

# **CARVEDILOL PHOSPHATE- carvedilol phosphate capsule, extended release Bryant Ranch Prepack**

## **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, for oral use  
Initial U.S. Approval: 1995

## **INDICATIONS AND USAGE**

Carvedilol phosphate extended-release capsules are an alpha-/beta-adrenergic blocking agent indicated for the treatment of:

- hypertension (1.3)

## **DOSAGE AND ADMINISTRATION**

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

- Hypertension: Start at 20 mg once daily and increase if needed for blood pressure control to 40 mg then 80 mg once daily over intervals of 1 to 2 weeks. (2.3)
- Elderly patients (> 65 years of age): When switching from higher doses of immediate-release carvedilol to 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: 10mg, 20mg, 40mg and 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 beta-blockers. (4) However, if deemed necessary, use with caution and at lowest effective dose. (5.5)
- Diabetes: Monitor glucose as beta-blockers may mask symptoms of hypoglycemia or worsen hyperglycemia. (5.6)

## **ADVERSE REACTIONS**

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

- Hypertension (≥5%): Dizziness.

**To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-406-7984 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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 beta-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: 2/2021**

## **FULL PRESCRIBING INFORMATION: CONTENTS\***

### **1 INDICATIONS AND USAGE**

1.3 Hypertension

### **2 DOSAGE AND ADMINISTRATION**

2.3 Hypertension

2.4 Hepatic Impairment

2.5 Geriatric Use

### **3 DOSAGE FORMS AND STRENGTHS**

### **4 CONTRAINDICATIONS**

### **5 WARNINGS AND PRECAUTIONS**

5.1 Cessation of Therapy

5.2 Bradycardia

5.3 Hypotension

5.4 Heart Failure/Fluid Retention

5.5 Non-allergic Bronchospasm

5.6 Glycemic Control in Type 2 Diabetes

5.7 Peripheral Vascular Disease

5.8 Deterioration of Renal Function

5.9 Major Surgery

5.10 Thyrotoxicosis

5.11 Pheochromocytoma

5.12 Prinzmetal's Variant Angina

5.13 Risk of Anaphylactic Reaction

5.14 Intraoperative Floppy Iris Syndrome

### **6 ADVERSE REACTIONS**

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

### **7 DRUG INTERACTIONS**

7.1 CYP2D6 Inhibitors and Poor Metabolizers

7.2 Hypotensive Agents

7.3 Cyclosporine

7.4 Digitalis Glycosides

7.5 Inducers/Inhibitors of Hepatic Metabolism

7.6 Amiodarone

7.7 Calcium Channel Blockers

7.8 Insulin or Oral Hypoglycemics

7.9 Proton Pump Inhibitors

7.10 Anesthesia

## **8 USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

## **10 OVERDOSAGE**

## **11 DESCRIPTION**

## **12 CLINICAL PHARMACOLOGY**

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Specific Populations

12.5 Drug-Drug Interactions

## **13 NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

## **14 CLINICAL STUDIES**

14.3 Hypertension

14.4 Hypertension with Type 2 Diabetes Mellitus

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

## **17 PATIENT COUNSELING INFORMATION**

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

---

## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

#### **1.3 Hypertension**

Carvedilol phosphate extended-release capsules are indicated for the management of essential hypertension [see *Clinical Studies (14.3, 14.4)*]. It 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**

<b>Daily Dose of Immediate-</b>	<b>Daily Dose of Carvedilol</b>
---------------------------------	---------------------------------

<b>Release Carvedilol Tablets</b>	<b>Phosphate Extended-Release Capsules*</b>
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 capsules should be swallowed as a whole capsule. Carvedilol phosphate extended-release capsules and/or its contents should not be crushed, chewed, or taken in divided doses.

Alternative Administration: The capsules may be carefully opened and the contents 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 contents sprinkled on other foods has not been tested.

## **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 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 (aged 65 years 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 carvedilol phosphate controlled-release minitablets that are coated with methacrylic acid copolymers and are available in the following strengths:

- 10 mg – white opaque/white opaque capsules, imprinted MUTUAL 899
- 20 mg – dark green opaque/dark green opaque capsules, imprinted MUTUAL 900
- 40 mg – yellow opaque/yellow opaque capsules, imprinted MUTUAL 901
- 80 mg – green opaque/green opaque capsules, imprinted MUTUAL 902

### **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 subjects with hypertension (338 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.

This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

## **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 patients with angina following the abrupt discontinuation of therapy with beta-blockers. The last 2 complications may occur with or without preceding exacerbation of the angina pectoris. As with other beta-blockers, 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 reinstated, 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.

## **5.2 Bradycardia**

In clinical trials with immediate-release carvedilol, bradycardia was reported in about 2% of hypertensive subjects. 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 the clinical trial of carvedilol phosphate extended-release capsules in hypertensive subjects, syncope was reported in 0.3% of subjects receiving carvedilol phosphate extended-release capsules compared with 0% of subjects 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 subjects 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 subjects.

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 (2.3)*]. 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.

## **5.5 Non-allergic Bronchospasm**

Patients with bronchospastic disease (e.g., chronic bronchitis, emphysema) should, in general, not receive beta-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 beta-agonists is minimized. 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, beta-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective beta-blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. Patients subject to spontaneous hypoglycemia or diabetic patients receiving insulin or oral hypoglycemic agents should be cautioned about these possibilities.

In a trial 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**

Beta-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 has resulted in deterioration of renal function. Patients at risk appear to be those with low blood pressure (systolic blood pressure less than 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 capsules 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**

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

## **5.11 Pheochromocytoma**

In patients with pheochromocytoma, an alpha-blocking agent should be initiated prior to

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

### **5.12 Prinzmetal's Variant Angina**

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

### **5.13 Risk of Anaphylactic Reaction**

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

### **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**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Carvedilol has been evaluated for safety in hypertensive subjects. The observed adverse event profile was consistent with the pharmacology of the drug and the health status of the subjects in the clinical trials. Adverse events reported for subjects with hypertension reflecting the use of either carvedilol phosphate extended-release capsules or immediate-release carvedilol are provided below. Excluded are adverse events considered too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population. Rates of adverse events were generally similar across demographic subsets (men and women, elderly and non-elderly, blacks and non-blacks).

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. 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 Subjects with Hypertension (Incidence  $\geq$ 1% in Subjects Treated with Carvedilol, Regardless of Causality)**

<b>Adverse Event</b>	<b>Carvedilol Phosphate Extended-Release Capsules (n = 253)</b>	<b>Placebo (n = 84)</b>
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 subjects in U.S. clinical trials and in 2,976 subjects 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 U.S. controlled clinical trials directly comparing carvedilol monotherapy in doses up to 50 mg (n = 1,142) with placebo (n = 462), 4.9% of carvedilol subjects discontinued for adverse events versus 5.2% of placebo subjects. 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 U.S. 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 U.S. placebo-controlled clinical trials for hypertension that occurred with an incidence of  $\geq$ 1% regardless of causality and that were more frequent in drug-treated subjects than placebo-treated subjects.

**Table 4. Adverse Events (% Occurrence) in U.S. Placebo-Controlled Hypertension Trials with Immediate-Release**

**Carvedilol (Incidence  $\geq$ 1% in Subjects Treated with Carvedilol, Regardless of Causality)\***

<b>Adverse Event</b>	<b>Carvedilol (n = 1,142)</b>	<b>Placebo (n = 462)</b>
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 trials, but the rates were equal or greater in subjects 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 subjects with hypertension.

**Incidence  $>$ 0.1% to  $\leq$ 1%**

*Cardiovascular:* Peripheral ischemia, tachycardia.

*Central and Peripheral Nervous System:* Hypokinesia.

*Gastrointestinal:* Bilirubinemia, increased hepatic enzymes (0.2% of hypertension patients were discontinued from therapy because of increases in hepatic enzymes) [*see Laboratory Abnormalities*].

*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  $\leq 0.1\%$  of subjects 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.

#### 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 subjects treated with carvedilol and those treated with placebo. However, transaminase elevations, confirmed by rechallenge, have been observed with carvedilol.

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 subjects.

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of 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 alpha-blocking R(+) enantiomer.

## 7.2 Hypotensive Agents

Patients taking a beta-blocker 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 a beta-blocker may cause hypotension and bradycardia. When concomitant treatment with a beta-blocker and clonidine is to be terminated, the beta-blocker 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 subjects suffering from chronic vascular rejection. In about 30% of subjects, 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 subjects. 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 beta-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

The concomitant administration of amiodarone or other CYP2C9 inhibitors such as fluconazole with carvedilol phosphate extended-release capsules may enhance the beta-blocking activity, 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 phosphate extended-release capsules are co-administered with diltiazem. As with other beta-blockers, if carvedilol phosphate extended-release capsules are administered 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

Beta-blockers 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 that depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used [see *Overdosage (10)*].

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

### Risk Summary

Available data regarding use of carvedilol phosphate extended-release capsules in pregnant women are insufficient to determine whether there are drug-associated risks of adverse developmental outcomes. There are risks to the mother and fetus associated with poorly controlled hypertension in pregnancy. The use of beta-blockers during the third trimester of pregnancy may increase the risk of hypotension, bradycardia, hypoglycemia, and respiratory depression in the neonate [see *Clinical Considerations*]. In animal reproduction studies, there was no evidence of adverse developmental outcomes at clinically relevant doses [see *Data*]. Oral administration of carvedilol to pregnant rats during organogenesis resulted in post-implantation loss, decreased fetal body weight, and an increased frequency of delayed fetal skeletal development at maternally toxic doses that were 50 times the maximum recommended human dose (MRHD). In addition, oral administration of carvedilol to pregnant rabbits during organogenesis resulted in increased post-implantation loss at doses 25 times the MRHD [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

### Clinical Considerations

*Disease-Associated Maternal and/or Embryo/Fetal Risk:* Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

*Fetal/Neonatal Adverse Reactions:* Neonates of women with hypertension who are treated with beta-blockers during the third trimester of pregnancy may be at increased risk for hypotension, bradycardia, hypoglycemia, and respiratory depression. Observe newborns for symptoms of hypotension, bradycardia, hypoglycemia, and respiratory depression and manage accordingly.

## Data

Animal Data: Studies performed in rats and rabbits given carvedilol during fetal organogenesis revealed increased post-implantation loss in rats at a maternally toxic dose of 300 mg/kg/day (50 times the MRHD as mg/m<sup>2</sup>) and in rabbits (in the absence of maternal toxicity) at doses of 75 mg/kg/day (25 times the MRHD as mg/m<sup>2</sup>). In the rats, there was also a decrease in fetal body weight at 300 mg/kg/day (50 times the MRHD as mg/m<sup>2</sup>) accompanied by an increased incidence of fetuses with delayed skeletal development. In rats, the no-effect level for embryo-fetal toxicity was 60 mg/kg/day (10 times the MRHD as mg/m<sup>2</sup>); in rabbits, it was 15 mg/kg/day (5 times the MRHD as mg/m<sup>2</sup>). In a pre- and post-natal development study in rats administered carvedilol from late gestation through lactation, increased embryo-lethality was observed at a maternally toxic dose of 200 mg/kg/day (approximately 32 times the MRHD as mg/m<sup>2</sup>), and pup mortality and delays in physical growth/development were observed at 60 mg/kg/day (10 times the MRHD as mg/m<sup>2</sup>) in the absence of maternal toxicity. The no-effect level was 12 mg/kg/day (2 times the MRHD as mg/m<sup>2</sup>). Carvedilol was present in fetal rat tissue.

## **8.2 Lactation**

### Risk Summary

There are no data on the presence of carvedilol in human milk, the effects on the breastfed infant, or the effects on milk production. Carvedilol is present in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for carvedilol phosphate extended-release capsules and any potential adverse effects on the breastfed infant from carvedilol phosphate extended-release capsules or from the underlying maternal condition.

## **8.4 Pediatric Use**

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

## **8.5 Geriatric Use**

The initial clinical trials of carvedilol phosphate extended-release capsules in subjects with hypertension did not include sufficient numbers of subjects aged 65 years or older to determine whether they respond differently from younger patients.

The following information is available for trials with immediate-release carvedilol. Of the 2,065 hypertensive subjects in U.S. clinical trials of efficacy or safety who were treated with carvedilol, 21% (436) were aged 65 years or older. Of 3,722 subjects receiving immediate-release carvedilol in hypertension clinical trials conducted worldwide, 24% were aged 65 years or older.

With the exception of dizziness in hypertensive subjects (incidence 8.8% in the elderly versus 6% in younger subjects), no overall differences in the safety or effectiveness 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. 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.

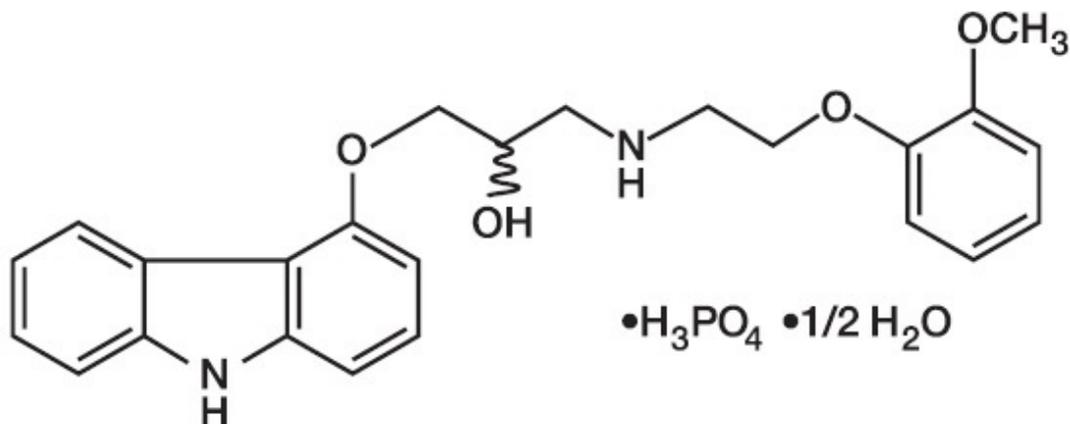
If peripheral vasodilation dominates, it may be necessary to administer adrenaline or noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant bradycardia, pacemaker therapy should be performed. For bronchospasm, beta-sympathomimetics (as aerosol or IV) or aminophylline 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 beta-adrenergic blocking agent with  $\alpha_1$ -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<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>•H<sub>3</sub>PO<sub>4</sub>•1/2 H<sub>2</sub>O.

Carvedilol phosphate extended-release capsules are available for once-a-day administration as controlled-release oral capsules containing 10, 20, 40, or 80 mg carvedilol phosphate. Carvedilol phosphate extended-release hard gelatin capsules are filled with carvedilol phosphate controlled-release minitablets that are coated with methacrylic acid copolymers. Inactive ingredients include crospovidone, hypromellose, lactose monohydrate, magnesium stearate, methacrylic acid ethyl acrylate, methacrylic acid methyl methacrylate, microcrystalline cellulose, polyethylene glycol, propylene glycol, silicon dioxide, talc and triethyl citrate. The capsule shell contains gelatin and titanium dioxide. The 20 mg capsule shell also contains FD&C blue #1, FD&C yellow #5 and FD&C yellow #6. The 40 mg capsule shell also contains D&C yellow #10 and FD&C yellow #6. The 80 mg capsule shell also contains D&C yellow #10 and FD&C blue #1. The imprinting ink for the 10 mg, 40 mg and 80 mg contains D&C yellow #10 lake, FD&C blue #1, FD&C blue #2, FD&C red #40, iron oxide black, propylene glycol and shellac glaze. The imprinting ink for the 20 mg contains ammonium hydroxide, propylene glycol, shellac glaze, simethicone and titanium dioxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Carvedilol is a racemic mixture in which nonselective beta-adrenoreceptor blocking activity is present in the S(-) enantiomer and alpha<sub>1</sub>-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency. Carvedilol has no intrinsic sympathomimetic activity.

### 12.2 Pharmacodynamics

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

Beta-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 beta-adrenoreceptor blocking effect is usually seen

within 1 hour of drug administration.

Alpha<sub>1</sub>-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 alpha<sub>1</sub>-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 beta<sub>1</sub>-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 at steady state in adult subjects with essential hypertension.

In hypertensive subjects 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<sub>max</sub>, 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 carvedilol phosphate extended-release capsules is slower and more prolonged compared with 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 capsules 10 to 80 mg. Within-subject and between-subject variability for AUC and C<sub>max</sub> is similar for carvedilol phosphate extended-release capsules 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<sub>max</sub> compared with carvedilol phosphate extended-release capsules administered with a standard meal. Decreases in AUC (27%) and C<sub>max</sub> (43%) were observed when carvedilol phosphate extended-release capsules were administered in the fasted state compared with administration after a

standard meal. Carvedilol phosphate extended-release capsules should be taken with food.

In a trial 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 with 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 beta-receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol for beta-blockade.

Compared with 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 with 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**

**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 ( $\pm 20\%$ ) to those

observed with immediate-release carvedilol tablets following repeat dosing in subjects with essential hypertension.

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

Hepatic Impairment: No trials have been performed with carvedilol phosphate extended-release capsules in subjects with hepatic impairment. Compared with healthy subjects, subjects 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 trials have been performed with carvedilol phosphate extended-release capsules in subjects 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 subjects with hypertension and moderate to severe renal impairment compared with a control group of subjects with hypertension and 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 subjects 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 trials were performed with immediate-release carvedilol tablets.

Cimetidine: In a pharmacokinetic trial 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 subjects with hypertension [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 subjects with hypertension. Likewise, hydrochlorothiazide had no effect on the pharmacokinetics of carvedilol.

Rifampin: In a pharmacokinetic trial 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 trial 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 as mg/m<sup>2</sup>) or in mice given up to 200 mg/kg/day (16 times the MRHD as mg/m<sup>2</sup>), 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.

In a combined fertility/developmental/post-natal toxicity study, rats were given carvedilol (12, 60, 300 mg/kg/day) orally by gavage for 2 weeks before mating and through mating, gestation, and weaning for females and for 62 days prior to and through mating for males. At a dosage of 300 mg/kg/day ( $\geq$  50 times the MRHD as mg/m<sup>2</sup>) carvedilol was toxic to adult rats (sedation, reduced weight gain) and was associated with a reduced number of successful matings, prolonged mating time, fewer corpora lutea and implants per dam, fewer live pups per litter, and delays in physical growth/development. The no-effect level for overt toxicity and impairment of fertility was 60 mg/kg/day (10 times the MRHD as mg/m<sup>2</sup>).

## **14 CLINICAL STUDIES**

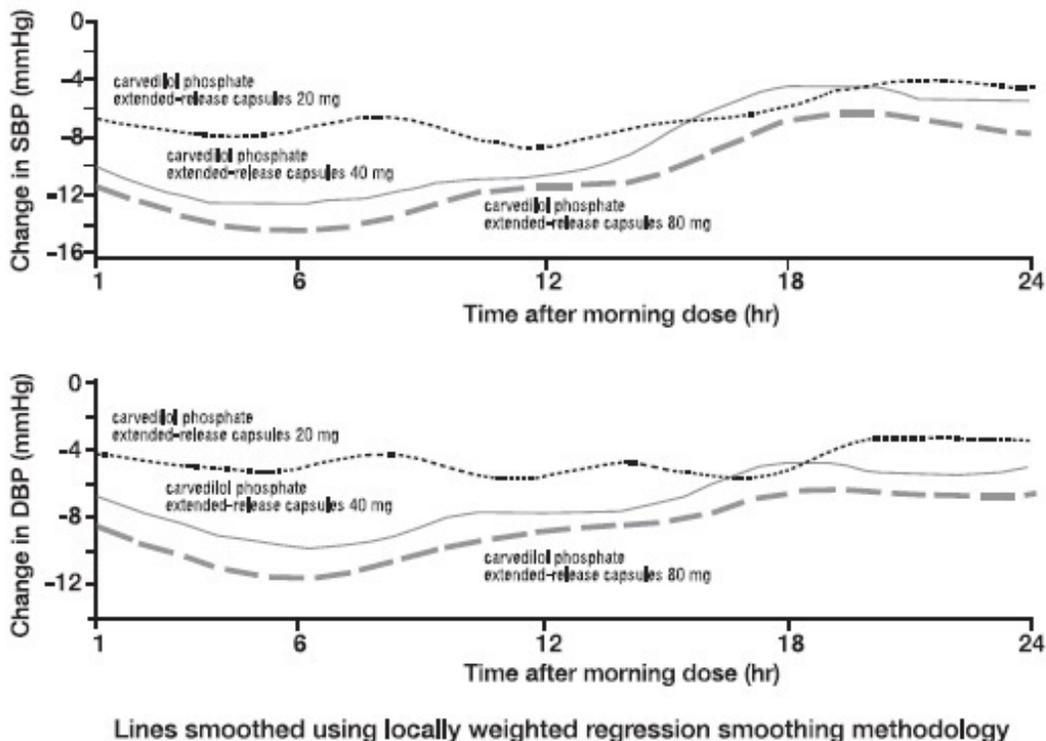
### **14.3 Hypertension**

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 subjects with essential hypertension (sitting diastolic blood pressure [DBP]  $\geq$ 90 and  $\leq$ 109 mm Hg). Of 337 evaluable subjects, a total of 273 subjects (81%) completed the trial. Of the 64 (19%) subjects withdrawn from the trial, 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 subjects 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 with 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 to 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 to 7 hr) ratio was approximately 0.6 for carvedilol phosphate extended-release capsules 80 mg. In this trial, 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**



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 trials, the starting dose did not exceed 12.5 mg. At 50 mg/day, carvedilol tablets 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 beta-blockers, responses were smaller in black than non-black subjects. 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 trial (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%. Carvedilol tablets were titrated to a mean dose of 17.5 mg twice daily and maintained for

5 months. Carvedilol tablets 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**

NDC: 63629-9634-1: 30 EXTENDED RELEASE CAPSULEs in a BOTTLE, PLASTIC

NDC: 63629-9634-2: 90 EXTENDED RELEASE CAPSULEs in a BOTTLE, PLASTIC

## **17 PATIENT COUNSELING INFORMATION**

*Advise the patient to read the FDA-approved patient labeling (Patient Information).*

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 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.

All listed brands are trademarks of their respective owners.

Distributed by:

Sun Pharmaceutical Industries, Inc.

Cranbury, NJ 08512

Rev 02, September 2017

## **PATIENT INFORMATION**

### **CARVEDILOL PHOSPHATE 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 condition:

- 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?*"

The 20 mg strength of this drug product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

## **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 capsules pass into your breast milk. Talk with your doctor about the best way to **Tell your doctor about all of the medicines you take** including prescription and over-the-counter 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 contents sprinkled over a spoonful of applesauce which should be eaten right away. The applesauce should not be warm.
  - Do not sprinkle contents 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 much 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 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 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.

Call your doctor for medical advice about side effects. **You may report side effects to FDA at 1-800-FDA-1088.**

### **How should I store carvedilol phosphate extended-release capsules?**

Store carvedilol phosphate extended-release capsules at 20° to 25°C (68° to 77°F).

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.

Please address medical inquiries to 1-800-406-7984.

## **What are the ingredients in carvedilol phosphate extended-release capsules?**

Active ingredient: carvedilol phosphate

Inactive ingredients: crospovidone, hypromellose, lactose monohydrate, magnesium stearate, methacrylic acid ethyl acrylate, methacrylic acid methyl methacrylate, microcrystalline cellulose, polyethylene glycol, propylene glycol, silicon dioxide, talc and triethyl citrate. The capsule shell contains gelatin and titanium dioxide. The 20 mg capsule shell also contains FD&C blue #1, FD&C yellow #5 and FD&C yellow #6. The 40 mg capsule shell also contains D&C yellow #10 and FD&C yellow #6. The 80 mg capsule shell also contains D&C yellow #10 and FD&C blue #1. The imprinting ink for the 10 mg, 40 mg and 80 mg contains D&C yellow #10 lake, FD&C blue #1, FD&C blue #2, FD&C red #40, iron oxide black, propylene glycol and shellac glaze. The imprinting ink for the 20 mg contains ammonium hydroxide, propylene glycol, shellac glaze, simethicone and titanium dioxide.

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.

Distributed by:  
Sun Pharmaceutical Industries, Inc.

Cranbury, NJ 08512

Rev 02, September 2017

**Carvedilol Phosphate ER 40 mg Capsules**



GTIN 00363629963416  
 Lot 208620  
 Exp 5/15/2025  
 SN 0123456789

Each extended-release capsule contains:  
 Carvedilol Phosphate, USP 40mg

Keep this and all drugs out of the reach of children.

Store at 20° to 25° C (68° to 77° F); excursions permitted to 15° to 30° C (59° to 86° F) (see USP controlled Room Temperature).

Dispense in a tight, light-resistant container as defined in the USP.

NDC 63629-9634-1

**Carvedilol Phosphate  
 Extended-Release Capsules**

**40mg**



Repackaged by:  
 Bryant Ranch Prepack, Inc.  
 Burbank, CA 91504 USA

Rx only  
**30 Capsules**  
 Manufactured by:  
 Frontida BioPharm  
 Inc.



**CARVEDIOL PHOSPHATE**

carvedilol phosphate capsule, extended release

**Product Information**

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:63629-9634(NDC:57664-665)
<b>Route of Administration</b>	ORAL		

**Active Ingredient/Active Moiety**

Ingredient Name	Basis of Strength	Strength
<b>CARVEDIOL PHOSPHATE</b> (UNII: EQT531S367) (CARVEDIOL - UNII:0K47UL67F2)	CARVEDIOL PHOSPHATE	40 mg

**Inactive Ingredients**

Ingredient Name	Strength
<b>CROSPVIDONE (120 .MU.M)</b> (UNII: 68401960MK)	
<b>HYPROMELLOSE, UNSPECIFIED</b> (UNII: 3NXW29V3WO)	
<b>LACTOSE MONOHYDRATE</b> (UNII: EWQ57Q8I5X)	
<b>MAGNESIUM STEARATE</b> (UNII: 70097M6I30)	
<b>METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A</b> (UNII: NX76LV5T8J)	
<b>METHACRYLIC ACID - METHYL METHACRYLATE COPOLYMER (1:1)</b> (UNII: 74G4R6TH13)	
<b>MICROCRYSTALLINE CELLULOSE</b> (UNII: OP1R32D61U)	
<b>POLYETHYLENE GLYCOL, UNSPECIFIED</b> (UNII: 3WJQ0SDW1A)	
<b>PROPYLENE GLYCOL</b> (UNII: 6DC9Q167V3)	
<b>SILICON DIOXIDE</b> (UNII: ETJ7Z6XBU4)	
<b>TALC</b> (UNII: 7SEV7J4R1U)	
<b>TRIETHYL CITRATE</b> (UNII: 8Z96QXD6UM)	
<b>GELATIN, UNSPECIFIED</b> (UNII: 2G86QN327L)	
<b>TITANIUM DIOXIDE</b> (UNII: 15FIX9V2JP)	
<b>D&amp;C YELLOW NO. 10</b> (UNII: 35SW5USQ3G)	
<b>ALUMINUM OXIDE</b> (UNII: LMI26O6933)	
<b>FD&amp;C BLUE NO. 1</b> (UNII: H3R47K3TBD)	
<b>FD&amp;C BLUE NO. 2</b> (UNII: L06K8R7DQK)	

<b>FD&amp;C RED NO. 40</b> (UNII: WZB9127XOA)	
<b>FERROSO FERRIC OXIDE</b> (UNII: XM0M87F357)	
<b>SHELLAC</b> (UNII: 46N107B71O)	
<b>FD&amp;C YELLOW NO. 6</b> (UNII: H77VEI93A8)	

### Product Characteristics

<b>Color</b>	YELLOW (yellow opaque/yellow opaque)	<b>Score</b>	no score
<b>Shape</b>	CAPSULE	<b>Size</b>	19mm
<b>Flavor</b>		<b>Imprint Code</b>	Mutual;901
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63629-9634-1	30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	05/11/2023	
2	NDC:63629-9634-2	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	05/11/2023	

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090132	11/08/2017	

**Labeler** - Bryant Ranch Prepack (171714327)

**Registrant** - Bryant Ranch Prepack (171714327)

### Establishment

Name	Address	ID/FEI	Business Operations
Bryant Ranch Prepack		171714327	REPACK(63629-9634) , RELABEL(63629-9634)

Revised: 5/2023

Bryant Ranch Prepack