PRODUCT MONOGRAPH

[Pr]Dom-CARVEDILOL

Carvedilol Tablets, House Standard

3.125, 6.25, 12.5 and 25 mg

Congestive Heart Failure Agent

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Carvedilol Tablets, House Standard

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablets: 3.125 mg, 6.25 mg, 12.5 mg and 25 mg	Colloidal Silicon Dioxide, Crospovidone, Hydroxypropyl Methylcellulose, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Polydextrose , Polyethylene Glycol, Povidone, Titanium Dioxide and Triethyl Citrate.

INDICATIONS AND CLINICAL USE

Dom-CARVEDILOL (carvedilol) is indicated for the treatment of mild, moderate or severe heart failure of ischemic or non-ischemic origin to increase survival and also, to reduce the combined risk of all-cause mortality and cardiovascular or non-cardiovascular hospitalizations.

In general, Dom-CARVEDILOL is used in conjunction with diuretics and an ACE inhibitor, with or without digitalis.

Dom-CARVEDILOL should be prescribed by a physician experienced in the treatment of heart failure.

Beta blockers can cause worsening heart failure (see WARNINGS AND PRECAUTIONS). Since carvedilol has beta-blocking properties, care must be taken during initiation and up-titration of the drug in heart failure patients, since worsening heart failure has been observed during this phase of treatment. In order to minimize the risk of these events, it is critical to carefully follow the recommended dosing for Dom-CARVEDILOL in patients with congestive heart failure (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Carvedilol is contraindicated in patients with:

- decompensated cardiac failure requiring intravenous inotropic therapy with sympathomimetic agents
- bronchial asthma or related bronchospastic conditions (see WARNINGS AND PRECAUTIONS)
- second- or third- degree AV block, or sick sinus syndrome (unless a permanent pacemaker is in place)
- cardiogenic shock
- severe hypotension (see WARNINGS AND PRECAUTIONS)
- severe bradycardia (see WARNINGS AND PRECAUTIONS)
- primary obstructive valvular heart disease
- clinically manifest hepatic impairment (jaundice, ascites, spider angiomata, esophageal varices, etc.)
- mental incapacity (e.g. severe Alzheimer's, alcoholism, drug abuse), unless closely supervised by an appropriate caregiver
- hypersensitivity to carvedilol or any component of carvedilol tablets. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

Warnings and precautions are listed in alphabetical order.

General

Abrupt Cessation of Therapy
In patients with heart failure treated chronically with carvedilol, abrupt cessation of therapy may lead to deterioration. Therefore discontinuation of carvedilol should be done gradually, if possible.

Patients with ischemic heart disease should be warned against abrupt discontinuation of beta-adrenergic blocking agents. There have been reports of severe exacerbation of angina, and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris, following abrupt discontinuation of beta-blocker therapy.

The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuing carvedilol in patients with angina pectoris, the dosage should be gradually reduced over a period of about 2 weeks and the patient should be carefully observed. The same frequency of administration should be maintained. In situations of greater urgency, carvedilol therapy should be discontinued stepwise and under conditions of closer observation. If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with the drug be re-instituted promptly, at least temporarily.

Oculomucocutaneous Syndrome
Various skin rashes and conjunctival xerosis have been reported with beta-blockers. A severe syndrome (oculomucocutaneous syndrome) whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one beta-

adrenergic blocking agent (practolol). This syndrome has not been observed in association with carvedilol or any other such agent. However, physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

Cardiovascular

Cardiac Failure

Worsening cardiac failure may occur during initiation and up-titration of carvedilol. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade may further depress myocardial contractility.

Cardiac failure should be controlled for at least 4 weeks before carvedilol treatment is initiated. In clinical trials of mild to moderate heart failure, patients were required to be on stable doses of diuretics and ACE inhibitors (if tolerated) prior to the initiation of carvedilol. Despite these steps to ensure stability, a small number of patients with mild to moderate heart failure developed worsening heart failure. During the initiation of therapy (doses of 3.125 to 6.25 mg b.i.d. over 2 to 4 weeks) 6.0% of patients developed worsening congestive heart failure. During up-titration (12.5 to 50 mg b.i.d. over 2 to 6 weeks), worsening heart failure was reported in 5.1% of treated patients treated with carvedilol and in 4.1% of placebo patients.

In a placebo-controlled trial of patients with severe heart failure (COPERNICUS trial), worsening heart failure occurred during up-titration although the frequency reported during the first 3 months was similar with carvedilol (15.4%) and with placebo (14.8%). When treatment was maintained beyond 3 months, worsening heart failure was reported less frequently in patients treated with carvedilol than with placebo. Worsening heart failure observed during long-term therapy is more likely to be related to the patients' underlying disease than to treatment with carvedilol.

Administration of carvedilol to patients with controlled heart failure must be carried out under careful supervision. If symptoms occur, diuretics should be increased and the carvedilol dose not advanced or even lowered until clinical stability resumes (see DOSAGE AND ADMINISTRATION). However, it may be necessary to discontinue carvedilol. Such episodes may not preclude subsequent successful titration of the drug or a favorable response to carvedilol.

Hypotension

Hypotension and postural hypotension in congestive heart failure patients occurred with a higher incidence in carvedilol-treated than in placebo-treated patients (see ADVERSE REACTIONS). The risk of these events was highest during initiation of therapy and during the first 30 days of dosing corresponding to the up-titration period. Therefore, it is of critical importance that the dosing recommendation be followed (see DOSAGE AND ADMINISTRATION).

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.

Primary Regurgitative Valvular Heart Disease

Carvedilol should be used with caution in patients with primary regurgitative valvular disease as experience in this patient population is limited.

Prinzmetal's Angina
Beta-blocking agents may provoke chest pain in patients with Prinzmetal's angina. There has been no clinical experience with carvedilol in these patients. Caution should be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.

Sinus Bradycardia
Severe sinus bradycardia may occur with the use of carvedilol. In such cases, dosage should be discontinued.

In clinical trials, patients with a resting heart rate of less than or equal to 68 beats/minute prior to initiation of carvedilol were not studied.

Endocrine and Metabolism

Diabetes
Carvedilol should be administered with caution to patients subject to spontaneous hypoglycemia, or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic blocking drugs may enhance hypoglycemia, in patients prone to this condition. Also, diabetics on insulin or oral hypoglycemic medication may have an increased tendency towards hypoglycemia when treated with these drugs. It may also be necessary to adjust the dosage of oral hypoglycemics or insulin. Early signs of acute hypoglycemia, especially tachycardia, may be masked or attenuated. Regular monitoring of blood glucose is therefore recommended when carvedilol is initiated, adjusted or discontinued.

Hyperthyroidism
In patients with thyrotoxicosis, possible deleterious effects from long-term use of carvedilol have not been appraised. Beta-blockade, in general, may mask the clinical signs of continuing hyperthyroidism or complications, and give a false impression of improvement. Therefore, abrupt withdrawal of carvedilol may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

Pheochromocytoma
The effect of carvedilol in patients with pheochromocytoma has not been studied. Since paradoxical hypertensive responses have been reported in a few patients with this tumor when treated with β-blockers, physicians should use caution when administering carvedilol to patients with pheochromocytoma.

Hepatic
Hepatocellular injury, confirmed by rechallenge, has occurred rarely with carvedilol therapy.

Hepatic injury has been reversible and has occurred after short-and/or long-term therapy with minimal clinical symptomatology. No deaths due to liver function abnormalities have been reported in association with the use of carvedilol.

At the first symptom/sign of liver dysfunction (e.g. pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness or unexplained "flu-like" symptoms) laboratory testing should be performed. If the patient has laboratory evidence of liver injury or jaundice, carvedilol treatment should be stopped and not restarted.

Hepatic Impairment
Since carvedilol undergoes first-pass metabolism in the liver, reduced hepatic metabolism could lead to greater systemic bioavailability of carvedilol in patients with hepatic impairment. Care should be taken in selecting an appropriate dosage regimen for these patients (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION). Physicians should be aware of the potential for increased manifestations of vasodilation (dizziness, postural hypotension, hypotension, syncope) or beta-blockade (bradycardia, AV block) in patients with mild hepatic impairment receiving carvedilol (see DOSAGE AND ADMINISTRATION).

Immune

Allergic Reaction
There may be increased difficulty in treating an allergic-type reaction in patients on beta - blockers. In these patients, the reaction may be more severe due to pharmacological effects of beta-blockers and problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis.

On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other; these doses can be associated with excessive alpha-adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of beta agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm and norepinephrine to overcome hypotension.

Ophthalmologic

Contact Lens Use
Wearers of contact lenses should bear in mind the possibility of reduced lacrimation.

Uveal Binding
Animal studies have shown that carvedilol binds to the melanin of the uveal tract. The significance of this in humans is not known but periodic ophthalmic examinations are advisable while the patient is taking carvedilol.

Peri-Operative Considerations
Because of the synergistic negative inotropic and vasodilating effects of carvedilol and anesthetic drugs, the potential for pronounced hypotension during anesthesia exists. If carvedilol treatment is to be continued preoperatively, particular care should be taken when anesthetic agents which depress myocardial function are used.

Renal

Rarely, use of carvedilol in patients with congestive heart failure has resulted in acute renal failure and deterioration of renal function, likely on a pre-renal basis. Patients at risk appear to be those with low blood pressure (systolic BP < 100 mmHg), 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 and the drug discontinued or dosage reduced if worsening of renal function occurs (see DOSAGE AND ADMINISTRATION).

Respiratory

Bronchospasm (e.g. chronic bronchitis and emphysema)

Patients with bronchospastic disease should, in general, not receive β-blockers (see CONTRAINDICATIONS).

In clinical trials of patients with congestive 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 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.

Special Populations

Geriatrics: Pharmacokinetic studies indicate that AUC and T_{max} values are increased in elderly patients. Plasma levels of carvedilol averaged about 38% higher in elderly compared to young subjects. Therefore, dosage adjustments should be made with particular caution (see DOSAGE and ADMINISTRATION).

Nursing Women: Carvedilol and/or its metabolites are excreted in breast milk. Therefore, breast feeding is not recommended during administration of carvedilol.

Pediatrics: Safety and efficacy in children have not been established.

Pregnant Women: There have been no clinical studies carried out to specifically examine the use of carvedilol in pregnant women. Beta-blockers reduce placental perfusion, which may result in intrauterine fetal death, immature and premature deliveries. In addition, adverse effects (especially hypoglycemia and bradycardia) may occur in the fetus and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period.

Animal reproduction studies have revealed no teratogenic potential for carvedilol. Embryotoxicity was observed only after large doses in rabbits. The relevance of these findings for humans is uncertain.

Carvedilol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS

Overview

Mild to Moderate Heart Failure - Controlled Trials
The most frequent adverse experiences reported in the double-blind phase of the US clinical trial experience (see Table 1) in patients with mild to moderate heart failure treated with carvedilol were dizziness (32.4%), fatigue (23.9%), dyspnea (21.3%), upper respiratory infection (18.3%) cardiac failure (15.3%) and chest pain (14.4%).

During the double-blind phase of six US placebo controlled trials, adverse experiences rated as serious were reported in 22.4% of patients treated with carvedilol and 31.8% in the placebo group. The most serious adverse experiences reported with carvedilol were cardiac failure (5.6%), syncope (1.8%), bradycardia (1.6%), hypotension (1.3%), myocardial infarction (0.9%), acute renal failure (0.8%), and AV block (0.7%).

Of the 1202 patients who received randomized treatment in these trials, 5.4% of patients treated with carvedilol withdrew because of adverse experiences compared with 8.0% of placebo patients. Bradycardia, fatigue, hypotension, dizziness and dyspnea were the most commonly reported adverse experiences leading to discontinuation in patients treated with carvedilol (see Table 1).

Six deaths occurred in 1319 patients enrolled in the screening phase (3 to 4 weeks), 11 deaths occurred in 1313 patients challenged with carvedilol (2 to 4 weeks). There were 8 deaths (3/765 carvedilol; 5/437 placebo) during up titration phase (2 to 6 weeks) and 47 deaths (20/765 carvedilol; 27/437 placebo) during the maintenance phase (up to 12 months) of the studies.

Withdrawals due to worsening heart failure in U.S placebo controlled trials were as follows: during challenge 1.4% of patients (18/1313 for 2 to 4 weeks); during up-titration 0.9% (7/765) of patients treated with carvedilol and 0%(0/437) of placebo patients (2 to 6 weeks); during the maintenance phase 0.7% (5/765) of patients treated with carvedilol and 2.3% (10/437) of placebo patients (up to 12 months).

Worsening renal function, including acute renal failure (see Table 1), has been seen in some patients (carvedilol 9.5% and placebo 7.6%). Patients at greatest risk include those with pre-existing renal insufficiency, hypotension and ischemic cardiomyopathy, previous renal insufficiency due to ACE inhibitors, diffuse vascular disease, or evidence of renal artery stenosis.

Severe Heart Failure – Controlled Trials
The most frequent adverse experiences reported in a clinical trial in patients with severe heart failure treated with carvedilol were dizziness (24.1%), hypotension (13.9%) and upper respiratory infection (13.6%) (see Table 2). Median study exposure was 10.4 months for both carvedilol and placebo patients.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Mild to Moderate Heart Failure - Controlled Trials

In six US placebo controlled trials, 1313 patients were challenged with carvedilol over a 2 - 4 week period. Of these patients, 1202 were randomized to double blind treatment with carvedilol (n=765) or placebo (n=437). 92.5% of those treated with carvedilol reported at least one adverse experience.

Adverse experiences rated as severe in intensity during the double-blind phase of these trials were reported in 24.3% of patients treated with carvedilol. The most frequent severe adverse experiences were cardiac failure (2.9%), fatigue (2.2%), dizziness (2.0%), dyspnea (1.8%), and syncope (1.7%).

Table 1 shows adverse events reported in patients with mild to moderate heart failure enrolled in U.S. placebo-controlled clinical trials. Shown are adverse events that occurred more frequently in carvedilol-treated patients than placebo-treated patients with an incidence >1% regardless of causality. Median study medication exposure was 6.3 months for carvedilol and placebo patients.

Table 1

Adverse Events (% Occurrence and % Withdrawal) Occurring More Frequently with carvedilol than with Placebo in Patients with Mild to Moderate Heart Failure Enrolled in U.S. Heart Failure Trials (Incidence >1%, Regardless of Causality; Withdrawal Rates due to Adverse Events)

	Adverse Reactions		Withdrawals	
	Carvedilol (n=765) % occurrence	Placebo (n=437) % occurrence	Carvedilol (n=765) % withdrawals	Placebo (n=437) % withdrawals
Autonomic Nervous System				
Sweating increased	2.9	2.1	-	-
Body as a Whole				
Fatigue	23.9	22.4	0.7	0.7
Chest Pain	14.4	14.2	0.1	-
Pain	8.6	7.6	-	0.2
Injury	5.9	5.5	-	-
Drug level increased	5.1	3.7	-	0.2
Edema generalized	5.1	2.5	-	-
Edema dependent	3.7	1.8	-	-
Fever	3.1	2.3	-	-
Edema legs	2.2	0.2	0.1	0.2
Edema peripheral	1.6	0.7	-	-
Allergy	1.4	0.2	-	-
Sudden death	1.3	1.1	-	-
Malaise	1.3	0.7	-	-
Hypovolemia	1.2	0.2	-	-
Cardiovascular				
Bradycardia	8.8	0.9	0.8	-
Hypotension	8.5	3.4	0.4	0.2
Syncope	3.4	2.5	0.3	0.2
Hypertension	2.9	2.5	0.1	-
AV block	2.9	0.5	-	-
Angina pectoris aggravated	2.0	1.1	-	-
Fluid overload	1.7	1.6	-	-
Central Nervous System				
Dizziness	32.4	19.2	0.4	-
Headache	8.1	7.1	0.3	-
Paresthesia	2.0	1.8	0.1	-
Hypesthesia	1.7	1.1	-	-
Vertigo	1.4	1.1	-	-
Confusion	1.3	0.9	-	-
Somnolence	1.2	0.9	-	0.2
Gastrointestinal				
Diarrhea	11.8	5.9	0.3	-
Nausea	8.5	4.8	-	-
Abdominal pain	7.2	7.1	0.3	-
Vomiting	6.3	4.3	0.1	-
Melena	1.4	1.1	-	-
Periodontitis	1.3	0.7	-	-
Hematologic				
Thrombocytopenia	2.0	0.5	0.1	-
Prothrombin decreased	1.3	1.1	-	-
Purpura	1.3	0.2	-	-

	Adverse Reactions		Withdrawals	
	Carvedilol (n=765) % occurrence	**Placebo (n=437) % occurrence**	**Carvedilol (n=765) % withdrawals**	**Placebo (n=437) % withdrawals**
Metabolic				
Hyperglycemia	12.2	7.8	0.1	-
Weight increase	9.7	6.9	0.1	0.5
Gout	6.3	6.2	-	-
BUN increased	6.0	4.6	0.3	0.2
NPN increased	5.8	4.6	0.3	0.2
Hypercholesterolemia	4.1	2.5	-	-
Dehydration	2.1	1.6	-	-
Hypervolemia	2.0	0.9	-	-
Hyperuricaemia	1.8	1.6	-	-
Hypoglycemia	1.6	1.4	0.1	-
SGPT increased	1.4	0.9	-	-
Hyponatremia	1.3	1.1	-	-
Phosphatase alkaline increase	1.2	1.1	-	-
SGOT increased	1.2	0.9	-	-
Glycosuria	1.2	0.7	-	-
Musculoskeletal				
Back Pain	6.9	6.6	-	-
Arthralgia	6.4	4.8	0.1	0.2
Myalgia	3.4	2.7	-	-
Resistance Mechanism				
Upper respiratory tract infection	18.3	17.6	-	-
Infection	2.2	0.9	-	-
Reproductive male				
Impotence	1.7	0.9	-	-
Respiratory				
Sinusitis	5.4	4.3	-	-
Bronchitis	5.4	3.4	-	0.2
Pharyngitis	3.1	2.7	-	-
Urinary/Renal				
Urinary tract infection	3.1	2.7	-	
Hematuria	2.9	2.1	-	-
Renal function abnormal	1.7	1.4	0.3	-
Albuminuria	1.6	1.1	-	-
Acute renal failure	1.2	0.5	0.3	-
Vision				
Vision abnormal	5	1.8	0.1	-

In addition to the events in Table 1, the following events occurred in more than 1% of patients treated with carvedilol but rates were equal to, or more common in, placebo-treated patients: asthenia, cardiac failure, flatulence, anorexia, dyspepsia, palpitation, ventricular tachycardia, atrial fibrillation, extrasystoles, bilirubinemia, hyperkalemia, arthritis, angina pectoris, insomnia, depression, amnesia, anemia, viral infection, dyspnea, coughing, respiratory disorder, pneumonia, rhinitis, rash, pruritus, and leg cramps.

Adverse experiences related to laboratory parameters reported in greater than 1% of patients are in Table 1. Adverse experiences related to laboratory parameters reported in ≤1% but more than 0.1%

of patients included increased hepatic enzymes (0.4% of congestive heart failure patients were discontinued from therapy because of increases in hepatic enzymes; see WARNINGS AND PRECAUTIONS, Hepatic Impairment), hypokalemia, hypertriglyceridemia, anemia, leukopenia.

Severe Heart Failure - Controlled Trial

In a clinical trial in severe heart failure that compared carvedilol in daily doses of 50 mg (n=1156) with placebo (n=1133), 9.4% of patients treated with carvedilol discontinued treatment for adverse experiences versus 11.2% of placebo patients.

Table 2 shows adverse events reported in patients with severe heart failure enrolled in multinational placebo-controlled clinical trial. Shown are adverse events that occurred more frequently in carvedilol-treated patients than placebo-treated patients with an incidence >1% regardless of causality.

Table 2

Adverse Events (% Occurrence and % Withdrawals) Occurring More Frequently with carvedilol than with Placebo in Patients with Severe Heart Failure (Incidence >1%, Regardless of Causality)

	Adverse Reactions		Withdrawals	
	Carvedilol (n=1156) % occurrence	Placebo (n=1133) % occurrence	Carvedilol (n=1156) % withdrawals	Placebo (n=1133) % withdrawals
Body as a Whole				
Asthenia	10.9	9.4	0.4	0.7
Infection	2.5	2.4	-	-
Back pain	2.9	1.4	-	-
Cardiovascular				
Hypotension	13.9	8.2	0.6	0.4
Bradycardia	10.3	2.7	0.6	-
Syncope	7.6	5.0	0.4	0.4
Angina pectoris	5.5	4.1	0.1	0.1
Hypertension	2.6	2.2	-	0.1
Postural hypotension	1.8	1.0	0.1	0.1
Sinus bradycardia	1.7	0.4	-	-
Palpitation	1.6	1.5	-	0.1
Gastrointestinal				
Diarrhea	4.8	3.1	0.3	-
Nausea	3.8	3.3	-	0.1
Gastrointestinal disorder	1.6	1.1	0.1	0.1
Hematologic				
Anemia	2.4	2.0	-	-

	Adverse Reactions		Withdrawals	
	Carvedilol (n=1156) % occurrence	Placebo (n=1133) % occurrence	Carvedilol (n=1156) % withdrawals	Placebo (n=1133) % withdrawals
Metabolic and Nutritional				
Weight gain	11.7	10.7	0.1	0.1
Peripheral edema	7.0	6.4	0.2	0.1
Generalized edema	6.0	4.9	0.2	0.2
Hyperglycemia	4.5	3.3	0.0	0.1
Gout	3.5	2.7	-	-
Hyperkalemia	3.3	1.9	0.2	0.1
Creatinine increased	2.9	1.4	-	0.1
Diabetes mellitus	2.0	1.7	-	-
Weight loss	1.4	1.1	-	-
GGT increased	1.3	1.1	-	-
Nervous System				
Dizziness	24.1	16.8	1.3	0.6
Headache	4.8	3.0	-	0.1
Paresthesia	1.7	1.4	-	-
Respiratory				
Upper respiratory infection	13.6	12.6	0.1	-
Dyspnea	11.2	11.0	0.5	0.3
Bronchitis	5.2	4.5	0.1	-
Cough increased	4.5	4.2	0.1	0.2
Lung disorder	4.0	3.2	0.1	-
Sinusitis	1.6	1.1	-	-
Special senses				
Blurred vision	2.8	2.2	0.2	0.1
Urogenital				
Kidney failure	1.6	1.3	0.1	-

In addition to the events in Table 2, when compared with placebo, carvedilol-treated patients had fewer of the following adverse events related to the cardiovascular system and occurring in or equal to 2% of patients: sudden death, atrial fibrillation, chest pain, congestive heart failure, heart failure, peripheral vascular disorder, unstable angina pectoris and ventricular tachycardia. Other adverse experiences occurring in greater or equal to 2% but reported less frequently in carvedilol-treated patients include: abdominal pain, pain in the extremity, hypokalemia, lung edema, pneumonia, abnormal kidney function and urinary tract infection.

Less Common Clinical Trials Adverse Drug Reactions (< 1%)

Hypertension and Heart Failure - Open and Controlled Trials

The following adverse events were reported as possibly or probably related in worldwide open or controlled trials with carvedilol in patients with hypertension or congestive heart failure at an incidence of > 0.1% to ≤ 1%:

Cardiovascular: Peripheral ischemia, tachycardia.

Central and Peripheral Nervous System: Hypokinesia.

General: Substernal chest pain, edema.

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

Respiratory System: Asthma.

Reproductive, Male: Decreased libido.

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

Special Senses: Tinnitus.

Urinary System: Micturition frequency.

Autonomic Nervous System: Dry mouth, sweating increased.

Metabolic and Nutritional: Diabetes mellitus.

The following adverse events were reported as possibly or probably related in worldwide open or controlled trials with carvedilol in patients with hypertension or congestive heart failure at an incidence of ≤ 0.1%, 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, decreased HDL, pancytopenia, and atypical lymphocytes.

Post-Market Adverse Drug Reactions

Reports of aplastic anemia and severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme) have been rare and received only when carvedilol was administered concomitantly with other medications associated with such reactions. Urinary incontinence in women (which resolved upon discontinuation of the medication) and interstitial pneumonitis have been reported rarely.

DRUG INTERACTIONS

Overview

Inducers and Inhibitors of Cytochrome P450: Since carvedilol undergoes substantial oxidative metabolism, care may be required in patients receiving inducers or inhibitors of cytochrome P450, as plasma concentrations may be altered. Pre-treatment with *rifampin* (600 mg daily for 12 days) decreased the AUC and C_{max} for carvedilol approximately 70% following a single oral dose of carvedilol. Co-administration of carvedilol and *cimetidine* (1000 mg/day) resulted in a 30% increase in median AUC for carvedilol. Despite the reduction in oral clearance, peak plasma concentrations of carvedilol were unchanged due to an apparent decrease in rate of absorption.

Interactions of carvedilol with strong inhibitors of CYP2D6 (such as quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would be expected to increase blood levels of the R(+) enantiomer of carvedilol. 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 (see ACTION and CLINICAL PHARMACOLOGY – Special Populations and Conditions – Genetic Polymorphism).

Drug-Drug Interactions

Antihypertensive Agents: When administered concomitantly with other drugs that are anti-hypertensive in action or have hypotension as part of their adverse effect profile, carvedilol may have additive effects to excessively lower blood pressure.

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

Antiarrhythmics and Calcium Channel Blockers: Isolated cases of conduction disturbance (rarely with hemodynamic compromise) have been observed when carvedilol is co-administered with anti-arrhythmic agents or calcium channel blockers such as diltiazem and verapamil that can slow cardiac conduction. As with other agents with β-blocking properties, if carvedilol is to be administered orally with antiarrhythmics that slow conduction or calcium channel blockers of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored.

Digoxin: Following concomitant administration of carvedilol and digoxin, peak concentration of digoxin increased by approximately 30% and steady-state trough concentrations of digoxin were increased by about 15%. Both digoxin and carvedilol slow AV conduction. Therefore, increased monitoring of digoxin levels is recommended when initiating, adjusting or discontinuing carvedilol.

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

Cyclosporine: Modest increases in mean trough cyclosporin concentrations were observed following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30% of patients, the dose of cyclosporin had to be reduced in order to maintain cyclosporin concentrations within the therapeutic range, while in the remainder no adjustment was needed. On the average for the group, the dose of cyclosporin was reduced about 20% in these patients. Due to wide inter-individual variability in the dose adjustment required, it is recommended that cyclosporin concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporin be adjusted as appropriate.

Fingolimod: Concomitant use of fingolimod with beta blockers may potentiate bradycardic effects and is not recommended. Where such coadministration is considered necessary, appropriate monitoring at treatment initiation, i.e. at least overnight monitoring, is recommended.

Nitroglycerin: The effect of carvedilol co-administration with nitroglycerin has not been studied. Carvedilol could blunt the reflex tachycardia produced by nitroglycerin through its beta-adrenergic blocking activity. When it is used with nitroglycerin in patients with angina pectoris, additional decreases in blood pressure may occur.

Insulin or Oral Hypoglycemics: Agents with beta-blocking properties may enhance the blood-sugar reducing effect of insulin and oral hypoglycemics. Therefore, in patients taking insulin or oral hypoglycemics, regular monitoring of blood glucose is recommended.

Tricyclic Antidepressants: The effect of carvedilol co-administration with tricyclic antidepressants has not been studied. As an increased incidence of tremor has been observed with other drugs of this class upon co-administration of tricyclic antidepressants, the possibility of a drug interaction cannot be excluded.

Warfarin: Carvedilol (12.5 mg twice daily for 7 days) did not have an effect on warfarin-induced increase in steady-state prothrombin time ratios and did not alter the pharmacokinetics of both enantiomers of warfarin following concomitant administration with warfarin in healthy volunteers.

Drug-Food Interactions

Grapefruit Juice: Following simultaneous administration of a single dose of 25 mg of carvedilol with 300 mL of grapefruit juice (an inhibitor of CYP3A4 and CYP1A2), AUC for carvedilol was approximately 16% higher than following administration of carvedilol with 300 mL of water.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Dosage must be individualized and patients closely monitored during initiation and up-titration by a physician experienced in the treatment of heart failure.

All patients in whom Dom-CARVEDILOL therapy is to be considered must be clinically stable for 4 weeks prior to initiation of Dom-CARVEDILOL.

Prior to initiation of Dom-CARVEDILOL therapy, patients should be on stable doses of diuretics and angiotensin converting enzyme inhibitors, with or without digitalis. In clinical trials, all patients shown to have benefit were on the above regimen unless they were intolerant to an ace inhibitor.

Recommended Dose and Dosage Adjustment

The recommended starting dose of Dom-CARVEDILOL is 3.125 mg twice daily for two weeks. If this dose is tolerated, it can then be increased to 6.25, 12.5 and 25 mg twice daily over successive intervals of at least 2 weeks. Patients should be maintained on the highest tolerated dose. The maximum recommended dose is 25 mg twice daily. The dose of Dom-CARVEDILOL should not be increased until symptoms of worsening heart failure or vasodilation have stabilized.

Patients should be advised that initiation of treatment and, to a lesser extent, dosage increases may be associated with transient symptoms of dizziness or light-headedness, and rarely syncope, within the first 2 hours after dosing. During these periods, they should avoid situations such as driving or dangerous tasks where symptoms could result in injury. In addition, Dom-CARVEDILOL should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects, especially during up-titration. Symptoms of hypotension do not often require treatment, but it may be useful to separate the time of dosing of Dom-CARVEDILOL from that of the ACE inhibitor, or to reduce temporarily the dose of the ACE inhibitor.

The risk/benefit of carvedilol therapy in clinically stable heart failure patients with a heart rate lower than 68 beats per minute should be carefully considered prior to initiation of Dom-CARVEDILOL since carvedilol has not been studied in these patients (see WARNINGS AND PRECAUTIONS).

Before each dose increase the patient should be seen in the office and evaluated for symptoms of worsening heart failure, vasodilation (dizziness, light-headedness, symptomatic hypotension) or bradycardia, in order to determine tolerability of Dom-CARVEDILOL. Transient worsening of heart failure may be treated with increased doses of diuretics, lowering the dose of Dom-CARVEDILOL or, if necessary, discontinuation of Dom-CARVEDILOL. Symptoms of vasodilation such as dizziness, light-headedness or decreasing blood pressure may respond to a reduction in the dose of diuretics. If these changes do not relieve symptoms, the dose of Dom-CARVEDILOL should be decreased. If the dose of Dom-CARVEDILOL was decreased, it should not be increased again until symptoms of worsening heart failure or vasodilation have been stabilized for 2 weeks. Initial difficulty with titration may not preclude later attempts to re-introduce or resume titration of Dom-CARVEDILOL; however, caution is required in these circumstances. If congestive heart failure patients experience bradycardia (pulse rate below 55 beats/min.), the dose of Dom-CARVEDILOL should be reduced, or may require discontinuation.

Elderly

The frequency and pattern of adverse reactions in patients ≥ 65 years was similar to that in younger patients. However, plasma levels of carvedilol are higher in older patients compared to younger patients (see WARNINGS AND PRECAUTIONS). Therefore, after initiating Dom-CARVEDILOL at the same dose in the elderly as in younger patients, up-titration should be done

more cautiously in the elderly. A lower total daily dose may be reached at the end of up-titration in such patients compared to younger patients.

Hepatic Insufficiency
Dom-CARVEDILOL is contraindicated in patients with clinically manifest liver disease (see CONTRAINDICATIONS). In patients with milder hepatic impairment, there is a potential for increased manifestations of vasodilation and beta-blockade (see ACTION AND CLINICAL PHARMACOLOGY-Pharmacokinetics, and WARNINGS AND PRECAUTIONS). Therefore, after initiating Dom-CARVEDILOL at the same dose in patients with hepatic impairment as in other patients, up-titration should be done more cautiously in patients with hepatic impairment. A lower total daily dose may be reached at the end of up-titration in such patients compared to other patients.

Renal Insufficiency
Acute, reversible renal failure has been seen in some patients treated with Carvedilol; particularly those with underlying renal impairment (see WARNINGS AND PRECAUTIONS). Therefore, after initiating Dom- CARVEDILOL at the same dose in patients with renal impairment as in other patients, up-titration should be done more cautiously in patients with renal impairment. Renal function (BUN and creatinine) should be checked in such patients as appropriate. If renal function has deteriorated, the dose of Dom-CARVEDILOL may need to be reduced or discontinued.

Discontinuation
Dom-CARVEDILOL should be gradually reduced over a period of about 2 weeks, if possible, and the patient should be carefully observed (see WARNINGS AND PRECAUTIONS-Abrupt Cessation of Therapy).

OVERDOSAGE

Cases of overdosage with carvedilol alone or in combination with other drugs have been reported. Quantities ingested in some cases exceeded 1000 mg. Clinical signs experienced included low blood pressure and heart rate. Standard supportive treatment was provided and individuals recovered.

In the event of inadvertent or intentional overdosage with carvedilol, there may be severe hypotension, excessive bradycardia, heart failure, cardiogenic shock, and cardiac arrest due to its pharmacologic activities. There may also be respiratory distress, bronchospasm, vomiting, disturbed consciousness, and generalized seizures.

Patients who have taken an overdose of carvedilol should be placed supine, with their legs raised. For removal of the drug shortly after ingestion, gastric lavage or pharmacologically induced emesis may be useful. Carvedilol is not removed by hemodialysis. In addition to these general procedures, the patient's vital signs should be monitored under intensive care conditions with continuous monitoring, if necessary.

The following additional supportive therapies can be used:

If excessive hypotension occurs, vasopressors, norepinephrine or noradrenaline should be administered with continuous monitoring of the circulatory system. Digitalis, diuretics, and if necessary, dopamine or dobutamine should be administered if cardiac failure occurs.

For excessive bradycardia, atropine 0.5 to 2 mg should be given intravenously. In addition, glucagon 1 to 10 mg given intravenously over 30 seconds initially, followed by a continuous infusion of 2 to 2.5 mg/h, has been shown to be effective when severe overdosage of beta blockers causes hypotension and or bradycardia. For therapy-resistant bradycardia, pacemaker therapy may be necessary.

For bronchospasm, beta-sympathomimetics (as aerosol or intravenously) or intravenous aminophylline should be given.

In the event of seizures, slow intravenous injection of diazepam or clonazepam is recommended.

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

For management of a suspected drug overdose,
contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Carvedilol is a cardiovascular agent for the treatment of congestive heart failure that combines beta-adrenoceptor blockade and vasodilation in a single racemic mixture. Nonselective beta-adrenoceptor blocking activity is present in the S(-) enantiomer and $alpha_1$-adrenoceptor blocking activity is present at equal potency in both the R(+) and S(-) enantiomers. Carvedilol has no intrinsic sympathomimetic activity. Its action on beta-receptors is 10 times stronger than on $alpha_1$-receptors.

Carvedilol reduces peripheral vascular resistance by vasodilation, thereby causing a fall in systemic blood pressure after acute administration, predominantly mediated through selective alpha 1-antagonism. Beta blockade prevents reflex tachycardia with the net result that heart rate is unchanged or decreased. Carvedilol reduces renin release through beta blockade.

The mechanism for the beneficial effects of carvedilol in congestive heart failure has not been established.

Pharmacodynamics

In two studies that compared the acute hemodynamic effects of carvedilol to baseline measurements in patients with congestive heart failure, there were significant reductions in systemic blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and

heart rate. Initial effects on cardiac output, stroke volume index and systemic vascular resistance were small and variable.

In terms of chronic hemodynamic effects (12 to 14 weeks), carvedilol significantly reduced systemic blood pressure, pulmonary artery pressure, right atrial pressure, systemic vascular resistance and heart rate while stroke volume index was increased.

Pharmacokinetics

Table 3 - Summary of Mean Carvedilol Pharmacokinetic Parameters in Young Healthy Volunteers After Single Dose Administration

C_{max}* (ng/mL)	t½ * (h)	AUC (0-t)* (ng.h/mL)	Clearance^ (mL/min)	Volume of Distribution at Steady-state^ (L)
60 - 75	7 - 10	220 - 330	497 - 718	115
* 25 mg oral dose ^ intravenous administration				

Absorption: Carvedilol is rapidly absorbed following oral administration, with peak plasma concentrations of carvedilol observed at 1 hour post-dose in fasting subjects. Despite being well-absorbed, absolute bioavailability is approximately 25% to 35% due to a significant degree of first-pass metabolism.

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 time to reach peak plasma concentrations (about 2.3 hours post-dose), with no significant difference in extent of bioavailability.

Distribution: Carvedilol is highly bound to plasma proteins, (greater than 98%) primarily to 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.

Metabolism: Following oral administration, the apparent mean terminal elimination half-life of carvedilol ranges from 7 to 10 hours. Plasma clearance ranges from 500 to 700 mL/min. Carvedilol is extensively metabolized with less than 2% of the dose excreted unchanged in the urine. Carvedilol is metabolized mainly by glucuronidation and aromatic ring oxidation by the cytochrome P450 system (primarily CYP2D6 and CYP2C9 isozymes). The metabolites of carvedilol are excreted mainly via the bile into the feces.

Excretion: Elimination is mainly biliary. The primary route of excretion is via the feces.

A minor part is eliminated via the kidneys in the form of various metabolites.

Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R (+)- carvedilol approximately 2- to 3-fold higher than S(-)-carvedilol following oral administration in healthy

subjects. The mean apparent terminal elimination half-life for R (+)-carvedilol ranges from 5 to 9 hours compared with 7 to 11 hours for the S (-) enantiomer.

There are at least 5 pharmacologically active metabolites of carvedilol: desmethyl, 4'-hydroxyphenyl, 5'-hydroxyphenyl, 1-hydroxycarbazolyl and 8-hydroxycarbazolyl metabolites. Each of these metabolites has two enantiomeric forms and each metabolite possesses different relative potencies with regard to α- and β-receptor blocking activities. Plasma concentrations of these metabolites are 10 to 50-fold lower than those observed for the parent compound. Therefore, even for metabolites that are more active or at least as active as carvedilol itself, they are present at such low concentrations that they would produce effects less than, or at least not greater than, the parent compound.

Special Populations and Conditions

Geriatrics: Compared to young subjects (18 to 43 years old), AUC values for carvedilol were, on average, 38% higher in elderly (65 to 76 years old) subjects. Moreover, AUC values were 50% higher for S (-)-carvedilol and 23% for R (+)-carvedilol in the elderly compared to the young subjects. Changes in C_{max} values for carvedilol and its enantiomers were less pronounced, approximately 8% to 17% higher in elderly subjects with no apparent change in T_{max}. Although the terminal elimination half-lives of carvedilol were similar in both young and elderly subjects, the initial decline in plasma concentrations in the elderly appeared to be slower than in the young subjects suggesting a decrease in systemic clearance of carvedilol in the elderly (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: In patients with cirrhotic liver disease, the absolute bioavailability of carvedilol was 4 times greater as compared to healthy subjects with median C_{max} and AUC values for carvedilol 4 to 7 times higher in patients with liver disease following oral administration (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS).

Renal Insufficiency: Although carvedilol is metabolized primarily by the liver, plasma concentrations of carvedilol have been reported to be increased in patients with renal impairment. Based on AUC data, approximately 40% to 50% higher plasma concentrations of carvedilol were observed in hypertensive patients with moderate to severe renal impairment compared to a control group of hypertensive patients with normal renal function. However, the ranges of AUC values were similar for both groups. Changes in Cmax data were less pronounced, approximately 12% to 26% higher in patients with impaired renal function.

The pharmacokinetics of carvedilol are not altered by hemodialysis.

Patients with Congestive Heart Failure: Steady-state plasma concentrations of carvedilol and its enantiomers increased proportionally over the 6.25 to 50 mg b.i.d. dose range in patients with congestive heart failure. Compared to healthy subjects, patients with Class IV congestive heart failure had increased mean AUC and Cmax values for carvedilol and its enantiomers with up to 50% to 100% higher values than normal volunteers. The mean apparent terminal elimination half-life for carvedilol was similar to that observed in healthy subjects.

Genetic Polymorphism: Carvedilol is subject to genetic polymorphism with poor metabolizers of debrisoquin (deficient in CYP2D6) exhibiting 2- to 3-fold higher plasma concentrations of the R (+)-carvedilol compared to extensive metabolizers. In contrast, plasma levels of S (-)-carvedilol are increased only about 20% to 25% in poor metabolizers, indicating that the metabolism of this enantiomer is affected to a lesser extent by CYP2D6 than R(+)-carvedilol. The pharmacokinetics of carvedilol enantiomers do not appear to be different in poor metabolizers of S-mephenytoin, i.e., deficient in CYP2C19.

STORAGE AND STABILITY

Dom-CARVEDILOL tablets should be stored at room temperature, between 15°C and 30°C, in tightly closed containers or dispensed in a tight, light-resistant container. Protect from high humidity.

Since the tablets discolor when exposed to light, they should be kept in light resistant container.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Tablets:

3.125 mg: Each white, oval shaped, film-coated, debossed with "CV" on one side and plain on the other side tablet contains 3.125 mg of carvedilol and the following non-medicinal ingredients: Colloidal Silicone Dioxide, Crospovidone, Hydroxypropyl Methylcellulose, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Polydextrose, Polyethylene Glycol, Titanium Dioxide, Triethyl Citrate and Povidone.

6.25 mg: Each white, oval shaped, film-coated, debossed with "CV" on one side and "6.25" the other side tablet contains 6.25 mg of carvedilol and the following non-medicinal ingredients: Colloidal Silicone Dioxide, Crospovidone, Hydroxypropyl Methylcellulose, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Polydextrose, Polyethylene Glycol, Titanium Dioxide, Triethyl Citrate and Povidone.

12.5 mg: Each white, oval shaped, film-coated, debossed with "CV" on one side and "12.5" the other side tablet contains 12.5 mg of carvedilol and the following non-medicinal ingredients: Colloidal Silicone Dioxide, Crospovidone, Hydroxypropyl Methylcellulose, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Polydextrose, Polyethylene Glycol, Titanium Dioxide, Triethyl Citrate and Povidone.

25 mg: Each white, oval shaped, film-coated, debossed with "CV" on one side and "25" the other side tablet contains 25 mg of carvedilol and the following non-medicinal ingredients: Colloidal Silicone Dioxide, Crospovidone, Hydroxypropyl Methylcellulose, Lactose, Magnesium Stearate, Microcrystalline Cellulose,

Polydextrose, Polyethylene Glycol, Titanium Dioxide, Triethyl Citrate and Povidone.

Packaging

Dom-CARVEDILOL is available in HDPE bottles in pack sizes of 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

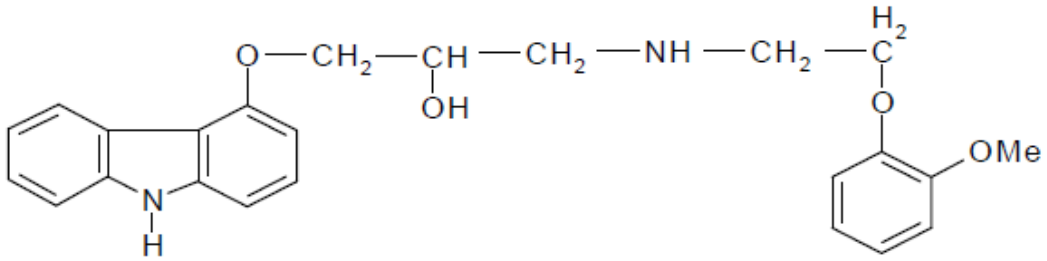
Drug Substance:

Common Name: Carvedilol

Chemical Name: 1-(9H-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol

Molecular Formula: $C_{24}H_{26}N_2O_4$

Structural Formula:



Molecular Weight: 406.49 g/mol

Physicochemical properties:

Description: White to off-white powder, Racemic form.

Melting point: 113°C - 117°C

Solubility: Insoluble in water, soluble in acetone and chloroform (1 g in 30 mL)

pKa value at 25°C: 7.9

CLINICAL TRIALS

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

[A single 12.5 mg (1 tablet) oral administration in the fasting state]
Dom-CARVEDILOL 12.5 mg Tablets (Dominion Pharmacal, Quebec, Canada) *vs.* COREG® 12.5 mg Tablets (SmithKline Beecham, Ontario, Canada)

Measured Data

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Mean
	Test A	Reference B	
AUC_T (ng·h/mL)	133.39 156.32 (73.29)	125.88 151.91 (78.49)	106
AUC_∞ (ng·h/mL)	140.83 164.03 (70.72)	134.80 160.47 (75.53)	104
C_{max} (ng/mL)	38.72 42.66 (47.41)	38.61 45.11 (54.11)	100
T_{max} (h)	1.03 (97.72)	0.81 (45.62)	---
$T_{1/2el}$ (h)	6.91 (62.90)	6.85 (52.48)	---

For T_{max}, and $T_{1/2el}$, the arithmetic mean only is presented.

STATISTICAL ANALYSIS

PARAMETER	POTENCY CORRECTED		MEASURED DATA	
	Ratio (%)*	90% CI	Ratio (%)*	90% CI
AUC_T (T/R)**	106	97 to 115	106	97 to 116
AUC_∞ (T/R)	104	96 to 113	104	96 to 114
C_{max} (T/R)	100	86 to 117	100	86 to 117

* Based on the geometric mean
** Test A/Reference B

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

[A single 12.5 mg (1 tablet) oral administration in the fasting state]

Dom-CARVEDILOL 12.5 mg Tablets (Dominion Pharmacal, Quebec, Canada) *v*s. COREG® 12.5 mg Tablets (SmithKline Beecham, Ontario, Canada)

Potency-Corrected Data

Parameter	Geometric Mean Arithmetic Mean (CV %)		Ratio
	Test A	Reference B	
AUC_T (ng·h/mL)	135.58 158.88 (73.29)	128.35 154.89 (78.49)	106
AUC_∞ (ng·h/mL)	143.15 166.72 (70.72)	137.45 163.62 (75.53)	104
C_{max} (ng/mL)	39.36 43.36 (47.41)	39.37 46.00 (54.11)	100
T_{max} (h)	1.03 (97.72)	0.81 (45.62)	---
$T_{1/2el}$ (h)	6.91 (62.90)	6.85 (52.48)	---

For T_{max}, and $T_{1/2el}$, the arithmetic mean only is presented.

STATISTICAL ANALYSIS

PARAMETER	POTENCY CORRECTED		MEASURED DATA	
	Ratio (%)*	90% CI	Ratio (%)*	90% CI
AUC_T (T/R)**	106	97 to 115	106	97 to 116
AUC_∞ (T/R)	104	96 to 113	104	96 to 114
C_{max} (T/R)	100	86 to 117	100	86 to 117

* Based on the geometric mean

** Test A/Reference B

In a US multicentre program, 1197 patients with stable symptomatic congestive heart failure, NYHA class II to IV, were challenged with a low dose of carvedilol (3.125 or 6.25 mg twice daily) for 2 to 4 weeks to determine tolerability. Of these patients, 1094 were then randomized to double-blind treatment with carvedilol (n=696) or placebo (n=398) and stratified to one of four studies based on baseline exercise performance, with the prestated objective to evaluate total mortality. The average duration of therapy on carvedilol was 6.5 months in this program. Patients entering the program had symptomatic congestive heart failure due to ischemic or non-ischemic cardiomyopathy with an ejection fraction ≤ 35%. All patients received conventional therapy, i.e. diuretics, angiotensin-converting enzyme (ACE) inhibitors, if tolerated, with or without digoxin.

On an intent-to-treat basis, total mortality in this program was 3.2% in the carvedilol group and 7.8% in the placebo group. Thus, a relative risk reduction of 65% (95% confidence limits 39 and 80%, p=0.001) was observed. Treatment with carvedilol was associated with a significant decrease in the relative risk of death from progressive pump failure (81 %, p=0.001) and the relative risk of sudden death (56%, p=0.033). The incidence of cardiovascular hospitalizations was 13% in the carvedilol group and 21% in the placebo group, with a relative risk reduction of 36% (95% confidence limits 14% and 53%, p=0.004).

Improved patient well-being was observed with carvedilol treatment in the US multicentre program, as indicated by a change in the NYHA class from baseline to endpoint for the four US phase III placebo-controlled studies. The overall between-group difference in distributions, stratified by protocol and baseline classification, was significant (p<0.001) and as also indicated by patient and physician global assessments during US Phase III trials, 78% of patients in the carvedilol group rated their condition as improved compared to 63% in the placebo group (p values over four studies from 0.001 to 0.032). However, exercise tolerance was not improved.

In a large multicenter trial of carvedilol, performed in Australia and New Zealand, 443 patients with stable symptomatic congestive heart failure NYHA Class I to III, were challenged with a low dose of carvedilol (3.125 mg or 6.25 mg twice daily) for 2 to 4 weeks to determine tolerability. Of these patients, 415 were then randomized to double-blind treatment with carvedilol (n=207) or placebo (n=208). The average duration of therapy on carvedilol was 16.1 months in this study. Patients entering the program had symptomatic congestive heart failure due to ischemic cardiomyopathy with an ejection fraction ≤ 45%. All patients received conventional therapy, i.e. diuretics, (ACE) inhibitors, if tolerated, with or without digoxin.

On an intent-to-treat basis, total mortality in this Australia and New Zealand trial was 10.1% in the carvedilol group and 13.9% in the placebo group, a non-statistically significant relative risk reduction of 29% (confidence limits -24% and 59%, p=0.231). Cardiovascular hospitalizations were 31% in the carvedilol group and 40% in the placebo group, a relative risk reduction of 28% (95% confidence limits: 1% and 48%, p=0.044). Patient well-being, as judged by NYHA class or Specific Activity Scale rating, as well as exercise tolerances were no different in the carvedilol group compared to the placebo group.

In the COPERNICUS trial, 2289 patients with severe heart failure were randomly assigned to treatment with placebo or carvedilol for up to 29 months. Patients had symptoms at rest or on minimal exertion and had a left ventricular ejection fraction < 25% (mean 20%), despite treatment

with diuretics (99%), an ACE inhibitor (89%), and digitalis (66% worldwide, 85% within Canada) for more than 2 months. Patients with cardiac impairment not related to left ventricular dysfunction were excluded as were patients with prior cardiac transplant, cardioplasty, unstable angina, myocardial infarction, destabilizing cardiac arrhythmias, or treatment within 1 month with an α-adrenoceptor antagonist (except for prostatism), a calcium channel blocker or a class I antiarrhythmic agent. The trial was followed by a data safety monitoring committee, which stopped the trial early after a median follow-up of 10.4 months because of an observed reduction in total mortality, the primary endpoint, from 19.7% per patient-year on placebo to 12.8% per patient-year on carvedilol, (a relative risk reduction of 35%; hazard ratio 0.65, 95% CI 0.52 and 0.81, and a P value adjusted for interim analyses of 0.0014). The results are summarized in Table 4 and Figure 1.

Table 4

Results of COPERNICUS

End point	Placebo N = 1133	Carvedilol N=1156	Hazard ratio (95% CI)	% Reduction	Nominal P value
Mortality	190	130	0.65 (0.52 – 0.81)	35	0.00013
Mortality + all hospitalization	507	425	0.76 (0.67 – 0.87)	24	0.00004
Mortality + CV hospitalization	395	314	0.73 (0.63 – 0.84)	27	0.00002
Mortality + CHF hospitalization	357	271	0.69 (0.59 – 0.81)	31	0.000004

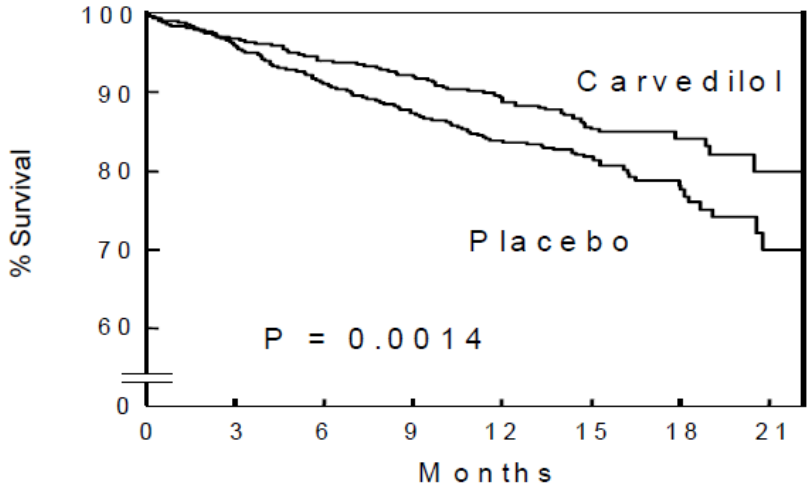


Figure 1: Survival analysis for COPERNICUS (intent-to-treat)

DETAILED PHARMACOLOGY

Beta-adrenoceptor blocking activity has been demonstrated in animal and human studies by showing that carvedilol 1) reduces exercise- and/or isoproterenol-induced tachycardia, and 2) reduces reflex orthostatic tachycardia. Significant beta-adrenoceptor blocking effect is usually seen within 1 hour of oral drug administration (in the fasting state). Carvedilol is not cardioselective, does not have intrinsic sympathomimetic activity, and possesses some membrane stabilizing activity.

Alpha 1-adrenoceptor blocking activity has been demonstrated in animal and human studies by showing that carvedilol 1) attenuates the pressor effects of phenylephrine but not of angiotensin II, 2) causes vasodilation; and 3) reduces peripheral vascular resistance. The onset of these effects is usually seen within 30 minutes of oral drug administration (in the fasting state).

In animal *in vivo* studies, and in human *in vitro* studies, carvedilol has been shown to have antioxidant activity. Some metabolites are ten-fold more potent than carvedilol in this regard, although these metabolites are found at serum concentrations ten-fold lower than those of carvedilol. The carbazole portion of the molecule is responsible for this antioxidant activity, which is found to be equally potent in each enantiomer; the beta-blocking and vasodilating actions reside in other parts of the molecular structure and both enantiomers of carvedilol are equally potent as antioxidants. The clinical significance of the antioxidant effect has not been established.

TOXICOLOGY

LD_{50} values in mg/kg after 14 days observation time (n=10 for all groups):

Species	Sex	Oral	I.P. (range)	I.V. (range)
Mouse	F	>8000	363 (273 to 445)	36 (31 to 40)
Mouse	M	>8000	568 (419 to 787)	27 (21 to 33)
Rat	F	>8000	769 (697 to 837)	25 (24 to 26)
Rat	M	>8000	1244 (1004 to 1430)	27 (24 to 26)

Almost all deaths occurred one to two days after dosing. No systemic clinical signs were observed in the animals treated orally. Animals dosed parenterally (except doses intraperitoneally) showed transient apathy and ptosis.

Long-Term Toxicity

Carvedilol was administered daily for 12 months to 5 dogs/sex/group at 0, 10, 30, 100, and 300 mg/kg given orally in two divided doses. Carvedilol was also administered daily in the food for 12 months to 30 rats/sex/group at doses of 30, 100, or 300 mg/kg and in another study for 18 months to 30 rats/sex/group at doses of 10, 31, 89, 261 mg/kg. Following oral administration, no toxic effects were seen at 10 mg/kg in the dog and at 30 mg/kg in the rat. These no-effect doses

are 14 and 42 times higher than a relatively high therapeutic dose in humans (based on a daily dose of 50 mg in a 70 kg patient).

Teratology Studies
Teratology studies show no evidence of carvedilol having teratogenic effects. In the fertility study, high doses resulted in reduced fertility and diminished general reproductive capacity in the F_0 generation and retardation in physical development in the F_1 generation. These adverse effects are regarded as nonspecific effects due to loading the parental generation with toxic dosages.

Mutagenicity Studies
No mutagenic potential of carvedilol was demonstrated in several *in vitro* and *in vivo* test systems.

Carcinogenicity Studies
Two-year carcinogenicity studies were conducted in both mice and rats. In the mouse study, groups of 50 mice/sex/group received daily doses of 20, 65 or 200 mg/kg in the diet. A group of 100 mice/sex/group were untreated and served as controls. In the rat study, groups of 50 rats/sex/group received 0, 200, 400, 800, or 1600 ppm carvedilol in the diet. These concentrations corresponded to daily dosages at the start of the study up to 21.7, 43, 86.7 and 169.5 mg/kg. Since the carvedilol dietary concentration did not change throughout the study and the animals gained weight, by the end of the study the actual daily dosages decreased to 9.5, 18.8, 38.1 and 74.7 mg/kg.

The results of the histopathologic examinations from these carcinogenicity studies indicated that carvedilol does not have either a tumorigenic or a carcinogenic potential.

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11. Comparative Bioavailability Study of Dom-CARVEDILOL 12.5 mg Tablets. Data on file at Dominion Pharmacal.

12. Product Monograph: COREG® (carvedilol) by GlaxoSmithKline Beecham Pharma. Date of Preparation: March 20, 2006. Control No. 103117.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

Dom-CARVEDILOL
(Carvedilol tablet)

Read this carefully before you start taking **Dom-CARVEDILOL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Dom-CARVEDILOL**.

What is Dom-CARVEDILOL used for?
Dom-CARVEDILOL is used to treat heart failure in adults.

How does Dom-CARVEDILOL work?
Dom-CARVEDILOL works by relaxing and widening your blood vessels. This makes it easier for your heart to pump blood around your body. This helps reduce your blood pressure and the strain on your heart.

What are the ingredients in Dom-CARVEDILOL?
Medicinal ingredient: carvedilol
Non-medicinal ingredients: colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, povidone, titanium dioxide, and triethyl citrate.

Dom-CARVEDILOL comes in the following dosage forms:
Film-coated Tablet: 3.125 mg, 6.25 mg, 12.5 mg and 25 mg

Do not use Dom-CARVEDILOL if:
- Your doctor did not prescribe it for you
- You are allergic to carvedilol or any of the other ingredients in Dom-CARVEDILOL
- You have severe heart failure that requires you to be in the hospital for treatment
- You have asthma, wheezing, bronchitis or other breathing problems
- You have an abnormal heart beat and do not have a permanent pacemaker in place
- You have severe heart damage and your heart is not able to pump enough blood to meet your body's needs
- You have very low blood pressure
- You have a very slow heart beat
- You have heart valve problems (primary obstructive valvular disease)
- You have severe liver disease
- You have problems making decisions (for example, if you have dementia, alcohol or drug problems). Do not use Dom-CARVEDILOL unless you are being cared for by an appropriate caregiver.
- Have one of the following rare hereditary diseases:
  - Galactose intolerance
  - Lapp lactase deficiency

  - Glucose-galactose malabsorption
- If you are 18 years or younger

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Dom-CARVEDILOL. Talk about any health conditions or problems you may have, including if you:

- Have a history of heart problems or disease
- Have or had kidney or liver problems
- Have low blood pressure
- Are pregnant or thinking of becoming pregnant
- Are breastfeeding
- Have diabetes. You could become less aware of the symptoms of hyperglycemia (high blood sugar) and you should monitor your blood sugar levels more carefully.
- Have thyroid problems
- Have Reynaud's syndrome. Dom-CARVEDILOL may increase the symptoms of coldness and/or spasms in your hands and feet or cramping pains in the legs when exercising.
- Have psoriasis (scaly red patches on your skin)
- Have problems with blood flow to your feet and legs (peripheral artery disease). Dom-CARVEDILOL can make your symptoms worse.
- Have a condition called pheochromocytoma (a tumour of the adrenal gland)
- Have allergic reactions or allergies
- Are having a planned surgery and will be given an anesthetic
- Wear contact lenses. You may suffer from eye dryness while using Dom-CARVEDILOL.

Other warnings you should know about:

Pregnancy: Dom-CARVEDILOL is not usually recommended for use during pregnancy. Your doctor will consider the benefit to you versus the risk to your unborn baby.

Breastfeeding: Dom-CARVEDILOL can pass into breast milk. Do not use Dom-CARVEDILOL if you are breastfeeding.

Driving and using machines: Before doing tasks that require special attention, wait until you know how you respond to Dom-CARVEDILOL.

Do not drink alcohol while taking Dom-CARVEDILOL.

You should have regular eye exams while taking Dom-CARVEDILOL.

Tell your health professional if you notice that your heart failure symptoms are getting worse, like an increase in shortness of breath, tiredness, dizziness, or swelling of the ankles. This may occur when your dose is increased and may indicate that your dose needs to be changed.

Do not stop taking Dom-CARVEDILOL all of a sudden. Under the care of your healthcare professional, it should be stopped slowly over 2 weeks.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Dom-CARVEDILOL:

- Alcohol
- Antidepressants used in the treatment of depression and mood disorders
- Antidiabetic drugs including insulin and oral medications
- Blood pressure drugs such as clonidine
- Cyclosporine used after organ transplants
- Digoxin, a heart medication
- Drugs used to treat stomach acid or heartburn (such as cimetidine)
- Drugs used to treat hypertension and irregular heartbeat (such as diltiazem and verapamil)
- Fingolimod, a medicine used to treat multiple sclerosis
- Grapefruit juice
- MAO inhibitors such as selegiline (Parkinson's Disease), tranylcypromine (depression)
- Nitroglycerin used to treat chest pain
- Rifampin used to treat tuberculosis
- Warfarin used to prevent blood clots

How to take Dom-CARVEDILOL:

Swallow the tablet **whole** with water. **DO NOT** chew, crush or break the tablet.

Take Dom-CARVEDILOL**:**

- exactly as prescribed
- every day
- twice a day, at about the same time every day
- with food

Usual adult dose:
Starting dose: 3.125 mg twice a day for 2 weeks
Maximum daily dose: 25 mg twice a day

Your doctor may start you on a different dose or change your dose over time depending on how Dom-CARVEDILOL works for you.

Do not stop taking Dom-CARVEDILOL without consulting your doctor. This can be dangerous.

Overdose:

If you think you have taken too much Dom-CARVEDILOL, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, take it as soon as you remember. You can take your next dose at the normal time, but do **NOT** take 2 doses within 6 hours of each other.

If you miss more than 2 doses of Dom-CARVEDILOL, contact your healthcare professional. Do **NOT** restart taking Dom-CARVEDILOL until you have spoken to your healthcare professional.

What are possible side effects from using Dom-CARVEDILOL?

These are not all possible side effects you may feel when taking Dom-CARVEDILOL. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

Side effects may include:
- headache
- trouble sleeping
- drowsiness
- weakness
- cough, stuffy and runny nose
- rash, itching
- abdominal pain, diarrhea, indigestion, nausea, vomiting
- back pain

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Breathing problems: trouble breathing, wheezing, shortness of breath and stuffy nose		✓	
COMMON **Allergic Reactions:** rashes, hot or itching skin			✓
Blurred vision		✓	
Chest pain		✓	
Constipation		✓	
Diarrhea		✓	
Dizziness when standing up		✓	
Fainting (passing out)		✓	
Headache		✓	
Impotence (in men): trouble getting or keeping an erection		✓	
Pain in the side including passing urine more or less frequently		✓	
Sleep disturbance: problems falling or staying asleep		✓	
Slowing of the heart rate		✓	
Nausea and vomiting		✓	
Swelling		✓	
Weight gain		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9
    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep your medication in a cool dry place away from direct heat or sunlight.

Keep out of reach and sight of children.

If you want more information about Dom-CARVEDILOL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website, (http://www.hc-sc.gc.ca), or by calling the manufacturer at 1-800-550-6060.

This leaflet was prepared by Dominion Pharmacal.

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