1.4.1

Prescribing Information (Summary of Product Characteristics)

1.4.1.1 Name of the medicinal Product

Carvedilol Tablets USP

1.4.1.1.1 Strength

6.25 mg/Tablet

1.4.1.1.2 Pharmaceutical Form

Oral Tablet

1.4.1.2 Qualitative and Quantitative Composition

1.4.1.2.1 Qualitative declaration

Carvedilol USP

1.4.1.2.2 Quantitative declaration

Sr. No	Ingredients Chemical Name	Specification	Standard Quantity/ Tablet (mg)	Reason for Inclusion
1	Carvedilol	USP	6.250	Alpha and beta blocking agent
2	Lactose Monohydrate	USP-NF	59.750	Diluent
3	Microcrystalline Cellulose (PH 102)	BP	50.000	Diluent
4	Colloidal Anhydrous Silica (Aerosil)	BP	2.000	Glidant
5	Crospovidone (Polyplasdone)	USP-NF	10.000	Disintegrant
6	Magnesium Stearate	BP	2.000	Lubricant
7	Colour Sunset Yellow Orange SC-SP-2029	In-House	4.000	Coating agent
8	Isopropyl Alcohol (IPA)	BP	40.000	Solvent
9	Dichloromethane (Methylene Dichloride)	BP	80.000	Solvent

1.4.1.3 Pharmaceutical Form

Solid Oral Dosage Form, Tablet

Orange coloured, round shaped, biconvex, film coated tablet, breakline on one side and plain on other side.

1.4.1.4 Clinical Particulars

1.4.1.4.1 Therapeutic Indications

Carvedilol is indicated for treatment of mild-to-severe chronic heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitors, and digitalis. Carvedilol is also indicated in left ventricular dysfunction following myocardial infarction and for the management of essential hypertension as alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

1.4.1.4.2 Posology and Method of Administration

Dose must be individualise. Patients should be maintained on lower doses if higher doses are not tolerated.

Heart Failure:

Recommended starting dose of carvedilol is 3.125 mg twice a day for two weeks. If well tolerated, dose may be increased slowly with intervals of not less than two weeks up to 6.25 mg twice a day, then up to 12.5 mg twice a day and finally up to 25 mg twice a day. The dosage should be increased to the highest tolerable level. Fluid retention should be treated by diuretics. Reduce the dose if patients experience bradycardia.

Left Ventricular Dysfunction following Myocardial Infarction:

Recommended starting dose of carvedilol is 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).

Hypertension:

Recommended starting dose of carvedilol 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 1 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. 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 action.

1.4.1.4.3 Contraindications

In Patients with history of serious hypersensitivity to carvedilol or to any of excipients of this product. In patient with bronchial asthma or related bronchospastic conditions, Second-or third-degree AV block, Sick sinus syndrome, Severe bradycardia, hypotension & Metabolic acidosis.

In patients with severe hepatic impairment, cardiogenic shock or who have decompensated heart failure requiring use of intravenous inotropic therapy.

1.4.1.4.4 Special Warnings and Special Precautions for Use

Carvedilol should be discontinued over 1 to 2 weeks whenever possible. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias upon abrupt cessation of therapy were observed.

Carvedilol may cause bradycardia, heart failure, hypotension and postural hypotension, syncope, worsening heart failure/fluid retention. Starting with low dose of carvedilol, administration with food, and gradual up-titration of carvedilol should decrease likelihood of syncope or excessive hypotension.

Plasma levels of carvedilol average about 50% higher in elderly compared with young subjects.

Avoid carvedilol in patients with bronchospastic disease (e.g., chronic bronchitis and emphysema However, if deemed necessary, use with caution and at lowest effective dose.

In diabetic patients, monitor glucose as carvedilol may mask symptoms of hypoglycemia or worsen hyperglycemia.

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

Lactation: Breast-feeding in not recommended in mothers receiving carvedilol.

1.4.1.4.5 Interaction with other medicinal products and other forms of interaction

Inhibitors of CYP2D6 isoenzyme, such as quinidine, fluoxetine, paroxetine, and propafenone, may increase blood levels of R(+) enantiomer of carvedilol.

Patients taking carvedilol with reserpine and MAO inhibitors should be observed closely for signs of hypotension and/or severe bradycardia.

Cyclosporine concentrations be monitored closely after initiation of carvedilol therapy due to modest increases in mean trough cyclosporine concentrations.

Concomitant use of digitalis glycosides and carvedilol can increase the risk of bradycardia.

Rifampicin reduced plasma concentrations of carvedilol by about 70%.

Amiodarone, and its metabolite desethyl amiodarone, inhibitors of CYP2C9 and P-glycoprotein increased concentrations of S(-)-enantiomer of carvedilol by at least 2fold. Concomitant administration of amiodarone or other CYP2C9 inhibitors such as fluconazole with carvedilol may enhance β-blocking properties of carvedilol resulting in further slowing of heart rate or cardiac conduction.

Conduction disturbance has been observed when carvedilol is coadministered with diltiazem.

Carvedilol may enhance blood-sugar-reducing effect of insulin and oral hypoglycemics.

1.4.1.4.6 Pregnancy and Lactation

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

Lactation: Breast-feeding in not recommended in mothers receiving carvedilol.

1.4.1.4.7 Effects on ability To Drive and use Machines

Carvedilol tablets may cause dizziness, tiredness or faintness. It is advisable not to drive a car, use machinery, or do anything that needs the patient to be alert if these symptoms are observed.

1.4.1.4.8 Undesirable Effects

Body as a Whole: Asthenia, fatigue, increased digoxin level, generalized edema, dependent edema, allergy, malaise, hypovolemia, fever, leg edema, dry mouth, sweting

Cardiovascular: Bradycardia, hypotension, syncope, angina pectoris, fluid overload, postural hypotension, aggravated angina pectoris, AV block, palpitation, hypertension, peripheral ischemia, tachycardia.

Central Nervous System: Dizziness, headache, hypesthesia, vertigo, paresthesia, somnolence, insomnia, hypokinesia, nervousness, sleep disorder, aggravated depression, impaired concentration, abnormal thinking, paroniria, emotional lability

Gastrointestinal: Diarrhea, nausea, vomiting, melena, periodontitis, bilirubinemia, increased hepatic enzymes

Metabolic and nutritional: Hyperglycemia, weight increase, increased BUN, increased NPN, hypercholesterolemia, peripheral edema, hyperuricemia, hypoglycemia, hyponatremia, increased alkaline phosphatase, glycosuria, hypervolemia, diabetes mellitus, GGT increased, weight loss, hyperkalemia, increased creatinine.

Musculoskeletal: Arthralgia, muscle cramps

Respiratory: Increased cough, rales, asthma

Hemopoietic system: Decreased prothrombin, purpura, thrombocytopenia.

Special senses: Abnormal vision, blurred vision, tinnitus

Urinary and Reproductive system: Decreased libido, Impotence, renal insufficiency, albuminuria, hematuria, increased micturition

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

1.4.1.4.9 Overdose

Symptoms: Hypotension, bradycardia, cardiac insufficiency, cardiogenic shock, and cardiac arrest. Respiratory problems, bronchospasms, vomiting, lapses of consciousness, and generalized seizures.

Treatment: Administer Atropine 2 mg IV for excessive bradycardia. To support cardiovascular function, administer glucagon, 5 to 10 mg IV rapidly over 30 seconds, followed by continuous infusion of 5 mg/hour and sympathomimetics (dobutamine, isoprenaline, adrenaline) at doses according to body weight and effect. Supportive treatment should be continued for a sufficiently long period of time.

1.4.1.5 Pharmacological Properties

1.4.1.5.1 Pharmacodynamics Properties

Carvedilol is a racemic mixture in which nonselective β-adrenoreceptor blocking activity is present in S(-) enantiomer and α1-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency. Carvedilol has no intrinsic sympathomimetic activity and reduces the peripheral vascular resistance by selective alpha1-receptor blockade and suppresses reninangiotensin through non-selective beta-blockade. β-adrenoreceptor blocking activity of carvedilol reduces cardiac output in normal subjects, reduces exercise- and/or isoproterenol-induced tachycardia and reduces reflex orthostatic tachycardia within 1 hour of administration. α1-adrenoreceptor blocking activity of carvedilol attenuates the pressor effects of phenylephrine, causes vasodilation, reduces peripheral vascular resistance within 30 minutes of administration.

1.4.1.5.2 Pharmacokinetic Properties

Carvedilol is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25% to 35% & terminal elimination half-life from 7 to 10 hours. Taking carvedilol with food should minimize the risk of orthostatic hypotension. Carvedilol is extensively metabolized primarily by aromatic ring oxidation and glucuronidation. Less than 2% of the dose was excreted unchanged in urine. Oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. Metabolites of carvedilol are excreted primarily via the bile into feces. Carvedilol is more than 98% bound to plasma proteins.

1.4.1.5.3 Preclinical Safety Data

Not stated.

1.4.1.6 Pharmaceutical Particulars

1.4.1.6.1 List of Excipients

Lactose Monohydrate (USP-NF)
Microcrystalline Cellulose (PH 102)(BP)
Colloidal Anhydrous Silica (Aerosil) (BP)
Crospovidone (Polyplasdone) (USP-NF)
Magnesium Stearate (BP)
Colour Sunset Yellow Orange SC-SP-2029 (In-House)

Isopropyl Alcohol (IPA) (BP)

Dichloromethane (Methylene Dichloride) (BP)

1.4.1.6.2 Incompatibilities

Not applicable.

1.4.1.6.3 Shelf Life

36 months

1.4.1.6.4 Special Precautions for Storage

Store below 30°C. Protect from light.

1.4.1.6.5 Nature and Contents of Container

Orange coloured, round shaped, biconvex, film coated tablet, breakline on one side and plain on other side. 14 Tablets are packed in a Alu-PVC Blister Pack. Such 2 Blisters are packed in a printed carton with a packing insert.

1.4.1.6.6 Special precaution for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

1.4.1.7 Marketing Authorization Holder And Manufacturing Site Addresses

1.4.1.7.1 Name and Address of Marketing Authorization Holder

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

1.4.1.7.2 Name and Address of manufacturing site(s)

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

1.4.1.8 Marketing Authorization Number

To be included after obtaining first registration.

1.4.1.9 Date of First <Registration> / Renewal of The <Registration>

It will be applicable after registration of this product.

1.4.1.10 Date of Revision of the Text

1.4.1.11 Dosimetry (If Applicable)

Not Applicable

1.4.1.12 Instructions for preparation of radiopharmaceuticals (if Applicable)

Not Applicable