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

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 >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 COPERNICUS trial.

Incidence >1% to ≤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.

Gastrointestinal: Melena, periodontitis.

Liver and Biliary System: SGPT increased, SGOT increased.

Metabolic and Nutritional: Hyperuricemia, hypoglycemia, hyponatremia, 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.

Reproductive, male: Impotence.

Special Senses: Blurred vision.

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 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 12.8 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 in >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 >1% but ≤3% and more frequently with carvedilol: Flu syndrome, cerebrovascular 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, the only cause of discontinuation >1%, and occurring more often on carvedilol was hypotension (1.5% on carvedilol, 0.2% on placebo).

Hypertension: Carvedilol Phosphate Extended-release Capsules were evaluated for safety in an 8-week double-blind trial in 337 subjects with essential hypertension. The profile of adverse events observed with Carvedilol Phosphate Extended-release Capsules was generally similar to that observed with immediate-release carvedilol tablets. The overall rates of

discontinuations due to adverse events were similar between Carvedilol Phosphate Extended-release Capsules and placebo.

Table 3. Adverse Events (%) Occurring More Frequently With Carvedilol Phosphate Extended-release Capsules Than With Placebo in Patients With Hypertension (Incidence ≥1% in Patients Treated With Carvedilol, Regardless of Causality)

	Carvedilol Phosphate Extended-release (n = 253)	Placebo (n = 84)
Nasopharyngitis	4	0
Dizziness	2	1
Nausea	2	0
Edema peripheral	2	1
Nasal congestion	1	0
Paresthesia	1	0
Sinus congestion	1	0
Diarrhea	1	0
Insomnia	1	0

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

Carvedilol has been evaluated for safety in hypertension in more than 2,193 patients in US clinical trials and in 2,976 patients in international clinical trials. Approximately 36% of the total treated population received carvedilol for at least 6 months. In general, carvedilol was well tolerated at doses up to 50 mg daily. Most adverse events reported during carvedilol therapy were of 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 versus 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% versus 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.

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

Table 4. Adverse Events (% Occurrence) in US Placebo-Controlled Hypertension Trials With Immediate-Release Carvedilol Tablets (Incidence ≥1% in Patients Treated With Carvedilol, Regardless of Causality)[*]

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

[*] Shown are events with rate >1% rounded to nearest integer.

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

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

Incidence >0.1% to ≤1%

Cardiovascular: Peripheral ischemia, tachycardia.

Central and Peripheral Nervous System: Hypokinesia.

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

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

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

Reproductive, male: Decreased libido.

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

Special Senses: Tinnitus.

Urinary System: Micturition frequency increased.

Autonomic Nervous System: Dry mouth, sweating increased.

Metabolic and Nutritional: Hypokalemia, hypertriglyceridemia.

Hematologic: Anemia, leukopenia.

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

6.2 Laboratory Abnormalities

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

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

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of immediate-release carvedilol tablets or Carvedilol Phosphate Extended-release Capsules. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Aplastic anemia.

Immune System Disorders: Hypersensitivity (e.g., anaphylactic reactions, angioedema, urticaria).

Renal and Urinary Disorders: Urinary incontinence.

Respiratory, Thoracic and Mediastinal Disorders: Interstitial pneumonitis.

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme.

7 DRUG INTERACTIONS

7.1 CYP2D6 Inhibitors and Poor Metabolizers

Interactions of carvedilol with potent inhibitors of CYP2D6 isoenzyme (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 (12.3)]*. 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-blocking R(+) enantiomer.

7.2 Hypotensive 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 observed closely for signs of hypotension and/or severe bradycardia.

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.

7.3 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.

7.4 Digitalis Glycosides

Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Therefore, increased monitoring of digoxin is recommended when initiating, adjusting, or discontinuing Carvedilol Phosphate Extended-release Capsules *[see Clinical Pharmacology (12.5)]*.

7.5 Inducers/Inhibitors of Hepatic Metabolism

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

7.6 Amiodarone

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

7.7 Calcium Channel Blockers

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

Carvedilol Phosphate Extended-release Capsules are to be administered orally with calcium channel blockers of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored.

7.8 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 *[see Warnings and Precautions (5.6)]*.

7.9 Proton Pump Inhibitors

There is no clinically meaningful increase in AUC and C_{max} with concomitant administration of Carvedilol Phosphate Extended-release Capsules with pantoprazole.

7.10 Anesthesia

If treatment with Carvedilol Phosphate Extended-release Capsules 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 (10)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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 maximum recommended human dose [MRHD] as mg/m^2) and in rabbits at doses of 75 mg/kg/day (25 times the MRHD as mg/m^2). 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/m^2), which 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/m^2); in rabbits it was 15 mg/kg/day (5 times the MRHD as mg/m^2). There are no adequate and well-controlled studies in pregnant women. Carvedilol Phosphate Extended-release Capsules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 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/m^2) 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 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 α- and β-blocking agents have included perinatal and neonatal distress.

8.4 Pediatric Use

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

In a double-blind trial, 161 children (mean age 6 years, range 2 months to 17 years; 45% younger than 2 years old) with chronic heart failure [NYHA class II-IV, left ventricular ejection fraction <40% for children with a systemic left ventricle (LV), and moderate-severe ventricular dysfunction qualitatively by echo for those with a systemic ventricle that was not an LV] who were receiving standard background treatment were randomized to placebo or to 2 dose levels of carvedilol. These dose levels produced placebo-corrected heart rate reduction of 4-6 heart beats per minute, indicative of β-blockade activity. Exposure appeared to be lower in pediatric subjects than adults. After 8 months of follow-up, there was no significant effect of treatment on clinical outcomes. Adverse reactions in this trial that occurred in greater than 10% of patients treated with immediate-release carvedilol and at twice the rate of placebo-treated patients included chest pain (17% versus 6%), dizziness (13% versus 2%), and dyspnea (11% versus 0%).

8.5 Geriatric Use

The initial clinical studies of Carvedilol Phosphate Extended-release Capsules 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.

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

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 7.3% (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% (547) were 65 years of age or older, and 15% (174) were 75 years of age or older. Of 3,025 patients receiving carvedilol in heart failure trials worldwide, 42% were 65 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 2,065 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 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 versus 6% in younger patients), no overall differences in the safety or effectiveness (see Figures 2 and 4) 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.

10 OVERDOSAGE

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

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

for excessive bradycardia: atropine, 2 mg IV.

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

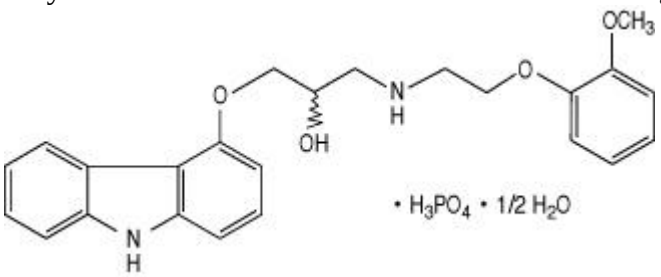
If peripheral vasodilation dominates, it may be necessary to administer adrenaline or noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant bradycardia, pacemaker therapy should be performed. For bronchospasm, β-sympathomimetics (as aerosol or IV) or aminophylline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

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

There is no experience of overdosage with Carvedilol Phosphate Extended-release Capsules. Cases of overdosage with carvedilol alone or in combination with other drugs have been reported. Quantities ingested in some cases exceeded 1,000 milligrams. Symptoms experienced included low blood pressure and heart rate. Standard supportive treatment was provided and individuals recovered.

11 DESCRIPTION

Carvedilol phosphate is a nonselective β-adrenergic blocking agent with α_1-blocking activity. It is (2*RS*)-1-(9*H*-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol phosphate salt (1:1) hemihydrate. It is a racemic mixture with the following structure:



Carvedilol phosphate is a white to almost-white solid with a molecular weight of 513.5 (406.5 carvedilol free base) and a molecular formula of $C_{24}H_{26}N_2O_4 \bullet H_3PO_4 \bullet 1/2\ H_2O$.

Carvedilol Phosphate is available for once-a-day administration as Extended-release oral capsules containing 10, 20, 40, or 80 mg carvedilol phosphate. Carvedilol Phosphate Extended-release hard gelatin capsules are filled with carvedilol phosphate immediate-release and extended-release microparticles that are drug-layered and then coated with methacrylic acid copolymers. Inactive ingredients include crospovidone, hydrogenated castor oil, hydrogenated vegetable oil, magnesium stearate, methacrylic acid copolymers, microcrystalline cellulose, and povidone.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Carvedilol is a racemic mixture in which nonselective β-adrenoreceptor blocking activity is present in the S(-) enantiomer and α_1-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency. Carvedilol has no intrinsic sympathomimetic activity.

12.2 Pharmacodynamics

Heart Failure and Left Ventricular Dysfunction Following Myocardial Infarction: The basis for the beneficial effects of carvedilol in patients with heart failure and in patients with left ventricular dysfunction following an acute myocardial infarction is not known. The concentration-response relationship for β_1-blockade following administration of Carvedilol Phosphate Extended-release Capsules is equivalent (±20%) to immediate-release carvedilol tablets.

Hypertension: The mechanism by which β-blockade produces an antihypertensive effect has not been established.

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

α_1-adrenoreceptor blocking activity has been demonstrated in human and animal studies, showing that carvedilol (1) attenuates the pressor effects of phenylephrine; (2) causes vasodilation; and (3) reduces peripheral vascular resistance. These effects contribute to the reduction of blood pressure and usually are seen within 30 minutes of drug administration.

Due to the α_1-receptor blocking activity of carvedilol, blood pressure is lowered more in the standing than in the supine position, and symptoms of postural hypotension (1.8%), including rare instances of syncope, can occur. Following oral administration, when postural hypotension has occurred, it has been transient and is uncommon when immediate-release carvedilol is administered with food at the recommended starting dose and titration increments are closely followed *[see Dosage and Administration (2)]*.

In a randomized, double-blind, placebo-controlled trial, the β_1-blocking effect of Carvedilol Phosphate Extended-release Capsules, as measured by heart rate response to submaximal bicycle ergometry, was shown to be equivalent to that observed with immediate-release carvedilol tablets at steady state in adult patients with essential hypertension.

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

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

12.3 Pharmacokinetics

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

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

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

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

Metabolism and Excretion: Carvedilol is extensively metabolized. Following oral administration of radiolabelled carvedilol to healthy volunteers, carvedilol accounted for only about 7% of the total radioactivity in plasma as measured by AUC. Less than 2% of the dose was excreted unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile

into the feces. Demethylation and hydroxylation at the phenol ring produce 3 active metabolites with β-receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol for β-blockade.

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

Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R(+)-carvedilol approximately 2 to 3 times higher than S(-)-carvedilol following oral administration of Carvedilol Phosphate Extended-release Capsules in healthy subjects. Apparent clearance is 90 L/h and 213 L/h for R(+)- and S(-)-carvedilol, respectively.

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

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

12.4 Specific Populations

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

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

Hypertension: For corresponding dose levels *[see Dosage and Administration (2)]*, the pharmacokinetics (AUC, C_{max}, and trough concentrations) observed with administration of Carvedilol Phosphate Extended-release Capsules were equivalent (±20%) to those observed with immediate-release carvedilol tablets following repeat dosing in patients with essential hypertension.

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

Hepatic Impairment: No studies have been performed with Carvedilol Phosphate Extended-release Capsules in patients with hepatic impairment. Compared to healthy subjects, patients with severe liver impairment (cirrhosis) exhibit a 4- to 7-fold increase in carvedilol levels. Carvedilol is contraindicated in patients with severe liver impairment.

Renal Impairment: No studies have been performed with Carvedilol Phosphate Extended-release Capsules in patients with renal impairment. Although carvedilol is metabolized primarily by the liver, plasma concentrations of carvedilol have been reported to be increased in patients with renal impairment after dosing with immediate-release carvedilol. Based on mean AUC data, approximately 40% to 50% higher plasma concentrations of carvedilol were observed in hypertensive patients with moderate to severe renal impairment compared to a control group of hypertensive patients with normal renal function. However, the ranges of AUC values were similar for both groups. Changes in mean peak plasma levels were less pronounced, approximately 12% to 26% higher in patients with impaired renal function.

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

12.5 Drug-Drug Interactions

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

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

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

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

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

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

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

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

14 CLINICAL STUDIES

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

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

14.1 Heart Failure

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

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

Four US multicenter, double-blind, placebo-controlled studies enrolled 1,094 patients (696 randomized to carvedilol) with NYHA class II-III heart failure and ejection fraction ≤0.35. The vast majority were on digitalis, diuretics, and an ACE inhibitor at study entry. Patients were

assigned to the studies based upon exercise ability. An Australia-New Zealand double-blind, placebo-controlled study enrolled 415 patients (half randomized to immediate-release carvedilol) with less severe heart failure. All protocols excluded patients expected to undergo cardiac transplantation during the 7.5 to 15 months of double-blind follow-up. All randomized patients had tolerated a 2-week course on immediate-release carvedilol 6.25 mg twice daily.

In each study, there was a primary end point, either progression of heart failure (1 US study) or exercise tolerance (2 US studies meeting enrollment goals and the Australia-New Zealand study). There were many secondary end points specified in these studies, including NYHA classification, patient and physician global assessments, and cardiovascular hospitalization. Other analyses not prospectively planned included the sum of deaths and total cardiovascular hospitalizations. In situations where the primary end points of a trial do not show a significant benefit of treatment, assignment of significance values to the other results is complex, and such values need to be interpreted cautiously.

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

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

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

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

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

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

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

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

Table 5. Results of COMET

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

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

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

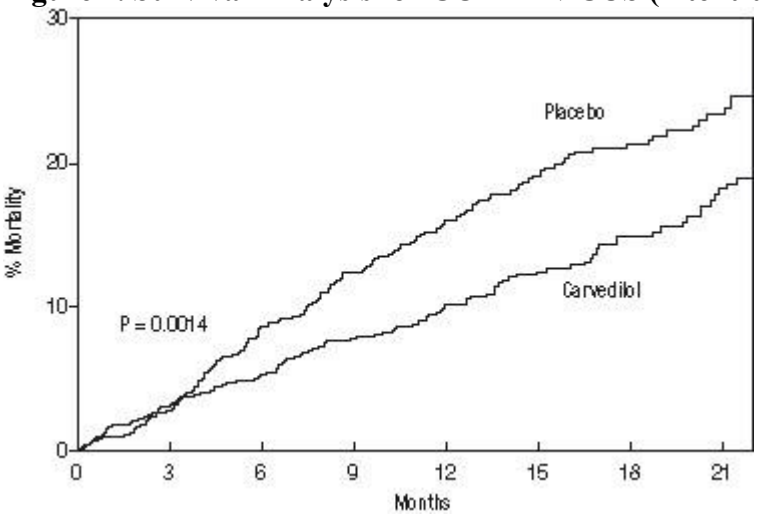
The primary end point of the trial was all-cause mortality, but cause-specific mortality and the risk of death or hospitalization (total, cardiovascular [CV], or heart failure [HF]) were also examined. The developing trial data were followed by a data monitoring committee, and mortality analyses were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

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

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

Cardiovascular = CV; Heart failure = HF

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



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

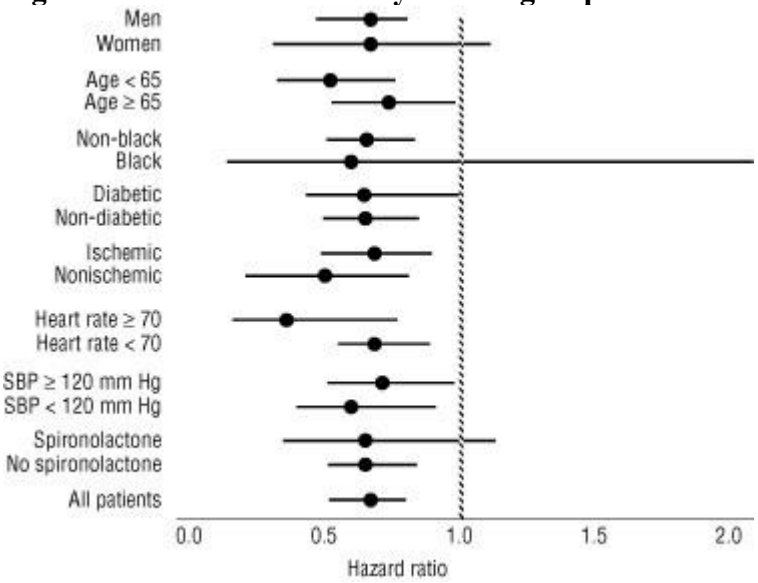
Patients' global assessments, in which carvedilol-treated patients were compared to placebo, were based on pre-specified, periodic patient self-assessments regarding whether clinical status post-treatment showed improvement, worsening, or no change compared to baseline. Patients treated with carvedilol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

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

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

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

Figure 2. Effects on Mortality for Subgroups in COPERNICUS



Although the clinical trials used twice-daily dosing, clinical pharmacologic and pharmacokinetic data provide a reasonable basis for concluding that once-daily dosing with Carvedilol Phosphate Extended-release Capsules should be adequate in the treatment of heart failure.

14.2 Left Ventricular Dysfunction Following Myocardial Infarction

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

All-cause mortality was 15% in the placebo group and 12% in the carvedilol group, indicating a 23% risk reduction in patients treated with carvedilol (95% CI 2% to 40%, p = 0.03), as shown in Figure 3. The effects on mortality in various subgroups are shown in Figure 4. Nearly all deaths were cardiovascular (which were reduced by 25% by carvedilol), and most of

these deaths were sudden or related to pump failure (both types of death were reduced by carvedilol). Another study end point, total mortality and all-cause hospitalization, did not show a significant improvement.

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

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

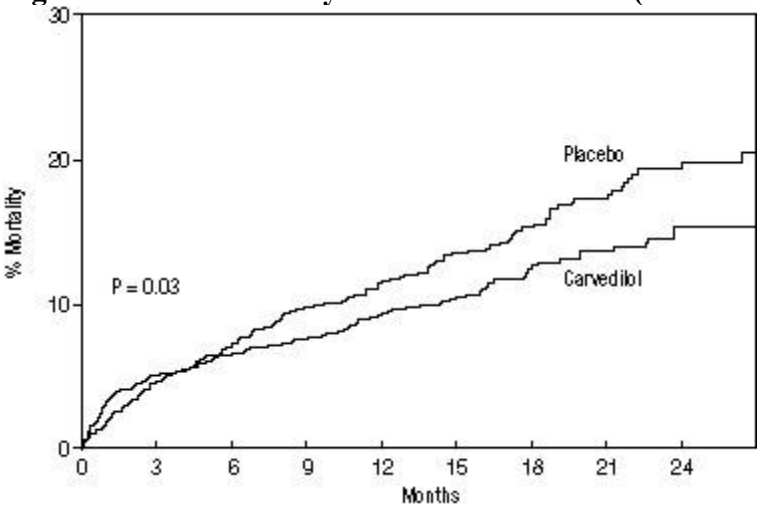
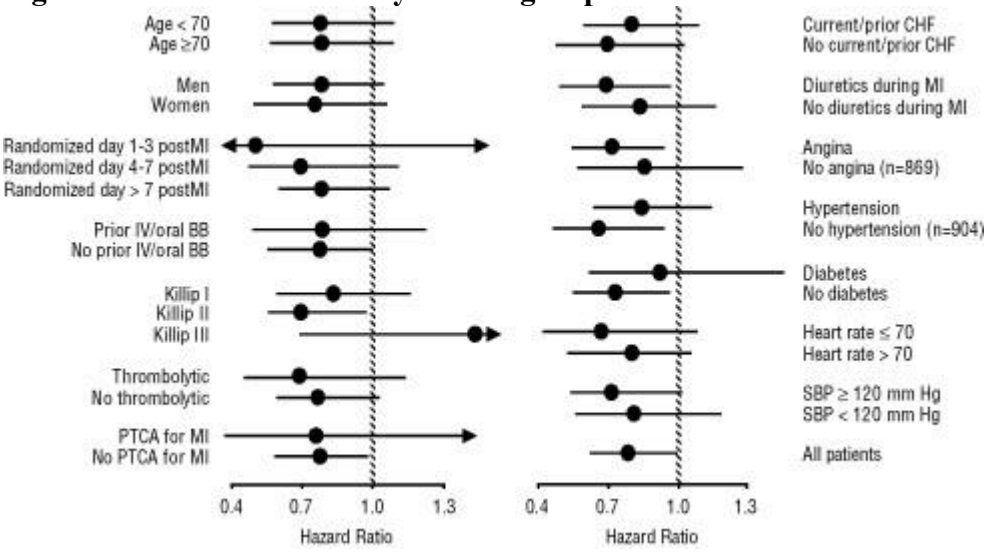


Figure 4. Effects on Mortality for Subgroups in CAPRICORN



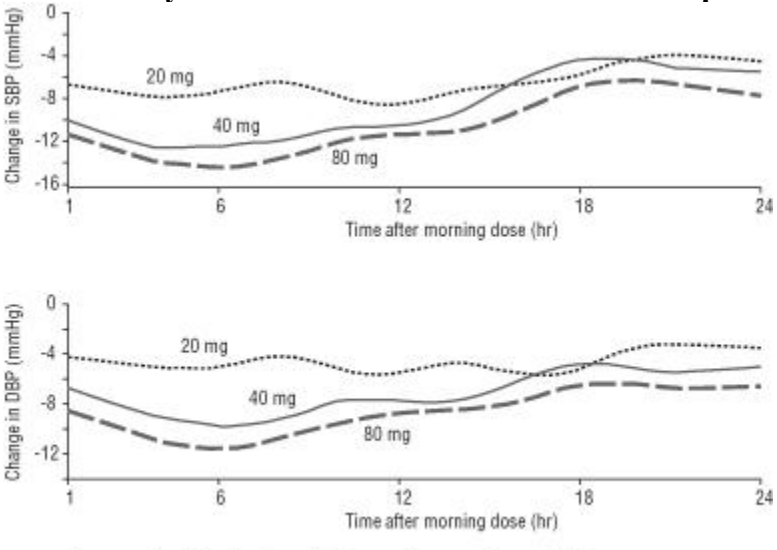
Although the clinical trials used twice-daily dosing, clinical pharmacologic and pharmacokinetic data provide a reasonable basis for concluding that once-daily dosing with Carvedilol Phosphate Extended-release Capsules should be adequate in the treatment of left ventricular dysfunction following myocardial infarction.

14.3 Hypertension

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

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

Figure 5. Changes from Baseline in Systolic Blood Pressure and Diastolic Blood Pressure Measured by 24-Hour ABPM with Carvedilol Phosphate Extended-release Capsules



Lines smoothed using locally weighted regression smoothing methodology.

Immediate-release carvedilol was studied in 2 placebo-controlled trials that utilized twice-daily dosing, at total daily doses of 12.5 to 50 mg. In these and other studies, the starting dose did not exceed 12.5 mg. At 50 mg/day, immediate-release carvedilol reduced sitting trough (12-hour) blood pressure by about 9/5.5 mm Hg; at 25 mg/day the effect was about 7.5/3.5 mm Hg. Comparisons of trough-to-peak blood pressure showed a trough-to-peak ratio for blood pressure response of about 65%. Heart rate fell by about 7.5 beats/minute at 50 mg/day. In general, as is true for other β-blockers, responses were smaller in black than non-black patients. There were no age- or gender-related differences in response. The dose-related blood pressure response was accompanied by a dose-related increase in adverse effects *[see Adverse Reactions (6)]*.

14.4 Hypertension With Type 2 Diabetes Mellitus

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

16 HOW SUPPLIED/STORAGE AND HANDLING

The hard gelatin capsules are available in the following strengths:

- 10 mg – white and green capsule shell printed with GSK COREG CR and 10 mg
- 20 mg – white and yellow capsule shell printed with GSK COREG CR and 20 mg
- 40 mg – yellow and green capsule shell printed with GSK COREG CR and 40 mg
- 80 mg – white capsule shell printed with GSK COREG CR and 80 mg

- 10 mg 30’s: NDC 60505-3678-3
- 20 mg 30’s: NDC 60505-3679-3
- 40 mg 30’s: NDC 60505-3680-3
- 80 mg 30’s: NDC 60505-3681-3

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

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.2).

17.1 Patient Advice

Patients taking Carvedilol Phosphate Extended-release Capsules should be advised of the following:

- Patients should not interrupt or discontinue using Carvedilol Phosphate Extended-release Capsules without a physician’s advice.

- Patients with heart failure should consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath.
- Patients 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 experiencing dizziness or fatigue, patients should avoid driving or hazardous tasks.
- Patients should consult a physician if they experience dizziness or faintness, in case the dosage should be adjusted.
- Patients should not crush or chew Carvedilol Phosphate Extended-release Capsules.
- Patients should take Carvedilol Phosphate Extended-release Capsules with food.
- Diabetic patients should report any changes in blood sugar levels to their physician.
- Contact lens wearers may experience decreased lacrimation.

17.2 FDA-Approved Patient Labeling

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

COREG CR is a registered trademark of GlaxoSmithKline.
TOPROL-XL is a registered trademark of the AstraZeneca group of companies.

Manufactured by:
GlaxoSmithKline
Research Triangle Park, NC 27709

Manufactured for:
Apotex Corp.
Weston, FL 33326

July 2011
CPA-AP:4PI

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION LEAFLET

Carvedilol Phosphate (car-VED-ah-lol FOS-fate) Extended-release Capsules

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

What is the most important information I should know about Carvedilol Phosphate Extended-release Capsules?

It is important for you to take your medicine every day as directed by your doctor. If you stop taking Carvedilol Phosphate Extended-release Capsules suddenly, you could have chest pain and a heart attack. If your doctor decides that you should stop taking Carvedilol Phosphate Extended-release Capsules, your doctor may slowly lower your dose over time before stopping it completely.

What are Carvedilol Phosphate Extended-release Capsules?

Carvedilol Phosphate Extended-release Capsules are a prescription medicine that belongs to a group of medicines called "beta-blockers". Carvedilol Phosphate Extended-release Capsules are used, often with other medicines, for the following conditions:

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

Carvedilol Phosphate Extended-release Capsules are not approved for use in children under 18 years of age.

Who should not take Carvedilol Phosphate Extended-release Capsules?

Do not take Carvedilol Phosphate Extended-release Capsules if you:

- have severe heart failure and require certain intravenous medicines that help support circulation.
- have asthma or other breathing problems.
- have a slow heartbeat or certain conditions that cause your heart to skip a beat (irregular heartbeat).
- have liver problems.
- are allergic to any of the ingredients in Carvedilol Phosphate Extended-release Capsules. *See "What are the ingredients in Carvedilol Phosphate Extended-release Capsules?"*

What should I tell my doctor before taking Carvedilol Phosphate Extended-release Capsules?

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

- have asthma or other lung problems (such as bronchitis or emphysema).
- have problems with blood flow in your feet and legs (peripheral vascular disease). Carvedilol Phosphate Extended-release Capsules can make some of your symptoms worse.
- have diabetes.
- have thyroid problems.
- have a condition called pheochromocytoma.
- have had severe allergic reactions.
- are scheduled for surgery and will be given anesthetic agents.
- are scheduled for cataract surgery and have taken or are currently taking Carvedilol Phosphate Extended-release Capsules.
- are pregnant or trying to become pregnant. It is not known if Carvedilol Phosphate Extended-release Capsules are safe for your unborn baby. You and your doctor should talk about the best way to control your high blood pressure during pregnancy.
- are breastfeeding. It is not known if Carvedilol Phosphate Extended-release passes into your breast milk. You should not breastfeed while using Carvedilol Phosphate Extended-release Capsules.

Tell your doctor about all of the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. Carvedilol Phosphate Extended-release Capsules and certain other medicines can affect each other and cause serious side effects. Carvedilol Phosphate Extended-release Capsules may affect the way other medicines work. Also, other medicines may affect how well Carvedilol Phosphate Extended-release Capsules work.

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

How should I take Carvedilol Phosphate Extended-release Capsules?

- Take Carvedilol Phosphate Extended-release Capsules exactly as prescribed. Take Carvedilol Phosphate Extended-release Capsules **one** time each day with food. **It is important that you take Carvedilol Phosphate Extended-release Capsules only one time each day.** To lessen possible side effects, your doctor might begin with a low dose and then slowly increase the dose.
- Swallow Carvedilol Phosphate Extended-release Capsules whole. Do not chew or crush Carvedilol Phosphate Extended-release Capsules.
- If you have trouble swallowing Carvedilol Phosphate Extended-release Capsules whole:

- The capsule may be carefully opened and the beads sprinkled over a spoonful of applesauce which should be eaten right away. The applesauce should not be warm.
- Do not sprinkle beads on foods other than applesauce.

- **Do not stop taking Carvedilol Phosphate Extended-release Capsules and do not change the amount of Carvedilol Phosphate Extended-release Capsules you take without talking to your doctor.**
- If you miss a dose of Carvedilol Phosphate Extended-release Capsules, take your dose as soon as you remember, unless it is time to take your next dose. Take your next dose at the usual time. Do not take 2 doses at the same time.
- If you take too many Carvedilol Phosphate Extended-release Capsules, call your doctor or poison control center right away.

What should I avoid while taking Carvedilol Phosphate Extended-release Capsules?
Carvedilol Phosphate Extended-release Capsules can cause you to feel dizzy, tired, or faint. Do not drive a car, use machinery, or do anything that needs you to be alert if you have these symptoms.

What are possible side effects of Carvedilol Phosphate Extended-release Capsules?
Serious side effects of Carvedilol Phosphate Extended-release Capsules include:

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

patients who had been on immediate-release carvedilol tablets before taking Carvedilol Phosphate Extended-release Capsules.

Common side effects of Carvedilol Phosphate Extended-release Capsules include shortness of breath, weight gain, diarrhea, and tiredness. If you wear contact lenses, you may have fewer tears or dry eyes that can become bothersome.

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

How should I store Carvedilol Phosphate Extended-release Capsules?

Store Carvedilol Phosphate Extended-release Capsules at less than 86°F (30°C).

Safely throw away Carvedilol Phosphate Extended-release Capsules that are out of date or no longer needed.

Keep Carvedilol Phosphate Extended-release Capsules and all medicines out of the reach of children.

General information about Carvedilol Phosphate Extended-release Capsules

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

This leaflet summarizes the most important information about Carvedilol Phosphate Extended-release Capsules. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Carvedilol Phosphate Extended-release Capsules that is written for healthcare professionals. You can also find out more about Carvedilol Phosphate Extended-release Capsules by calling 1-800-667-4708. This call is free.

What are the ingredients in Carvedilol Phosphate Extended-release Capsules?

Active ingredient: carvedilol phosphate

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

Carvedilol Phosphate Extended-release Capsules come in the following strengths: 10 mg, 20 mg, 40 mg, 80 mg.

What is high blood pressure (hypertension)?

Blood pressure is the force of blood in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too much. High blood pressure makes the heart work harder to pump blood through the body and causes damage to blood vessels. Carvedilol Phosphate Extended-release Capsules can help your blood vessels relax so

your blood pressure is lower. Medicines that lower blood pressure may lower your chance of having a stroke or heart attack.

Manufactured by:
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February 2011
CPA-AP:2PIL