SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. Name of the medicinal product

CARVICARD 3.125 (CARVEDILOL TABLETS USP 3.125 MG)
CARVICARD 6.25 (CARVEDILOL TABLETS USP 6.25 MG)
CARVICARD 12.5 (CARVEDILOL TABLETS USP 12.5 MG)
CARVICARD 25 (CARVEDILOL TABLETS USP 25 MG)

2. Qualitative and quantitative composition

COMPOSITION :

CARVICARD 3.125: Each uncoated tablet contains:
Carvedilol USP …3.125 mg
Excipients (QS)

CARVICARD 6.25: Each uncoated tablet contains:
Carvedilol USP …6.25 mg
Excipients (QS)

CARVICARD 12.5: Each uncoated tablet contains:
Carvedilol USP …12.5 mg
Excipients (QS)

CARVICARD 25: Each uncoated tablet contains:
Carvedilol USP …25 mg
Excipients (QS)

Sr. No.	Ingredients	Spec.	Qty. in mg/ Tab For 3.125 mg	Qty. in mg/ Tab For 6.25 mg	Qty. in mg/ Tab For 12.5 mg	Qty. in mg/ Tab For 25 mg	Function
1	Carvedilol	USP	3.125	6.250	12.500	25.000	Active
2	Dibasic Calcium Phosphate	BP	59.880	56.750	56.500	50.000	Diluent
3	Lactose	BP	50.000	50.000	47.000	41.000	Diluent
4	Maize Starch	BP	10.000	10.000	7.000	7.000	Binder
5	Maize Starch (for paste)	BP	7.000	7.000	7.000	7.000	Binder
6	Quinoline Yellow Supra	IHS	---	0.021	---	---	Colourant
7	Erythrosine	IHS	---	---	0.021	---	Colourant
8	Sunset Yellow	IHS	---	---	---	0.021	Colourant
9	Sodium Starch Glycolate (Type A)	BP	3.000	3.000	3.000	3.000	Super-Disintegrant
	Purified Water*	IHS	Q.S.	Q.S.	Q.S.	Q.S.	Solvent
	Lubrication						
10	Purified Talc	BP	1.000	1.000	1.000	1.000	Glidant
11	Magnesium Stearate	BP	1.000	1.000	1.000	1.000	Lubricant
12	Croscarmellose Sodium	BP	2.000	2.000	2.000	2.000	Disintegrant

13	Maize Starch (Dried) (Additional)**	BP	1.700	1.700	1.700	1.700	Binder
14	Sodium Starch Glycolate (Type A)	BP	3.000	3.000	3.000	3.000	Super-Disintegrant
	Total		**140.000**	**140.000**	**140.000**	**140.000**	

* Additional quantity of Maize Starch is added to compensate the loss on drying.
** Purified Water is used as solvents so does not appear in the final product.

USP: United States Pharmacopoeia
BP: British Pharmacopoeia
IHS - IN- House Specification

3. Pharmaceutical form

Uncoated Tablets

4. Clinical particulars

4.1 Therapeutic indications

- Essential hypertension.
- Chronic stable angina pecioris
- Adjunctive treatment in moderate to severe stable heart failure.

4.2 Posology and method of administration

Carvedilol is available in 4 strengths: 3.125 mg, 6.25 mg, 12.5 mg and 25 mg

Essential hypertension

Carvedilol may be used for the treatment of hypertension alone or in combination with other antihypertensives, especially thiazide diuretics. Once daily dosing is recommended, however the recommended maximum single dose is 25 mg and the recommended maximum daily dose is 50 mg

Adults:

The recommended initial dose is 12.5 mg once a day for the first two days. Thereafter, the treatment is continued at the dose 25 mg/day. If necessary, the dose may be further increased gradually at intervals of at least two weeks.

Elderly:

The recommended initial dose in hypertension is 12.5 mg once a day, which may also be sufficient for continued treatment. However, if the therapeutic response is inadequate at this dose, the dose may be further increased gradually at intervals of at least two weeks.

Chronic stable angina pectoris

Adults:

The recommended initial dose is 12.5 mg twice daily for two days. Thereafter, the treatment is continued at the dose 25 mg twice daily, If necessary, the dose may be further increased gradually at intervals of at least two weeks, The recommended maximum daily dose is 100 mg in two doses (50 mg twice daily).

Elderly:

The recommended initial dose is 12.5 mg twice daily for two days. Thereafter, the treatment is continued at the dose 25 mg twice daily, which is the recommended maximum daily dose.

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Heart failure

Treatment of moderate to severe heart failure in addition to conventional basic therapy with diuretics, ACE inhibitors, digitalis, and/or vasodilators, The patient should be clinically stable (no change in NYHA-class, no hospitalization due to heart failure) and the basic therapy must be stabilized for at least 4 weeks prior to treatment. Additionally, the patient should have a reduced left ventricular ejection fraction and heart frequency should be > 50 bpm and systolic blood pressure > 85 mm Hg.

The Initial dose is 3.125 mg twice a day for two weeks. If the Initial dose is well tolerated, the carvedilol dose can be increased at intervals of at least two weeks, first to 6.25 mg twice daily, then 12.5 mg twice daily followed by 25 mg twice daily, it is recommended that the dose is increased to the highest level tolerated by the patient

The recommended maximum dose is 25 mg given twice daily for patients weighing less than 85 kg and 50 mg twice daily tor patients weighing more than 85 kg, provided that the heart failure is not severe. A dose increase to 50 mg twice daily should be performed carefully under close medical supervision of the patient.

Transient worsening of symptoms of heart failure may occur at the beginning of treatment, or due to a dose increase, especially in patients with severe heart failure and/or under high dose diuretic treatment. This does not usually call for discontinuation of treatment, but the dose should not be increased. The patient should be monitored by a physician/cardiologist after starting carvedilol treatment or increasing the dose. Before each dose increase, an examination should be performed for potential symptoms of worsening heart failure or for symptoms of excessive vasodilation (e,g. renal function, body weight blood pressure, heart rate and heart rhythm). Worsening of heart failure or fluid retention is treated by increasing the dose of diuretic, and the dose of carvedilol should not be increased until the patient is stabilized. If bradycardia appears or in case of lengthening of AV conduction, the level of digoxin should first be monitored. Occasionally it may be necessary to reduce the carvedilol dose or temporarily discontinue treatment altogether. Even in these cases, carvedilol! dose titration can often be successfully continued.

If carvedilol therapy is discontinued for more than two weeks, it should be reinitiated at 3.125 mg twice daily and increased gradually in accordance with the above recommendation.

Renal insufficiency

Dosage must be determined for ea.ch patient individually, but according to pham1aookinetlc parameters there Is no evidence that dose adjustment of carvedilol in patients with renal failure is necessary.

Moderate hepatic dysfunction

Dose adjustment may be required.

Children and adolescents

There is insufficient data on the efficacy and safety of carvedilol in children and adolescents under 18 years of age.

Elderly

Elderly patients may be more susceptible to the effects of carvedilol and should be monitored more carefully.

As with other blocker blockers and especially in coronary patients treatment with carvedilol should be withdrawn gradually.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Method of administration

The tablets do not need to be taken with a meal. However, it is recommended that heart failure patients take their carvedilol medication with food to allow the absorption to be slower and the risk of orthostatic hypotension to be reduced.

4.3 Contraindications

- Hypersensitivity to carvedilol or to any of the excipients listed.
- Unstable/decompensated heart failure
- Clinically manifest liver dysfunction
- 2nd and 3rd degree AV block (unless a permanent pacemaker is in place)
- Severe bradycardia (<50 bpm)
- Sick sinus syndrome (including sino-atrial block)
- Severe hypotensio11 (systolic blood pressure <85 mmHg}
- Cardiogenic shock
- Chronic Obstructive Pulmonary Disease (COPD) with bronchospasm or asthma.

4.4 Special warnings and precautions for use

Chronic congestive heart failure

Carvedilol should be administered principally in addition to diuretics, ACE inhibitors, digitalis and/or vasodilators. Therapy should only be initiated if the patient is stabilized on conventional basic therapy for at least 4 weeks. Decompensated patients have to be re-compensated. Patients with severe heart failure, salt and volume depletion, elderly patients or patients with low basic blood pressure should be monitored for approximately 2 hours after the first dose or after dose increase as hypotension may occur.

In congestive heart failure patients, worsening cardiac failure or fluid retention may occur during up-titration of carvedilol. If such symptoms occur, diuretics should be increased, and the carvedilol dose should not be advanced until clinical stability resumes. Occasionally it may be necessary to lower the carvedilol dose or, in rare cases, temporarily discontinue it. Such episodes do not preclude subsequent successful titration of carvedilol. Carvedilol should be used with caution in combination with digitalis glycosides, as both drugs slow AV conduction.

Renal function in congestive heart failure

Reversible deterioration of renal function has been observed with carvedilol therapy In chronic heart failure patients with low blood pressure (systolic BP <100 mmHg\ ischemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency. In heart failure patients with these risk factors, renal function should be monitored during dose titration of carvedilol. If significant worsening of renal function occurs, the carvedilol dose must be reduced, or therapy must be discontinued

Left ventricular dysfunction following acute myocardial infarction. Before treatment with carvedilol is initiated the patient must be clinically stable and should have received an ACE Inhibitor for at least the preceding 48 hours, and the dose of the ACE inhibited should have been stable for at least the preceding 24 hours.

First degree AV block

Because of its negative dromotropic action, carvedilol should be administered with caution to patients with first degree heart block.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Chronic obstructive pulmonary disease

Carvedilol should be used with caution in patients with chronic obstructive pulmonary disease (COPD) with a bronchospastic component who are not receiving oral or inhaled medication, and only if the potential benefit outweighs the potential risk.

In patients with a tendency to bronchospasm, respiratory distress can occur as a result. of a possible increase in airway resistance. Patients should be closely monitored during initiation and up-titration to carvedilol and the dose of carvedilol should be reduced if any evidence of bronchospasm is observed during treatment.

Diabetes

Care should be taken in the administration of carvedilol to patients with diabetes mellitus, aa the early signs and symptoms of acute hypoglycemia may be masked or attenuated. In chronic heart failure patients with diabetes, the use of carvedilol may be associated with worsening control of blood glucose. Therefore, close monitoring of diabetic patients receiving carvedilol is required by means of regular blood glucose measurements and adjustment of antidlab0tic medication as necessary.

Peripheral vascular disease

Carvedilol should be used with caution in patients with peripheral vascular disease as beta-blockers can precipitate or aggravate symptoms of arterial insufficiency.

Raynaud's phenomenon

Carvedilol should be used with caution in patients suffering from peripheral circulatory disorders (e.g. Raynaud's phenomenon) as tile re may be exacerbation of symptoms.

Thyrotoxicosis

Carvedilol may obscure the symptoms of thyrotoxicosis

Anesthesia and major surgery

Caution should be exercised in patients undergoing general surgery, because of the synergistic negative inotropic effects of carvedilol and anesthetic drugs.

Bradycardia

Carvedilol may induce bradycardia. if the patient's pulse rate decreases to less than 55 beats per minute, the dosage of carvedilol should be reduced

Hypersensitivity

Care should be taken in administering carvedilol to patients with a history of serious hypersensitivity reactions, and in those undergoing desensitization therapy, as beta-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions.

Severe skin reactions

Very rare cases of severe skin reaction such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported during treatment with carvedilol.

Psoriasis

Patients with a history of psoriasis associated with beta-blocker therapy should take carvedilol only after consideration of the risk-benefit ratio.

Concomitant use of calcium channel blockers and other antiarrhythmic drugs Careful monitoring of ECG and blood pressure is necessary in patients receiving concomitant therapy witl7 calcium channel blockers of the verapamil or diltiazem type or other antiarrhythmic drugs, specifically amiodarone. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypo tension and atrio-ventricular block.

Phaeochromocytoma

In patients with phaeochromocytoma, an alpha-blocking agent should be initiated prime to the use of any beta-blocking agent. Although carvedilol has both alpha- and beta-blocking pharmacological

activities, there is no experience with its use in this condition. Caution should therefore be taken in the administration of carvedilol to patients suspected of having phaeochromocytoma,

Prinzmetal's variant angina

Agents with non-selective beta blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There is no clinical experience with carvedilol in these patients although the alpha-blocking activity of carvedilol may prevent such symptoms. Caution should, however, be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.

Metabolic acidosis

Carvedilol should be used with caution in patients with metabolic acidosis

Contact lenses

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

Carvedilol treatment should not be discontinued abruptly, particularly in patients suffering from ischemic heart disease. The withdrawal of carvedilol should be gradual (over a period of two weeks).

Poor metabolizers of debrisoquine

Patients who are known as poor metabolizers of debrisoquine, should be closely monitored during initiation of therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Telmisartan

Pharmacokinetic interactions

Carvedilol is a substrate as well as an inhibitor of P-glycoprotein. Therefore. the bioavailability of drugs transported by

P-glycoprotein may be increased with concomitant administration of carvedilol. In addition, the bioavailability of carvedilol can be modified by inducers or inhibitors of p-glycoprotein.

Inhibitors as well as inducers of CYP2D6 and CYP2C9 can modify the systemic and/or presystemic metabolism of carvedilol stereo-selectively, leading to increased or decreased plasma concentrations of R and S-carvedilol. Patients receiving medicines that induce (e.g. rifampicin, carbamazepine and barbiturates) or inhibit (e.g. paroxetine, fluoxetine, cinacalcet, bupropion, amidoamine and fluconazole) these CYP enzymes have to be monitored closely during concomitant treatment with carvedilol Some examples observed in patients or in healthy subjects are listed.

below but the list is not exhaustive.

Digoxin:

Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Both digoxin and carvedilol slow AV conduction. Increased monitoring of digoxin levels is recommended when initiating, adjusting, or discontinuing carvedilol.

Rifampicin and cimetidine:

In a study in 12 healthy subjects, rifampicin reduced plasma concentrations of carvedilol by about 70%, most likely by induction of P-glycoprotein leading to a decrease of the intestinal absorption of carvedilol. Cimetidine increased AUC by about 30% but caused no change in Cmax. Care may be required in those patients receiving inducers of mixed function oxidases e.g. rifampicin, as serum levels of carvedilol may be reduced, or inhibitors of mixed function oxidases e.g. cimetidine, as serum levels of carvedilol may be increased. However, based on the relatively small effect of cimetidine on carvedilol drug levels., the likelihood of any clinically important interaction is minimal

Ciclosporin
Two studies in renal and cardiac transplant patients receiving oral ciclosporin have shown an increase in ciclosporin plasma concentrations following initiation of carvedilol treatment. In about 30% of patients, the dose of ciclosporin had to be reduced in order to maintain ciclosporin concentrations within the therapeutic range, while in the remainder no adjustment was needed. On average, the dose of ciclosporin was reduced by about 20% in these patients. Due to wide interindividual variability in the dose adjustment required, it is recommended that ciclosporin concentrations be monitored closely after initiation of carvedilol therapy and that the dose of ciclosporin be adjusted as appropriate.

Amiodarone:
In patients with heart failure, amiodarone decreased the clearance of S-carvedilol likely by inhibition of CYP2C9. The mean R-carvedilol plasma concentration was not altered. Consequently, there is a potential risk of increased β-blockade caused by a raise of 'the plasma S-carvedilol concentration.

Fluoxetine and paroxetine:
In a randomized, cross-over study in 10 patients with heart failure, co-administration of fluoxetine, a strong inhibitor of CYP2D6, resulted in stereoselective inhibition of carvedilol metabolism with a 77% increase in mean R(+) enantiomer AUC. However, no difference in adverse events, blood pressure or heart rate were noted between treatment groups.
The effect of repeated doses of paroxetine, a strong CYP2D6 inhibitor, on the pharmacokinetics of a single oral dose of carvedilol was studies in 12 healthy volunteers. Exposure to R-carvedilol increased by an average of 150% and exposure to S-carvedilol by an average of 90% after concomitant administration with paroxetine.

Pharmacodynamic interactions
Digoxin:
The combined use of beta-blockers and digoxin may result in additive prolongation of atrioventricular (AV) conduction time.

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.

Antiarrythmics and calcium channel blockers:
In combination with carvedilol these medicines can increase the risk of AV conduction disturbances. Isolated cases of conduction disturbance (rarely with haemodynamic compromise) have been observed when carvedilol is co-administered with diltiazem, verapamil and/or amiodarone. As with other agents with beta-blocking properties, If carvedilol is to be administered orally with calcium channel blockers of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored as the risk of AV conduction disorders or risk of cardiac failure are increased (synergistic effect).

Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrio-ventricular block.
Close monitoring should be done when co-administering carvedilol, and either a class I antiarrhythmic or amiodarone (oral). Bradycardia, cardiac arrest, and ventricular fibrillation have been reported shortly after initiation of beta-blocker
treatment in patients receiving amiodarone.

Antihypertensive:
As with other agents with beta-blocking activity, carvedilol may potentiate the effect of other concomitantly administered drugs that are anti-hypertensive in action (e.g. alpha1-receptor antagonists) or have hypotension as part of their adverse effect profile such as barbiturates, phenothiazines, tricyclic antidepressants, vasodilating agents and alcohol.

Anaesthetic agents:
Careful attention must be paid during anaesthesia due to the synergistic negative inotropic and hypotensive effects of carvedilol and anaesthetic drugs.

Insulin or oral hypoglycaemics:
Agents with beta-blocking properties may enhance the blood sugar-reducing effect of insulin and oral hypoglycaemics. The signs of hypoglycaemia may be masked or attenuated (especially tachycardia). In patients taking insulin or oral hypoglycaemics, regular monitoring of blood glucose is therefore recommended.

Catecholamine-depleting agents:
Patients taking both agents with beta-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.

Beta-agonist bronchodilators:
Non-cardioselective beta blockers oppose the bronchodilator effects of beta-agonist bronchodilators. Careful monitoring of patients is recommended.
The following classes of interactions apply generally beta-blockers

Epinephrine:
There are ten reports of pronounced hypertension and bradycardia in patients treated with non-selective beta-receptor blockers (including pindolol and propranolol) along with epinephrine (adrenaline). These clinical observations have been confirmed in studies with healthy research subjects. It has also been proposed that epinephrine as a supplement to local anaesthetics may elicit these reactions with Intravascular administration. The risk should be substantially reduced with cardioselective beta-receptor blockers.

Phenylpropanolamine:
Phenylpropanolamine (norephedrine) in single doses of 50 mg may increase diastolic blood pressure to pathological values in healthy research subjects.

Propranolol generally inhibits the increase in blood pressure elicited by phenylpropanolamine. However, beta-receptor blockers may elicit paradoxical hypertensive reactions in patients who are taking large doses or phenylpropanolamine. In a couple of cases hypertensive crises have been reported during treatment with just phenylpropanolamine.

NSAIDs·
NSAID-type antiphlogistics inhibit the antihypertensive effect of beta-receptor blockers. It is mainly indomethacin that has been studied. This interaction appears not to occur with sulindac. No such interactions were established in a study involving diclofenac. There is no clinical experience of the combination of carvedilol with NSAIDs.
Barbituric acid preparation: Combinations with barbituric acid preparations should be avoided.
Nitrates: Increased hypotensive effects.
Ergotamine: Vasoconstriction increased.
Neuromuscular blocking agents: Increased neuromuscular block.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no adequate clinical experience with carvedilol in pregnant women.
Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development., parturition and postnatal development. The potential risk for humans is unknown.
Carvedilol should not be used during pregnancy unless the potential benefit outweighs the potential risk. The treatment should be stopped 2-3 days before expected birth. If this is not possible the newborn has to be monitored for the flrst.2-3 days of life.
Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death, and immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia) may occur in the foetus and neonate. There may be an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Animal studies have not shown substantive evidence of teratogenicity with carvedilol.

Breast-feeding
Animal studies demonstrated that carvedilol or its metabolites are excreted in breast milk. It is not known whether carvedilol is excreted in human milk. Breast-feeding is therefore not recommended during administration of carvedilol.

Fertility
There are no fertility data for humans.

4.7 Effects on ability to drive and use machines
This medicinal product has minor influence on the ability to drive and use machines. Some individuals may have reduced alertness especially on initiation and adjustment of medication.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

4.8 Undesirable effects

Very common: ≥ 1/10; Common: ≥ 1/100 and < 1/10 ; Uncommon: ≥ 1/1000 and < 1/100;
Rare: ≥ 1/10,000 and < 1/1000; Very rare: < 1/10,000

Infections and infestations

Common: Bronchitis, pneumonia, upper respiratory tract infection, urinary tract infection

Blood and lymphatic system disorders

Common: Anaemia

Rare: Thrombocytopaenia

Very rare: Leukopenia

Immune system disorders

Very rare: Hypersensitivity (allergic reaction)

Metabolism and nutrition disorders

Common: Weight increase, hypercholesterolaemia, impaired blood glucose control (hyperglycaemia, hypoglycaemia) in patients with pre-existing diabetes

Psychiatric disorders

Common: Depression, depressed mood

Uncommon: Sleep disorders, confusion

Nervous system disorders

Very common: Dizziness, headache

Uncommon: Presyncope, syncope, paraesthesia

Eye disorders

Common: Visual impairment, lacrimation decreased (dry eye), eye irritation

Cardiac disorders

Very common: Cardiac failure

Common: Bradycardia, oedema, hypervolaemia, fluid overload

Uncommon: Atrioventricular block, angina pectoris

Vascular disorders

Very common: Hypotension

Common: Orthostatic hypotension, disturbances of peripheral circulation (cold extremities, peripheral vascular disease, exacerbation of intermittent claudication and Reynaud's phenomenon)

Respiratory, thoracic and mediastinal disorders

Common: Dyspnoea, pulmonary oedema, asthma in predisposed patients

Rare: Nasal congestion

Gastrointestinal disorders

Common: Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain

Rare: dry mouth

Hepatobiliary disorders

Very rare: Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gammaglutamyltransferase (GGT) increased

Skin and subcutaneous tissue disorders

Uncommon: Skin reactions (e.g. allergic exanthema, dermatitis, urticaria, pruritus, psoriatic and lichen planus like skin lesions and increased sweating), alopecia

Very rare: Severe cutaneous adverse reactions (e.g. Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis)

Musculoskeletal and connective tissue disorders

Common: Pain in extremities

Renal and urinary disorders
Common: Renal failure and renal function abnormalities in patients with diffuse vascular disease and/or underlying renal insufficiency, micturition disorders
Very rare: Urinary incontinence in women
Reproductive system and breast disorders
Uncommon: Erectile dysfunction
General disorders and administration site conditions
Very common: Asthenia (fatigue)
Common: Pain

Description of *selected adverse reactions*
Dizziness, syncope, headache and asthenia are usually mild and are more likely to occur at the beginning of treatment.
In patients with congestive heart failure, worsening cardiac failure and fluid retention may occur during up-titration of carvedilol dose (see section 4.4).
Cardiac failure is a commonly reported adverse event in both placebo and carvedilol-treated patients (14.5% and 15.4% respectively, in patients with left ventricular dysfunction following acute myocardial infarction).
Reversible deterioration of renal function has been observed with carvedilol therapy in chronic heart failure patients with low blood pressure, ischaemic heart disease and diffuse vascular disease and/or underlying renal insufficiency (see section 4.4).
As a class, beta-adrenergic receptor blockers may cause latent diabetes to become manifest, manifest diabetes to be aggravated, and blood glucose counter-regulation to be inhibited.
Carvedilol may cause urinary incontinence in women which resolves upon discontinuation of the medication.
Special populations
Studies In elderly patients with hypertension or angina showed that there was no difference in the undesirable effects profile when compared with younger patients. A further study, which included elderly patients with coronary artery disease, showed no significant difference in reported undesirable effects when compared with those reported for younger patients.

4.9 Overdose
Symptoms and signs
In the event of overdose, there may be severe hypotension, bradycardia, heart failure, cardiogenic shock and cardiac arrest. There may also be respiratory problems, bronchospasm, vomiting, disturbed consciousness and generalized seizures.
Treatment
In addition to general supportive treatment, the vital parameters must be monitored and corrected, if necessary, under intensive care conditions.
Atropine can be used for excessive bradycardia, while to support ventricular function intravenous glucagon, or sympathomimetics (dobutamine, isoprenaline) are recommended. If positive inotropic effect is required, phosphodiesterase inhibitors (PDE) should be considered.
If peripheral vasodilation dominates the intoxication profile then norfenephrine or noradrenaline should be administered with continuous monitoring of the circulation. In the case of drug-resistant bradycardia, pacemaker therapy should be initiated.

For bronchospasm, β-sympathomimetics (as aerosol or intravenous) should be given, or aminophylline may be administered intravenously by slow injection or infusion. In the event of seizures, slow intravenous injection of diazepam or clonazepam is recommended.
Carvedilol is highly protein-bound. Therefore, it cannot be eliminated by dialysis.
In cases of severe overdose with symptoms of shock, supportive treatment must be continued for a sufficiently long period, i.e. until the patient's condition has stabilised, as a prolongation of elimination half-life and redistribution of carvedilol from deeper compartments are to be expected.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha and beta blocking agents..
ATC code: C07AG02
Carvedilol is a vasodilatory non-selective beta-blocker, which reduces the peripheral vascular resistance by selective alpha 1- receptor blockade and suppresses the renin-angiotensin system through non-selective beta-blockade. Plasma renin activity is reduced and fluid retention is rare.
Carvedilol has no intrinsic sympathomimetic activity (ISA). Like propranolol, it has membrane stabilising properties.
Carvedilol is a racemate of two stereoisomers. Both enantiomers were found to have alpha-adrenergic blocking activity in animal models. Non-selective $beta_1$- and $beta_2$- adrenoceptor blockade is attributed mainly to the S(-) enantiomer.
The antioxidant properties of carvedilol and its metabolites have been demonstrated in *in vitro* and *in vivo* animal studies and *in vitro* in a number of human cell types.
In hypertensive patients, a reduction in blood pressure is not associated with a concomitant increase in peripheral resistance, as observed with pure beta-blocking agents. Heart rate is slightly decreased. Stroke volume remains unchanged. Renal blood flow and renal function remain normal, as does peripheral blood flow, therefore, cold extremities, often observed with beta-blockers, are rarely seen. In hypertensive patients carvedilol increases the plasma norepinephrine concentration.
In prolonged treatment of patients with angina, carvedilol has been seen to have an anti-ischaemic effect and to alleviate pain. Haemodynamic studies demonstrated that carvedilol reduces ventricular pre- and after-load. In patients with left ventricular dysfunction or congestive heart failure, carvedilol has a favourable effect on haemodynamics and left ventricular ejection fraction and dimensions.
Carvedilol has no negative effect on the serum lipid profile or electrolytes. The ratio of HDL (high-density lipoproteins) and LDL (low-density lipoproteins) remains normal.

5.2 Pharmacokinetic properties

Absorption
Carvedilol is rapidly absorbed after oral administration. In healthy subjects, maximum serum concentration is achieved approximately 1 hour after administration. The absolute bioavailability of carvedilol in humans is approximately 25%.

There is a linear relationship between dose and serum concentrations of carvedilol. Food intake did not affect the bioavailability or the maximum serum concentration, although the time needed to reach maximum serum concentration is prolonged.

Distribution
Carvedilol is highly lipophilic. The plasma protein binding is about 98 to 99%. The volume of distribution is approximately 2 l / kg and increases in patients with liver cirrhosis.

Biotransformation
In humans and in animal species studied, carvedilol is extensively metabolized to several metabolites which are excreted primarily in bile. The first pass effect after oral administration is about 60-75%. The enterohepatic circulation of the parent substance was demonstrated in animals.
Carvedilol is extensively metabolized in the liver, glucuronidation being one of the main reactions. The demethylation and hydroxylation at the phenol ring produce 3 active metabolites with blocking activity of beta-adrenergic receptors.
According to preclinical studies, the beta-blocking activity of the metabolite 4 - hydroxyphenol is approximately 13 times higher than that of carvedilol. The three active metabolites have a weak vasodilating activity, compared with carvedilol. In humans, their concentrations are about 10 times lower than the parent substance. Two of the carbazole-hydroxy metabolites are extremely potent antioxidants, showing a potency 30-80 times that of carvedilol.

Elimination
The average half-life of elimination of carvedilol is approximately 6 hours. The plasma clearance is approximately 500-700 ml / min. Elimination is mainly via the bile, and excretion mainly via the faeces. A minor part is eliminated renally in the form of various metabolites.

5.3 Preclinical safety data
No additional data of relevance.

6. Pharmaceutical particulars
6.1 List of excipients

Sr. No.	**Name of the Ingredients**	**Specification**
1.	Calcium Hydrogen Phosphate (Dibasic Calcium Phosphate)	BP
2.	Lactose	BP
3.	Maize Starch	BP
4.	Sodium Starch Glycolate	BP
5.	Purified Water	Inhouse
6.	Purified Talc	BP
7.	Magnesium Stearate	BP
8.	Croscarmellose Sodium	BP
9.	Quinoline Yellow Supra	Inhouse
10.	Erythrosine	Inhouse
11.	Sunset Yellow	Inhouse

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

6.2 Incompatibilities
None reported

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store below 30°C.
Protect from direct sunlight, heat and moisture.
Keep all medicines out of reach of children.

6.5 Nature and contents of container
Blister pack of 3 x 10 tablets

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder
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8. Marketing authorisation number(s)
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9. Date of first authorisation/renewal of the authorisation
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10. Date of revision of the text
06.05.2022