CARVEDILOL- carvedilol tablet, film coated
DIRECT RX

CARVEDILOL

INDICATIONS & USAGE SECTION

1.2 Left Ventricular Dysfunction Following Myocardial Infarction

Carvedilol Tablet is 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 less than or equal to 40% (with or without symptomatic heart failure) [see Clinical Studies (14.2)].

1.3 Hypertension

Carvedilol Tablet is 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)].

DOSAGE & ADMINISTRATION SECTION

Carvedilol Tablet should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects.

2.2 Left Ventricular Dysfunction Following Myocardial Infarction

DOSAGE MUST BE INDIVIDUALIZED AND MONITORED DURING UP-TITRATION. Treatment with Carvedilol Tablet 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 Tablets be started at 6.25 mg twice daily and increased after 3 to 10 days, based on tolerability, to 12.5 mg twice daily, then again to the target dose of 25 mg twice daily. A lower starting dose may be used (3.125 mg twice 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 Tablet is 6.25 mg twice daily. If this dose is tolerated, using standing systolic pressure measured about 1 hour after dosing as a guide, the dose should be maintained for 7 to 14 days, and then increased to 12.5 mg twice 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 25 mg twice daily if tolerated and needed. The full antihypertensive effect of Carvedilol Tablets is seen within 7 to 14 days. Total daily dose should not exceed 50 mg.

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

2.4 Hepatic Impairment

Carvedilol Tablets should not be given to patients with severe hepatic impairment [see Contraindications (4)].

3 DOSAGE FORMS AND STRENGTHS

The white, oval shaped, biconvex, film-coated tablets are available in the following strengths: 3.125 mg – Each white, oval shaped, biconvex, film-coated tablet engraved with 254 on one side and plain on the

other side, 6.25 mg – Each white, oval shaped, biconvex, film-coated tablet engraved with 255 on one side and plain on the other side, 12.5 mg – Each white, oval shaped, biconvex, film-coated tablet engraved with 256 on one side and plain on the other side, and 25 mg – Each white, oval shaped, biconvex, film-coated tablet engraved with 257 on one side and plain on the other side.

DOSAGE & ADMINISTRATION SECTION

The white, oval shaped, biconvex, film-coated tablets are available in the following strengths: 3.125 mg – Each white, oval shaped, biconvex, film-coated tablet engraved with 254 on one side and plain on the other side, 6.25 mg – Each white, oval shaped, biconvex, film-coated tablet engraved with 255 on one side and plain on the other side, 12.5 mg – Each white, oval shaped, biconvex, film-coated tablet engraved with 256 on one side and plain on the other side, and 25 mg – Each white, oval shaped, biconvex, film-coated tablet engraved with 257 on one side and plain on the other side.

CONTRAINDICATIONS SECTION

Carvedilol Tablet is contraindicated in the following conditions:

- Bronchial asthma or related bronchospastic conditions. Deaths from status asthmaticus have been reported following single doses of Carvedilol Tablet.
- 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 Tablet.
- Patients with severe hepatic impairment
- Patients with a history of a serious hypersensitivity reaction (e.g., Stevens-Johnson syndrome, anaphylactic reaction, angioedema) to any component of this medication or other medications containing Carvedilol Tablet.

WARNINGS AND PRECAUTIONS SECTION

5.1 Cessation of Therapy

Patients with coronary artery disease, who are being treated with Carvedilol Tablets, 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 Tablet is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. Carvedilol Tablet should be discontinued over 1 to 2 weeks whenever possible. If the angina worsens or acute coronary insufficiency develops, it is recommended that Carvedilol Tablet 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 Tablet abruptly even in patients treated only for hypertension or heart failure.

5.2 Bradycardia

In clinical trials, Carvedilol Tablet caused bradycardia in about 2% of hypertensive patients, 9% of heart failure patients and 6.5% of myocardial infarction patients with left ventricular dysfunction. If pulse rate drops below 55 beats/minute, the dosage should be reduced.

5.3 Hypotension

Postural hypotension occurred in 1.8% and syncope in 0.1% of hypertensive patients, 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, hypotension or postural hypotension occurred in 20.2% of patients receiving Carvedilol Tablet 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 Tablet, 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 (2.2, 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 Tablet. If such symptoms occur, diuretics should be increased and the Carvedilol Tablet dose should not be advanced until clinical stability resumes [see Dosage and Administration (2)]. Occasionally it is necessary to lower the Carvedilol Tablet dose or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of, or a favorable response to Carvedilol Tablet.

5.5 Non-Allergic Bronchospasm

Patients with bronchospastic disease (e.g., chronic bronchitis and emphysema) should, in general, not receive β-blockers. Carvedilol Tablet may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if Carvedilol Tablet is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous β-agonists is minimized.

In clinical trials of patients with heart failure, patients with bronchospastic disease were enrolled if they did not require oral or inhaled medication to treat their bronchospastic disease. In such patients, it is recommended that Carvedilol Tablet 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. Studies designed to examine the effects of Carvedilol Tablet on glycemic control in patients with diabetes and heart failure have not been conducted. In a study designed to examine the effects of Carvedilol Tablet on glycemic control in a population with mild-to-moderate hypertension and well-controlled type 2 diabetes mellitus, Carvedilol Tablet 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 Tablet 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 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 Tablet was stopped. In patients with these risk factors it is recommended that renal function be monitored during up-titration of Carvedilol Tablet and the drug discontinued or dosage reduced if worsening of renal function occurs.

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.

5.9 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 Tablet 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 Tablet 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 Tablet in these patients although the α-blocking activity may prevent such symptoms. However, caution should be taken in the administration of Carvedilol Tablet 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 α -1 blockers (Carvedilol Tablet is 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.

ADVERSE REACTIONS SECTION

6.1 Clinical Studies Experience

Carvedilol Tablet 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 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).

Left Ventricular Dysfunction Following Myocardial Infarction:

Carvedilol Tablet 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 Tablet and 980 who received placebo. Approximately 75% of the patients received Carvedilol Tablet for at least 6 months and 53% received Carvedilol Tablet for at least 12 months. Patients were treated for an average of 12.9 months and 12.8 months with Carvedilol Tablet and placebo, respectively.

The following adverse events were reported with a frequency of greater than 1% but less than or equal to 3% and more frequently with Carvedilol Tablet: 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 greater than 1%, and occurring more often on Carvedilol Tablet was hypotension (1.5% on Carvedilol Tablet, 0.2% on placebo).

Hypertension:

Carvedilol Tablet has been evaluated for safety in hypertension in more than 2,193 patients in U.S. clinical trials and in 2,976 patients in international clinical trials. Approximately 36% of the total treated population received Carvedilol Tablet for at least 6 months. Most adverse events reported during therapy with Carvedilol Tablet were of mild to moderate severity. In U.S. controlled clinical trials directly comparing Carvedilol Tablet in doses up to 50 mg (n = 1,142) to placebo (n = 462), 4.9% of patients receiving Carvedilol Tablet 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 Tablet group for postural hypotension (1% versus 0). The overall incidence of adverse events in U.S. placebo-controlled trials increased with increasing dose of Carvedilol Tablet. 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.

Table 1 shows adverse events in U.S. placebo-controlled clinical trials for hypertension that occurred with an incidence of greater than or equal to 1% regardless of causality, and that were more frequent in drug-treated patients than placebo-treated patients.

Table 1. Adverse Events (%) Occurring in U.S. Placebo-Controlled Hypertension Trials (Incidence greater than or equal to 1%, Regardless of Causality) *

	Carvedilol Tablet (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 greater than 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 Tablet in worldwide open or controlled trials with Carvedilol Tablet in patients with hypertension or heart failure.

Incidence greater than 0.1% to less than or equal 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 less than or equal to 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 Tablet. 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 Tablet and those treated with placebo. However, transaminase elevations, confirmed by rechallenge, have been observed with Carvedilol Tablet. In a long-term, placebo-controlled trial in severe heart failure, patients treated with Carvedilol Tablet had lower values for hepatic transaminases than patients treated with placebo, possibly because improvements in cardiac function induced by Carvedilol Tablet led to less hepatic congestion and/or improved hepatic blood flow.

Carvedilol Tablet 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.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Carvedilol Tablet. 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.

DRUG INTERACTIONS SECTION

7.1 CYP2D6 Inhibitors and Poor Metabolizers

Interactions of Carvedilol Tablet 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 Tablet [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 uptitration, 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-pressureand heart-ratelowering 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 Tablet 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 Tablet 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 Tablet are administered concomitantly. Therefore, increased monitoring of digoxin is recommended when initiating, adjusting, or discontinuing Carvedilol Tablet [see Clinical Pharmacology (12.5)].

7.5 Inducers/Inhibitors of Hepatic Metabolism

Rifampin reduced plasma concentrations of Carvedilol Tablet by about 70% [see Clinical Pharmacology (12.5)]. Cimetidine increased AUC by about 30% but caused no change in Cmax [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 Tablet by at least 2-fold [see Clinical

Pharmacology (12.5)]. The concomitant administration of amiodarone or other CYP2C9 inhibitors such as fluconazole with Carvedilol Tablet may enhance the β-blocking properties of Carvedilol Tablet 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 preexisting treatment with the other.

7.7 Calcium Channel Blockers

Conduction disturbance (rarely with hemodynamic compromise) has been observed when Carvedilol Tablets is coadministered with diltiazem. As with other agents with β-blocking properties, if Carvedilol Tablets is to be 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

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 Anesthesia

If treatment with Carvedilol Tablet 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.

USE IN SPECIFIC POPULATIONS SECTION

8.1 PregnancyPregnancy Category C.

Studies performed in pregnant rats and rabbits given Carvedilol Tablet revealed increased post-implantation loss in rats at doses of 300 mg/kg/day (50 times the maximum recommended human dose [MRHD] as mg/m2) and in rabbits at doses of 75 mg/kg/day (25 times the MRHD as mg/m2). In the rats, there was also a decrease in fetal body weight at the maternally toxic dose of 300 mg/kg/day (50 times the MRHD as mg/m2), 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/m2); in rabbits it was 15 mg/kg/day (5 times the MRHD as mg/m2). There are no adequate and well-controlled studies in pregnant women. Carvedilol Tablet 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 Tablet 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 postpartum in neonates from rats treated with 60 mg/kg/day (10 times the MRHD as mg/m2) and above during the last trimester through day 22 of lactation. Because many drugs are excreted in human milk 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 Tablets 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% less than 2 years old) with chronic heart failure [NYHA class II to IV, left ventricular ejection fraction less than 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 two dose levels of Carvedilol Tablet. These dose levels produced placebo-corrected heart rate reduction of 4 to 6 heartbeats 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 Carvedilol Tablet 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

Of the 975 myocardial infarction patients randomized to Carvedilol Tablet 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 U.S. clinical trials of efficacy or safety who were treated with Carvedilol Tablet, 21% (436) were 65 years of age or older. Of 3,722 patients receiving Carvedilol Tablet 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 Figure 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.

OVERDOSAGE SECTION

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 Tablet.

Cases of overdosage with Carvedilol Tablet 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.

DESCRIPTION SECTION

Carvedilol is a nonselective β-adrenergic blocking agent with α1-blocking activity. It is (±)-1-(carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol. Carvedilol Tablet is a racemic mixture with the following structure:

Carvedilol is a white, oval-shaped, biconvex film-coated tablet containing 3.125 mg, 6.25 mg, 12.5 mg, or 25 mg of Carvedilol Tablet. Inactive ingredients consist of colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium citrate dihydrate, sucrose, and titanium dioxide.

Carvedilol Tablet is a white to off-white powder with a molecular weight of 406.5 and molecular formula of $C_{24}H_{26}N_2O_4$. It is freely soluble in dimethylsulfoxide; soluble in methylene chloride and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in ethyl ether; and practically insoluble in water, gastric fluid (simulated, TS, pH 1.1), and intestinal fluid (simulated, TS without pancreatin, pH 7.5).

CLINICAL PHARMACOLOGY SECTION

12.1 Mechanism of Action

Carvedilol Tablet is a racemic mixture in which nonselective β-adrenoreceptor blocking activity is present in the S(-) enantiomer and α1-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency. Carvedilol Tablet has no intrinsic sympathomimetic activity.

12.2 Pharmacodynamics

Left Ventricular Dysfunction Following Myocardial Infarction

The basis for the beneficial effects of Carvedilol Tablet in patients with left ventricular dysfunction following an acute myocardial infarction is not established.

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 Tablet (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. α1-adrenoreceptor blocking activity has been demonstrated in human and animal studies, showing that Carvedilol Tablet (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 α1-receptor blocking activity of Carvedilol Tablet, 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 Carvedilol Tablet is administered with food at the recommended starting dose and titration increments are closely followed [see Dosage and Administration (2)].

In hypertensive patients with normal renal function, therapeutic doses of Carvedilol Tablet 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 Tablet and placebo.

Carvedilol Tablet 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

Carvedilol Tablet is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25% to 35% due to a significant degree of firstpass metabolism. Following oral administration, the apparent mean terminal elimination half-life of Carvedilol Tablet

generally ranges from 7 to 10 hours. Plasma concentrations achieved are proportional to the oral dose administered. When administered with food, the rate of absorption is slowed, as evidenced by a delay in the time to reach peak plasma levels, with no significant difference in extent of bioavailability. Taking Carvedilol Tablet with food should minimize the risk of orthostatic hypotension.

Carvedilol Tablet is extensively metabolized. Following oral administration of radiolabelled Carvedilol Tablet to healthy volunteers, Carvedilol Tablet accounted for only about 7% of the total radioactivity in plasma as measured by area under the curve (AUC). Less than 2% of the dose was excreted unchanged in the urine. Carvedilol Tablet 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 Tablet 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 Tablet for β-blockade.

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

Carvedilol Tablet undergoes stereoselective first-pass metabolism with plasma levels of R(+)-Carvedilol Tablet approximately 2 to 3 times higher than S(-)-Carvedilol Tablet following oral administration in healthy subjects. The mean apparent terminal elimination half-lives for R(+)-Carvedilol Tablet range from 5 to 9 hours compared with 7 to 11 hours for the S(-)-enantiomer.

The primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-Carvedilol Tablet 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 Tablet, with a potential contribution from 3A4. CYP2C9 is thought to be of primary importance in the O-methylation pathway of S(-)-Carvedilol Tablet.

Carvedilol Tablet 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 Tablet compared to extensive metabolizers. In contrast, plasma levels of S(-)-Carvedilol Tablet 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 Tablet. The pharmacokinetics of Carvedilol Tablet do not appear to be different in poor metabolizers of S-mephenytoin (patients deficient in cytochrome P450 2C19).

Carvedilol Tablet is more than 98% bound to plasma proteins, primarily with albumin. The plasma-protein binding is independent of concentration over the therapeutic range. Carvedilol Tablet is a basic, lipophilic compound with a steady-state volume of distribution of approximately 115 L, indicating substantial distribution into extravascular tissues. Plasma clearance ranges from 500 to 700 mL/min.

12.4 Specific Populations

Geriatric

Plasma levels of Carvedilol Tablet average about 50% higher in the elderly compared to young subjects.

Hepatic Impairment

Compared to healthy subjects, patients with severe liver impairment (cirrhosis) exhibit a 4 to 7 fold increase in Carvedilol Tablet levels. Carvedilol Tablet is contraindicated in patients with severe liver impairment.

Renal Impairment

Although Carvedilol Tablet is metabolized primarily by the liver, plasma concentrations of Carvedilol Tablet have been reported to be increased in patients with renal impairment. Based on mean AUC data,

approximately 40% to 50% higher plasma concentrations of Carvedilol Tablet 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 Tablet does not appear to be cleared significantly by hemodialysis.

12.5 Drug-Drug Interactions

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

Amiodarone

In a pharmacokinetic study conducted in 106 Japanese patients with heart failure, coadministration of small loading and maintenance doses of amiodarone with Carvedilol Tablet resulted in at least a 2 fold increase in the steady-state trough concentrations of S(-)-Carvedilol Tablet [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 Tablet by 30% with no change in Cmax [see Drug Interactions (7.5)].

Digoxin

Following concomitant administration of Carvedilol Tablet (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 Tablet (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 Tablet 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 Tablet.

Rifampin

In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin (600 mg daily for 12 days) decreased the AUC and Cmax of Carvedilol Tablet by about 70% [see Drug Interactions (7.5)].

Torsemide

In a study of 12 healthy subjects, combined oral administration of Carvedilol Tablet 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 Tablet (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

NONCLINICAL TOXICOLOGY SECTION

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In 2-year studies conducted in rats given Carvedilol Tablet at doses up to 75 mg/kg/day (12 times the MRHD when compared on a mg/m2 basis) or in mice given up to 200 mg/kg/day (16 times the MRHD on a mg/m2 basis), Carvedilol Tablet had no carcinogenic effect.

Carvedilol Tablet 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 greater than or equal to 200 mg/kg/day (greater than or equal to 32 times the MRHD as mg/m2) Carvedilol Tablet was toxic to adult rats (sedation, reduced weight gain) and was associated with a reduced number of successful matings, prolonged mating time, significantly fewer corpora lutea and implants per dam, and complete resorption of 18% of the litters. The no-observed-effect dose level for overt toxicity and impairment of fertility was 60 mg/kg/day (10 times the MRHD as mg/m2).

CLINICAL STUDIES SECTION

14.2 Left Ventricular Dysfunction Following Myocardial Infarction

CAPRICORN was a double-blind study comparing Carvedilol Tablet and placebo in 1,959 patients with a recent myocardial infarction (within 21 days) and left ventricular ejection fraction of less than or equal to 40%, with (47%) or without symptoms of heart failure. Patients given Carvedilol Tablet received 6.25 mg twice daily, titrated as tolerated to 25 mg twice daily. Patients had to have a systolic blood pressure greater than 90 mm Hg, a sitting heart rate greater than 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 Tablet 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 Tablet group, indicating a 23% risk reduction in patients treated with Carvedilol Tablet (95% CI 2 to 40%, p = 0.03), as shown in Figure 1. The effects on mortality in various subgroups are shown in Figure 2. Nearly all deaths were cardiovascular (which were reduced by 25% by Carvedilol Tablet), and most of these deaths were sudden or related to pump failure (both types of death were reduced by Carvedilol Tablet). 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 Tablet (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 Tablet in heart failure.

Figure 1. Survival Analysis for CAPRICORN (Intent-to-Treat)
Figure 2. Effects on Mortality for Subgroups in CAPRICORN

14.3 Hypertension

Carvedilol Tablet 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, Carvedilol Tablet 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 peak antihypertensive effect occurred 1 to 2 hours after a dose. 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 Tablet, 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 Tablet was titrated to a mean dose of 17.5 mg twice daily and maintained for 5 months. Carvedilol Tablet 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)].

HOW SUPPLIED SECTION

Carvedilol Tablets are available as follows:

3.125 mg- Each white, oval shaped, biconvex, film-coated tablet engraved with 254 on one side and plain on the other side contains 3.125 mg of Carvedilol. Tablets are supplied as follows:

NDC 43547-254-10 in bottles of 100 tablets

NDC 43547-254-50 in bottles of 500 tablets

NDC 43547-254-11 in bottles of 1000 tablets

6.25 mg- Each white, oval shaped, biconvex, film-coated tablet engraved with 255 on one side and plain on the other side contains 6.25 mg of Carvedilol. Tablets are supplied as follows:

NDC 43547-255-10 in bottles of 100 tablets

NDC 43547-255-50 in bottles of 500 tablets

NDC43547-255-11 in bottles of 1000 tablets

12.5 mg- Each white, oval shaped, biconvex, film-coated tablet engraved with 256 on one side and plain on the other side, and contains 12.5 mg of Carvedilol. Tablets are supplied as follows:

NDC 43547-256-10 in bottles of 100 tablets

NDC 43547-256-50 in bottles of 500 tablets

NDC 43547-256-11 in bottles of 1000 tablets

25 mg- Each white, oval shaped, biconvex, film-coated tablet engraved with 257 on one side and plain on the otherside contains 25 mg of Carvedilol. Tablets are supplied as follows:

NDC 43547-257-10 in bottles of 100 bottles

NDC 43547-257-50 in bottles of 500 tablets

NDC 43547-257-11 in bottles of 1000 tablets

Store below 30°C (86°F). Protect from moisture.

Dispense in a tight, light-resistant container

PATIENT MEDICATION INFORMATION SECTION

See FDA-Approved Patient Labeling (17.2).

17.1 Patient Advice

Patients taking Carvedilol Tablet should be advised of the following:

- Patients should take Carvedilol Tablet with food.
- Patients should not interrupt or discontinue using Carvedilol Tablet 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 symptomsof 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.
- 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 is provided as a tear off leaflet with this full prescribing information.

Manufactured By:

Shasun Pharmaceuticals Limited,

Unit-II, R.S. No.:32, 33 and 34, Shasun Road, Periyakalapet, Puducherry -605014. India

Mfg. Lic. No. 05 13 1523

Manufactured for:

Beximco Pharmaceuticals USA Inc.

4110 Regal Oaks Drive, P.O. Box 1060, Suwanee, GA 30024, USA

Distributed by:

Solco healthcare U.S., LLC

Cranbury, NJ 08512

code: 020002067

Revised - 12/2012

PATIENT INFORMATION – Rx only

Carvedilol Tablet

Read the Patient Information that comes with Carvedilol Tablet before you start taking them 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 Tablet, ask your doctor or pharmacist.

WHAT IS Carvedilol Tablet?

Carvedilol Tablet is a prescription medicine that belongs to a group of medicines called “betablockers”. Carvedilol Tablet is used, often with other medicines, for the following conditions:

- To treat patients with high blood pressure (hypertension)
- To treat patients who had a heart attack that worsened how well the heart pumps

Carvedilol Tablet is not approved for use in children under 18 years of age.

WHO SHOULD NOT TAKE CARVEDILOL Tablet?

Do not take Carvedilol Tablet if you:

- Have severe heart failure and are hospitalized in the intensive care unit or require certain intravenous medications that help support circulation (inotropic medications)
- Are prone to asthma or other breathing problems
- Have a slow heartbeat or a heart that skips a beat (irregular heartbeat)
- Have liver problems

- Are allergic to any of the ingredients in Carvedilol Tablet.
  The active ingredient is Carvedilol Tablet. See the end of this leaflet for a list of all the ingredients in Carvedilol Tablet.

WHAT SHOULD I TELL MY DOCTOR BEFORE TAKING CARVEDILOL Tablet?

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 Tablet can make some of your symptoms worse.
- Have diabetes
- Have thyroid problems
- Have a condition called pheochromocytoma
- Have had severe allergic reactions
- Are pregnant or trying to become pregnant. It is not known if Carvedilol Tablet is 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 Tablet passes into your breast milk. You should not breastfeed while using Carvedilol Tablet.
- Are scheduled for surgery and will be given anesthetic agents
- Are scheduled for cataract surgery and have taken or are currently taking Carvedilol Tablet.
- Are taking prescription or non-prescription medicines, vitamins, and herbal supplements. Carvedilol Tablet and certain other medicines can affect each other and cause serious side effects. Carvedilol Tablet may affect the way other medicines work. Also, other medicines may affect how well Carvedilol Tablet work.

Keep a list of all the medicines you take. Show this list to your doctor and pharmacist before you start a new medicine.

HOW SHOULD I TAKE Carvedilol Tablet?

It is important for you to take your medicine every day as directed by your doctor. If you stop taking Carvedilol Tablet suddenly, you could have chest pain and/or a heart attack. If your doctor decides that you should stop taking Carvedilol Tablet, your doctor may slowly lower your dose over a period of time before stopping it completely.
- Take Carvedilol Tablet exactly as prescribed. Your doctor will tell you how many Tablet to take and how often. In order to minimize possible side effects, your doctor might begin with a low dose and then slowly increase the dose.
- Do not stop taking Carvedilol Tablet and do not change the amount of Carvedilol Tablet you take without talking to your doctor.
- Tell your doctor if you gain weight or have trouble breathing while taking Carvedilol Tablet.
- Take Carvedilol Tablet with food.
- If you miss a dose of Carvedilol Tablet, 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 Tablet, call your doctor or poison control center right away.

WHAT SHOULD I AVOID WHILE TAKING Carvedilol Tablet?
- Carvedilol Tablet 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 Tablet?
- Low blood pressure (which may cause dizziness or fainting when you stand up). If these happen, sit or lie down right away and tell your doctor.
- Tiredness. If you feel tired or dizzy you should not drive, use machinery, or do anything that needs

you to be alert.
- Slow heartbeat.
- Changes in your blood sugar. If you have diabetes, tell your doctor if you have any changes in your blood sugar levels.
- Carvedilol Tablet may hide some of the symptoms of low blood sugar, especially a fast heartbeat.
- Carvedilol Tablet may mask the symptoms of hyperthyroidism (overactive thyroid).
- Worsening of severe allergic reactions.
- 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 Tablet. These reactions can be life-threatening.

Other side effects of Carvedilol Tablet include shortness of breath, weight gain, diarrhea, and fewer tears or dry eyes that become bothersome if you wear contact lenses.

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

How should I store Carvedilol Tablet?
- Store Carvedilol Tablet at 20° to 25°C (68° to 77°F). Keep the Tablet dry.
- Safely, throw away Carvedilol Tablet that are out of date or no longer needed.
- Keep Carvedilol Tablet and all medicines out of the reach of children.

GENERAL INFORMATION ABOUT Carvedilol Tablet

Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use Carvedilol Tablet for a condition for which they were not prescribed. Do not give Carvedilol Tablet to other people, even if they have the same symptoms you have. They may harm them.

This leaflet summarizes the most important information about Carvedilol Tablet. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Carvedilol Tablet that is written for healthcare professionals

WHAT ARE THE INGREDIENTS IN Carvedilol Tablet?

Active Ingredient: Carvedilol Tablet.

Inactive Ingredients: colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium citrate dihydrate, sucrose, and titanium dioxide.

Carvedilol Tablet Tablet come in the following strengths: 3.125 mg, 6.25 mg, 12.5 mg and 25 mg

Manufactured By:

Shasun Pharmaceuticals Limited,

Unit-II, R.S. No.:32, 33 and 34, Shasun Road, Periyakalapet, Puducherry -605014. India

Mfg. Lic. No. 05 13 1523

Manufactured for:

Beximco Pharmaceuticals USA Inc.

4110 Regal Oaks Drive, P.O. Box 1060, Suwanee, GA 30024, USA

Distributed by:

Solco healthcare U.S., LLC

Cranbury, NJ 08512

code: 020002067

Revised - 12/2012

CONTAINER LABELS

PRINCIPAL DISPLAY PANEL - 3.125 mg

NDC 43547-254-10 Rx only

Carvedilol Tablet

Tablet USP

3.125 mg

100 Tablet

Solco

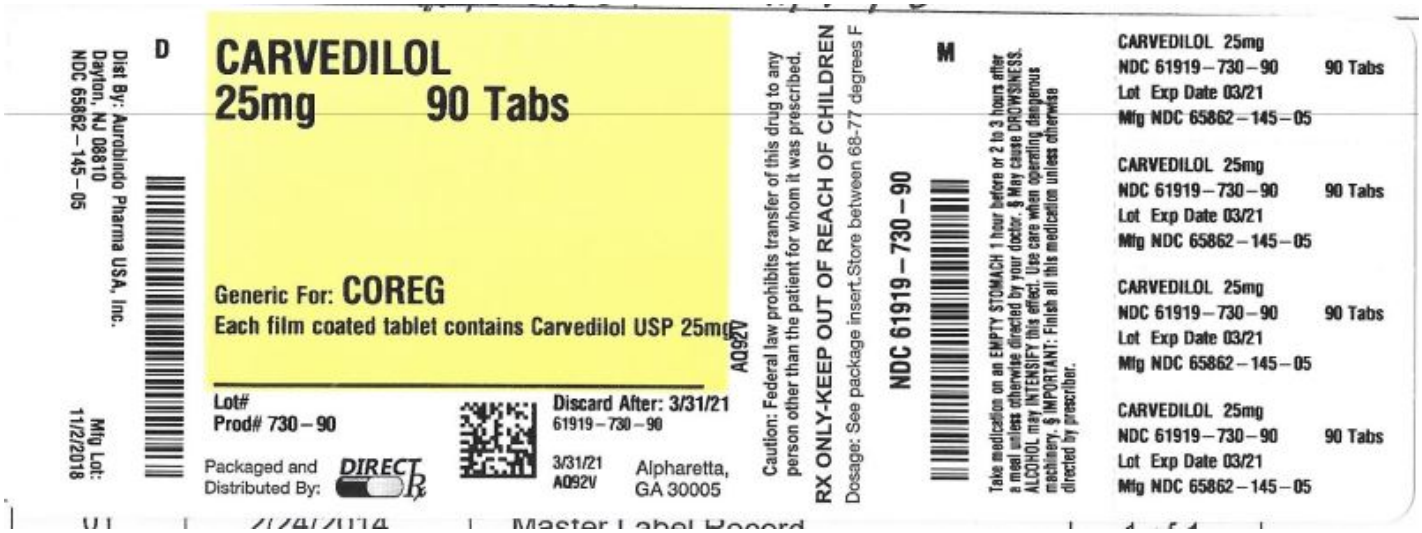
Healthcare U.S.

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

Patients taking carvedilol should be advised of the following:

Patients should take carvedilol with food.
Patients should not interrupt or discontinue using carvedilol 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.
Diabetic patients should report any changes in blood sugar levels to their physician.
Contact lens wearers may experience decreased lacrimation.

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL



CARVEDILOL

carvedilol tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61919-533(NDC:43547-257)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CARVEDILOL (UNII: 0K47UL67F2) (CARVEDILOL - UNII:0K47UL67F2)	CARVEDILOL	25 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 68401960MK)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
SODIUM CITRATE (UNII: 1Q73Q2JULR)	
SUCROSE (UNII: C151H8M554)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	white	**Score**	no score
Shape	OVAL	**Size**	15mm
Flavor		**Imprint Code**	257
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61919-533-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	01/01/2014	
2	NDC:61919-533-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	01/01/2014	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078384	01/01/2014	

CARVEDILOL

carvedilol tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:61919-730(NDC:65862-145)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
CARVEDILOL (UNII: 0K47UL67F2) (CARVEDILOL - UNII:0K47UL67F2)	CARVEDILOL	25 mg

Inactive Ingredients	
Ingredient Name	Strength
CROSPOVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	
POVIDONE K30 (UNII: U725QWY32X)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SUCROSE (UNII: C151H8M554)	
HYPROMELLOSE 2910 (5 MPA.S) (UNII: R75537T0T4)	

Product Characteristics			
Color	white (White to Off-white)	Score	no score
Shape	OVAL	Size	13mm
Flavor		Imprint Code	E;04
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61919-730-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/22/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078332	04/22/2019	

Labeler - DIRECT RX (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
DIRECT RX		079254320	relabel(61919-533) , repack(61919-533, 61919-730)

Revised: 4/2019 DIRECT RX