SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Carvsanna 6.25 mg tablets
Carvsanna 12.5 mg tablets
Carvsanna 25 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 6.25 mg, 12.5 mg or 25 mg carvedilol.

Excipient with known effect: 89 mg/86 mg/171 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

6.25 mg tablets: white, biconvex, capsule shaped tablets debossed “C” with breakline and “2” on one side and plain on the other.
12.5 mg tablets: white, biconvex, capsule shaped tablets debossed “C” with breakline and “3” on one side and plain on the other.
25 mg tablets: white, biconvex, capsule shaped tablets debossed “C” with breakline and “4” on one side and plain on the other.

The tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Carvsanna is available in 3 strengths: 6.25 mg, 12.5 mg and 25 mg.

Posology

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 two weeks or more rarely.

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 two weeks or more rarely.

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 two weeks or more rarely. The recommended maximum daily dose is 100 mg in divided doses (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.

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 hospitalisation due to heart failure) and the basic therapy must be stabilised 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 (see section 4.3).

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 two weeks or more rarely, 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 in patients weighing less than 85 kg and 50 mg twice daily in 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 usually not 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 vasodilatation (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 stabilised. If bradycardia appears or in case of lengthening of AV conduction time, 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 impairment
Dosage must be determined for each patient individually, but according to pharmacokinetic parameters

there is no evidence that dose adjustment of carvedilol in patients with renal failure is necessary.

Hepatic impairment
Carvedilol is contraindicated in patients with clinically manifest hepatic impairment (see sections 4.3 and 5.2).
In patients with moderate hepatic impairment a dose adjustment may be required.

Paediatric population
The safety of carvedilol in children and adolescents below 18 years of age has not been established. Carvedilol is therefore not recommended for use in children and adolescents below 18 years of age (see also section 5.2).

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

As with other β-blockers and especially in coronary patients, the withdrawal of carvedilol should be done gradually (see section 4.4).

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 the active substance or to any of the excipients listed in section 6.1.
- Unstable/decompensated heart failure.
- Clinically manifest hepatic impairment.
- Metabolic acidosis.
- Second and third degree AV block (unless a permanent pacemaker is in place).
- Severe bradycardia (< 50 bpm).
- Sick sinus syndrome (including sino-atrial block).
- Severe hypotension (systolic blood pressure < 85 mmHg).
- Cardiogenic shock.
- Bronchial asthma or other respiratory diseases with a bronchospastic component (e.g., chronic obstructive pulmonary disease).
- Acute pulmonary embolism
- Prinzmetal angina
- Cor pulmonale
- Untreated pheochromocytoma
- Concomitant therapy with MAO inhibitors (except for MAO-B inhibitors)
- Concomitant therapy with intravenous verapamil, diltiazem or other antiarrhythmics
- Breast-feeding.

4.4 Special warnings and precautions for use

Chronic Congestive Heart Failure

As a general rule, carvedilol should always be administered in addition to existing standard therapy for heart failure, i.e., diuretics, digitalis, ACE inhibitors and/or other vasodilators. Carvedilol treatment may be initiated by a doctor with experience in cardiology only if the patient is stable on conventional basic heart failure therapy, i.e., the dose of the existing standard therapy must have been stable for at least four weeks prior to initiation of carvedilol.

In particular in patients with severe heart failure (NYHA ≥ III) or salt and/or fluid depletion (e.g., with high doses of diuretics) and in elderly patients (≥ 70 years) or patients with low baseline blood pressure (e.g., systolic < 100 mmHg), a marked drop in blood pressure can occur as of the first dose of carvedilol or at subsequent dose increases. As a result, these patients require medical monitoring for 2 hours following administration of the first dose of carvedilol and when increasing the dose, in order to avoid uncontrolled hypotensive reactions.

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 mm Hg), ischaemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency. Accordingly, patients with these risk factors should have their renal function frequently monitored during titration of carvedilol therapy. If renal function deteriorates, the carvedilol dose should be reduced or therapy should 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 inhibitor should have been stable for at least the preceding 24 hours.
Carvedilol must be used with caution in patients with unstable angina pectoris, as only limited clinical experience is available for use in this condition.

Hypertension

In essential hypertension, carvedilol can be used alone or in combination with other antihypertensive agents, in particular thiazide diuretics. If (pre)treatment with a diuretic is already ongoing, the recommendation is to briefly suspend this if possible prior to initiation of carvedilol therapy to prevent an excessive drop in blood pressure.

Since there is limited clinical experience, carvedilol should not be administered in patients with labile or secondary hypertension, complete bundle branch block situations, a tendency to drops in blood pressure when changing position (orthostasis), acute inflammatory heart diseases, changes in the heart valves or cardiac outflow tract with haemodynamic effects, end-stage peripheral arterial perfusion disorders, or concomitant therapy with α1- or α2- receptor antagonists.

If, in justified and exceptional cases, carvedilol and clonidine are used concomitantly, discontinuation of clonidine must take place gradually if treatment with carvedilol was ended a few days previously.

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

Chronic obstructive pulmonary disease
In patients with a tendency to bronchospasm, respiratory distress can occur as a result of a possible increase in airway resistance. Patients with respiratory diseases with a bronchospastic component must therefore not be treated with carvedilol (see section 4.3).

Diabetes
Care should be taken in the administration of carvedilol to patients with diabetes mellitus, as the early signs and symptoms of acute hypoglycaemia may be masked or attenuated. As a result, blood glucose concentrations must be monitored regularly at treatment initiation and at changes of the carvedilol

dose in these patients. The antidiabetic therapy may also have to be adjusted accordingly (see section 4.5).
Particularly in the event of a strict fast, careful medical monitoring of blood glucose concentrations is required.
β-receptor blockers can increase insulin resistance and mask the symptoms of hypoglycaemia. However, numerous studies have demonstrated that vasodilatory β-receptor blockers like carvedilol have a more favourable effect on the glucose and lipid profile.

Peripheral vascular disease
Carvedilol should be used with caution in patients with peripheral vascular disease as β-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 there may be exacerbation of symptoms.

Hyperthyroidism
Carvedilol may obscure the symptoms of hyperthyroidism.

Anaesthesia and major surgery
Caution should be exercised in patients undergoing general surgery, because of the synergistic negative inotropic effects of carvedilol and anaesthetic 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 desensitisation therapy, as β-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions.

Risk of anaphylactic reaction
While taking β-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more sensitive to repeated exposure, whether accidental, diagnostic or therapeutic. Such patients may not respond to the usual doses of epinephrine used to treat allergic reactions.

Severe skin reactions
Very rare cases of severe skin reactions, such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported during treatment with carvedilol (see also section 4.8). Carvedilol should be permanently discontinued in patients experiencing severe skin reactions possibly attributable to carvedilol.

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

Concomitant use of calcium channel blockers
Careful monitoring of ECG and blood pressure is necessary in patients receiving concomitant therapy with calcium channel blockers of the verapamil or diltiazem type or other antiarrhythmic drugs (specifically amiodarone).

Pheochromocytoma
In patients with pheochromocytoma, an α-blocking agent must be initiated prior to the use of any β-blocking agent. Although carvedilol has both α-and β-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 pheochromocytoma.

Prinzmetal's variant angina
Agents with non-selective β-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 α-blocking activity of carvedilol may prevent such symptoms. Carvedilol is contraindicated in patients with confirmed Prinzmetal angina (see section 4.3). Caution should be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.

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

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

Elderly patients
Elderly patients can be more sensitive to carvedilol and must be monitored more carefully.
Like with other β-receptor blockers, carvedilol should be discontinued gradually, especially in coronary patients.

Excipient(s)

Lactose
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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 stereoselectively, leading to increased or decreased plasma concentrations of R and S-carvedilol. Patients receiving medicines that induce (e.g. rifampicine, carbamazepine and barbiturates) or inhibit (e.g. paroxetine, fluoxetine, quinidine, cinacalcet, bupropion, amiodarone or fluconazole) these CYP enzymes have to be monitored closely during concomitant treatment with carvedilol as serum carvedilol concentrations may be reduced by enzyme inducers and increased by the enzyme inhibitors. Some examples observed in patients or in healthy subjects are listed below but the list is not exhaustive.

Cardiac glycosides: Digoxin concentrations are increased by up to 20% and digitoxin concentrations by approximately 13% in hypertensive patients when digoxin or respectively digitoxin 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 (see section 4.4).

Rifampicin: In a study in 12 healthy subjects, rifampicin administration decreased the carvedilol plasma levels by about 60%, most likely by induction of P-glycoprotein leading to a decrease of the intestinal absorption of carvedilol.

Ciclosporin and tacrolimus: 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 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.
For intravenously administered ciclosporin, no interaction with carvedilol is expected. In addition, there are indications that CYP3A4 is involved in the metabolism of carvedilol. As tacrolimus is a substrate of P-glycoprotein and CYP3A4, its pharmacokinetics may also be influenced by carvedilol due to these interaction mechanisms.

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: In a randomised, 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.

Alcohol: Concomitant intake of alcohol can influence the antihypertensive effect of carvedilol and cause various adverse reactions. Consumption of alcohol has been shown to have acute hypotensive effects, which may potentiate the antihypertensive effect of carvedilol. As carvedilol is poorly soluble in water but dissolves easily in ethanol, the presence of alcohol could influence the speed and/or extent of intestinal absorption of carvedilol by increasing its solubility. Carvedilol has also been shown to be partially metabolised by CYP2E1, an enzyme that is known to be both induced and inhibited by alcohol.

Grapefruit juice: Consumption of a single dose of 300 mL grapefruit juice led to a 1.2-fold increase in carvedilol AUC compared to water. Although the clinical relevance of this observation is unclear, it is advisable for patients to avoid concomitant intake of grapefruit juice at least until a stable dose-effect relationship has been achieved.

Pharmacodynamic interactions

Insulin or oral hypoglycaemics: Agents with β-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 β-blocking properties and a drug that can deplete catecholamines (e.g. reserpine, guanethidine, methyldopa, guanfacine and monoamine oxidase inhibitors) should be observed closely for signs of hypotension and/or severe bradycardia.

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

Calcium channel blockers of the verapamil or diltiazem type, amiodarone or other antiarrhythmics: Combination with carvedilol can increase the risk of AV conduction disturbances (see section 4.4). 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 β-blocker treatment in patients receiving amiodarone. There is a risk of cardiac failure in case of class Ia or Ic antiarrhythmics concomitant intravenous therapy. If carvedilol must be taken in combination with calcium antagonists of the verapamil or diltiazem type, amiodarone, or other antiarrhythmics, like with other drugs with β-blocking properties, monitoring of blood pressure, heart rate, and heart rhythm (ECG) is recommended (see also section 4.4).

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

Nitrates: Increased hypotensive effects.

Antihypertensive drugs: As with other agents with β-blocking activity, carvedilol may potentiate the effect of other concomitantly administered drugs that are antihypertensive in action (e.g. α_1-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 monitoring of vital signs is recommended during anaesthesia due to the synergistic negative inotropic and hypotensive effects of carvedilol and anaesthetic drugs (see section 4.4).

NSAIDs, oestrogens and corticosteroids: The antihypertensive effect of carvedilol is decreased due to water and sodium retention.

Sympathomimetics with α-mimetic and β-mimetic effects: Risk of hypertension and excessive bradycardia.

Beta-agonist bronchodilators: Non-cardioselective β-blockers oppose the bronchodilator effects of β-agonist bronchodilators. Careful monitoring of patients is recommended.

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 have shown reproductive toxicity (see section 5.3).

β-receptor blockers reduce placental perfusion. As a consequence, intrauterine early foetal death, abortion and premature delivery can occur. Furthermore, adverse effects (in particular hypoglycaemia and bradycardia) may occur in both the foetus and neonate. In the postnatal period, there is an increased risk of cardiac and pulmonary complications in the neonate.
Carvedilol should therefore not be used during pregnancy unless the potential benefit outweighs the potential risk.

Treatment with β-receptor blockers should be discontinued 72-48 hours before the expected delivery. If this is not possible, the neonate must be monitored for the first 48-72 hours of life.

Breast-feeding
Studies in lactating animals demonstrated that carvedilol and/or its metabolites were excreted in the milk of rats. The excretion of carvedilol in human breast milk has not been investigated. Carvedilol is contraindicated during breast-feeding. In the event of carvedilol treatment, therefore, breast-feeding must be discontinued.

Fertility
Animal studies found disturbances in female fertility following carvedilol treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects of carvedilol on patients' fitness to drive or to operate machinery.

Because of individually variable reactions (e.g. dizziness, tiredness), the ability to drive, operate machinery, or work without firm support may be impaired. This applies particularly at the start of treatment, after dose increases, on changing products, and in combination with alcohol.

4.8 Undesirable effects

(a) Summary of the safety profile
The frequency of adverse reactions is not dose-dependent, with the exception of dizziness, visual impairment, bradycardia and a deterioration in heart failure.

(b) Tabulated list of adverse reactions
The risk of most adverse reactions associated with carvedilol is similar across all indications. Exceptions are described in subsection (c).

The frequencies of adverse events are ranked according to the following: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (< 1/10,000)	Not known
Infections and infestations		Bronchitis, pneumonia, upper respiratory tract infection, urinary tract infection				
Blood and lymphatic system disorders		Anaemia		Thrombocytopaenia	Leukopenia	
Immune system disorders					Hypersensitivity (allergic reaction)	
Metabolism and nutrition disorders		Weight increased, hypercholesterolaemia, impaired blood glucose control (hyperglycaemia, hypoglycaemia) in patients with pre-existing diabetes				
Psychiatric disorders		Depression, depressed mood	Sleep disorder, confusion, nightmares, hallucinations		Psychosis	

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (< 1/10,000)	Not known
Nervous system disorders	Dizziness, headache	Presyncope, syncope	Paraesthesia			
Eye disorders		Visual impairment, lacrimation decreased (dry eye), eye irritation				
Cardiac disorders	Cardiac failure	Bradycardia, hypervolaemia, fluid overload	Atrioventricular block, angina pectoris			
Vascular disorders	Hypotension	Orthostatic hypotension, disturbances of peripheral circulation (cold extremities, peripheral vascular disease, exacerbation of intermittent claudication and Reynaud's phenomenon)				
Respiratory, thoracic and mediastinal disorders		Dyspnoea, pulmonary oedema, asthma in predisposed patients		Nasal congestion		

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (< 1/10,000)	Not known
Gastrointestinal disorders		Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain	Constipation	Dry mouth		
Hepatobiliary disorders					Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT) increased	
Skin and subcutaneous tissue disorders			Skin reactions (e.g. allergic exanthema, dermatitis, urticaria, pruritus, psoriatic and lichen planus like skin lesions and hyperhidrosis)		Severe skin reactions (e.g. Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis)	Alopecia
Musculoskeletal and connective tissue disorders		Pain in extremity				

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (< 1/10,000)	Not known
Renal and urinary disorders		Renal failure and renal function abnormalities in patients with diffuse vascular disease and/or underlying renal impairment, micturition disorders			Urinary incontinence in women	
Reproductive system and breast disorders			Erectile dysfunction			
General disorders and administration site conditions	Asthenia (fatigue)	Pain, oedema				

(c) 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, β-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.

Sinoatrial arrest in predisposed patients (e.g., elderly patients or patients with pre-existing bradycardia, sinoatrial node dysfunction or AV block).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

In the event of overdose, there may be severe hypotension, bradycardia, heart failure, cardiogenic shock, sinoatrial arrest and cardiac arrest. There may also be respiratory problems, bronchospasm, vomiting, disturbed consciousness and generalised seizures.

Management

In addition to general supportive treatment, the vital parameters must be monitored and corrected, if necessary, under intensive care conditions and mechanical ventilation may be necessary in some cases.

Absorption of carvedilol in the gastrointestinal tract can be limited by gastric lavage, administration of activated charcoal and use of a laxative.

Patients should be placed in the supine position. Countermeasures include:

- for bradycardia:
  Atropine; for treatment-refractory bradycardia, a pacemaker should be used.

- for hypotension or shock:
  plasma replacement with sympathomimetics if required.

The β-blocking effect of carvedilol can be reduced or even counteracted in a dose-dependent manner through slow IV administration of bodyweight-adjusted sympathomimetics such as isoprenaline, dobutamine, orciprenaline or adrenaline. If a positive inotropic effect is required, administration of a phosphodiesterase inhibitor, such as milrinone, can be considered. If necessary, glucagon can be given, potentially followed by a continuous infusion.

If the intoxication picture leans toward peripheral vasodilation, the administration of norfenefrine or norepinephrine is required with continuous monitoring of circulation.

In the event of bronchospasm, β-sympathomimetics (as an aerosol, or IV if the effect is insufficient) or aminophylline IV as a slow injection or infusion can be given.

In the event of seizures, slow IV administration of diazepam or clonazepam is recommended.

Important note:
In the event of severe intoxication with symptoms of shock, treatment with countermeasures should be continued for a sufficiently long time, as a prolongation of the elimination half-life and a redistribution of carvedilol from deeper compartments must be expected. The duration of treatment with the countermeasures depends on the severity of the overdose. The countermeasures should be continued until the patient is stabilised.

Carvedilol is not eliminated by dialysis, as the drug, presumably because it is highly bound to plasma proteins, is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha and beta blocking agents, ATC code: C07AG02

Mechanism of action

Carvedilol is a racemate of two stereoisomers, R- and S-carvedilol, with concomitant α- und β-blocking properties in the therapeutic dosing range. The S-enantiomer competitively and non-selectively inhibits β-adrenergic receptors, while both enantiomers have the same specific α1-adrenergic receptor-blocking properties. It therefore has negative chrono-, dromo-, bathmo- and inotropic effects on the heart. At high concentrations, carvedilol has weak to moderate calcium channel-blocking action. It has no intrinsic sympathomimetic activity and (like propranolol) has membrane-stabilising properties.

Pharmacodynamic effects

In addition to the cardiovascular effects caused by β-adrenergic receptor blockade which are described in more detail below, carvedilol also reduces peripheral vascular resistance through selective blockade of the α1-adrenergic receptors. Furthermore, its calcium channel-blockade action can increase blood flow to specific vascular beds, such as cutaneous circulation. Through its β-blocking effect, carvedilol suppresses the renin-angiotensin-aldosterone system, reducing the release of renin and thereby making fluid retention rarer. It alleviates the hypertensive effect of phenylephrine (an α1-adrenergic receptor agonist), but not that of angiotensin II. Carvedilol has been found to have organ-protective effects which are probably at least partially attributable to additional properties related to its adrenergic receptor blockade effect. It has potent antioxidative properties associated with both enantiomers, and it is a scavenger of reactive oxygen radicals. A decrease in oxidative stress during chronic treatment of patients with carvedilol was found in clinical studies that measured various markers. Furthermore, it has antiproliferative effects on human vascular smooth muscle cells. A normal HDL-LDL cholesterol ratio is maintained during carvedilol therapy. In patients with hypertension and dyslipidaemia, a positive influence on the lipid profile was demonstrated.

Clinical efficacy and safety

Clinical studies found the following results for carvedilol:

Hypertension
Carvedilol lowers blood pressure in hypertensive patients through a combination of β-blockade and α1-mediated vasodilation. The antihypertensive effect is not accompanied by an increase in total peripheral resistance, and peripheral blood flow is maintained. The heart rate is moderately decreased. Renal perfusion and renal function normally remain unchanged. Carvedilol maintains stroke volume and reduces total peripheral resistance.

Carvedilol causes an increase in plasma norepinephrine concentrations in hypertensive patients.

Coronary heart disease
In patients with coronary heart disease, carvedilol has an anti-ischaemic and anti-angina effect, including in long-term treatment. Studies on the acute haemodynamic effect found a reduction in ventricular preload (pulmonary artery pressure and pulmonary capillary pressure) and afterload (peripheral resistance).

Chronic heart failure
In patients with ischaemic or non-ischaemic chronic heart failure, carvedilol significantly reduced mortality and hospitalisation rates and improved symptoms and left ventricular function. The effect of carvedilol is dose-dependent.

In a large-scale, international, double-blind, placebo-controlled, multicentre mortality study (COPERNICUS), 2,289 patients with severe stable chronic ischaemic or non-ischaemic heart failure already receiving optimum standard therapy (e.g., diuretics, ACE inhibitors, if necessary digitalis and/or vasodilators) were randomised to either carvedilol (1,156 patients) or placebo (1,133 patients). Patients had left ventricular systolic dysfunction with an average ejection fraction of < 20%. All-cause mortality adjusted to 1 year was 12.8% in the carvedilol group, which was 35% lower than the placebo group at 19.7% ($p = 0.00013$). The advantage of carvedilol treatment in terms of patient survival was consistent across all examined subpopulations, such as high-risk patients (EF < 20%, common rehospitalisation). 41% fewer patients died of sudden cardiac death in the carvedilol group than the placebo group (5.3% versus 8.9%).

The combined secondary endpoints of mortality or hospitalisation due to heart failure (31% reduction), mortality or cardiovascular hospitalisation (27% reduction) and all-cause mortality or hospitalisation (24% reduction) were all significantly lower in the carvedilol group than in the placebo group ($p \leq 0.00004$ in all cases).

The incidence of severe adverse reactions during the study was lower in the carvedilol group than the placebo group (39% versus 45.4%). Including in the titration phase, heart failure did not worsen in the carvedilol group compared to the placebo group.

Paediatric population

The safety and efficacy of carvedilol in children and adolescents could not be established due to the limited number and limited scope of studies. Available studies concentrated on the treatment of paediatric heart failure, which is, however, different from the disease in adults in terms of both its characteristics and aetiology. Although a range of preliminary investigations and observational studies on this disease, including studies on heart failure as a consequence of muscular dystrophy, have reported possible positive effects of carvedilol, the efficacy results from randomised controlled studies are contradictory and inconclusive.

Safety data from these studies show that the adverse events were generally comparable in the carvedilol-treated groups and the control groups. However, due to the small number of participants

compared to adult studies as well as the general lack of an optimum dosage regimen for children and adolescents, available data are inadequate to establish a paediatric safety profile for carvedilol. The use of carvedilol in paediatric patients is therefore not recommended due to a lack of meaningful information on the benefits and risks.

5.2 Pharmacokinetic properties

Absorption

Following intake of a 25 mg capsule, carvedilol is rapidly absorbed by healthy subjects in approx. 1.5 hours (tmax) with peak plasma concentrations (Cmax) of 21 mcg/L. Following oral intake, carvedilol is subject to a marked first-pass metabolism effect, which results in an absolute bioavailability of approx. 25% in male subjects. Carvedilol is a racemate, and the S-enantiomer, with an absolute oral bioavailability of 15%, seems to be metabolised more rapidly than the R-enantiomer, which has an absolute oral bioavailability of 31%. Peak plasma concentrations of R-carvedilol are about twice as high as those of S-carvedilol.

In vitro studies have shown that carvedilol is a substrate of the intestinal transporter P-glycoprotein. The role of P-glycoprotein in the distribution of carvedilol was also confirmed in vivo in healthy subjects.

Distribution

Carvedilol is highly lipophilic and is approx. 95% bound to plasma proteins. The volume of distribution is between 1.5 and 2 L/kg. In patients with cirrhosis of the liver, the volume of distribution is increased.

Biotransformation

In humans, carvedilol is almost completely metabolised via oxidation and conjugation in the liver to a variety of metabolites which are primarily excreted via the bile. Enterohepatic circulation was demonstrated in animals.

3 active metabolites with β-blocking properties are formed through demethylation and hydroxylation at the phenol ring. Preclinical studies found that this effect is approx. 13-fold more potent for the 4'-hydroxyphenol metabolite than for carvedilol. Compared to carvedilol, the 3 active metabolites have only a slight vasodilatory effect. The concentrations of the 3 active metabolites in humans are approx. 10-fold lower than the parent substance. Two of the hydroxycarbazole metabolites of carvedilol are extremely potent antioxidants, having demonstrated a 30- to 80-fold more powerful effect than carvedilol.

The vasodilatory effect component can be potentiated in slow metabolisers.

Human pharmacokinetic studies found that the oxidative metabolism of carvedilol is stereoselective. Results from an in vitro study indicated that various cytochrome P450 isoenzymes, including CYP2D6, CYP3A4, CYP2E1, CYP2C9 and CYP1A2, may be involved in the oxidation and hydroxylation processes.

Studies in healthy subjects and patients found that the R-enantiomer is primarily metabolised by CYP2D6 and the S-enantiomer by CYP2D6 and CYP2C9.

Genetic polymorphism
The results of human pharmacokinetic studies found that CYP2D6 plays an important role in the metabolism of R- and S-carvedilol. As a result, plasma concentrations of R- and S-carvedilol are increased in slow metabolisers. In terms of the clinical relevance, the results are inconclusive.

Elimination

Following a single oral dose of 50 mg carvedilol, approx. 60% of the dose was secreted into the bile and eliminated in the faeces as metabolites within 11 days. Following a single oral dose, only approx. 16% of the dose is excreted in the urine as carvedilol or its metabolites. Renal excretion of the parent compound accounts for less than 2%. Following an intravenous infusion of 12.5 mg carvedilol, plasma clearance in health subjects reached approx. 600 mL/min and the elimination half-life was approx. 2.5 hours.

The elimination half-life of a 50 mg capsule in the same healthy subjects was 6.5 hours, which is consistent with the absorption half-life from the capsule. Following oral administration, the total body clearance of S-carvedilol is approx. double that of R-carvedilol.

Linearity/non-linearity

There is a linear correlation between the dose and peak plasma concentrations (Cmax).

Special populations

Hepatic impairment
A pharmacokinetic study in patients with cirrhosis of the liver found that systemic availability (AUC) of carvedilol in patients with liver impairment was 6.8-fold higher than in subjects with a healthy liver. Carvedilol is therefore contraindicated in patients with clinically manifest hepatic impairment (see section 4.3).

Renal impairment
In patients with hypertension and renal impairment, the AUC, elimination half-life and peak plasma concentrations do not change significantly. Renal excretion of the parent compound is decreased in patients with renal impairment, but changes in pharmacokinetic parameters are slight. Autoregulation of renal blood flow and glomerular filtration are maintained throughout long-term carvedilol treatment. In patients with moderate to severe renal impairment, no dose adjustment is necessary (see section 4.2).

Carvedilol is not eliminated through dialysis, as it cannot cross the dialysis membrane, likely due to its high plasma protein binding.

Patients with heart failure
In one study with 24 Japanese heart failure patients, the clearance of R- and S-carvedilol was significantly lower than initially expected based on data from healthy subjects. These results indicate that the pharmacokinetics of R- and S-carvedilol may be significantly changed by heart failure.

Paediatric population
Investigations in children and adolescents found significantly higher weight-adjusted clearance compared to adults.

Elderly patients
The pharmacokinetics of carvedilol in hypertensive patients was not significantly influenced by age. In a study in elderly hypertensive patients, the adverse reaction profile was not found to be different in comparison to younger patients. In another study which enrolled elderly patients with coronary heart disease, there were no differences in terms of the reported adverse reactions compared to those reported for younger patients. Therefore, no adjustment of the initial dose is necessary in elderly patients (see section 4.2).

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and development, genotoxicity or carcinogenic potential.

Standard tests revealed no evidence of a mutagenic or tumorigenic potential of carvedilol.

The administration of carvedilol at toxic doses (≥ 200 mg/kg, ≥ 100 x MRHD) to adult female rats led to lower fertility (decrease in mating frequency, fewer corpora lutea, fewer intrauterine implants). Carvedilol was not found to have teratogenic effects in embryotoxicity studies in rats and rabbits. However, embryo-/foetotoxic effects and fertility disturbances did occur in rabbits at doses below maternotoxic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline
Lactose monohydrate
Crospovidone
Povidone
Silica, colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister (PVC/PVdC-Aluminium)
6.25 mg: 18 months
12.5 mg and 25 mg: 2 years

Blister (OPA/Aluminium/PVC-Aluminium)
2 years

6.4 Special precautions for storage

Blister (PVC/PVdC-Aluminium)
6.25 mg:
Do not store above 30°C
Store in the original package in order to protect from light.
12.5 mg and 25 mg:
Store in the original package in order to protect from light.
This medicinal product does not require any special temperature storage conditions.

Blister (OPA/Aluminium/PVC-Aluminium)
Store in the original package in order to protect from light.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Blister (PVC/PVdC-Aluminium) or blister (OPA/Aluminium/PVC-Aluminium)
Pack sizes: 10, 14, 28, 30, 50, 56, 60, 98 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

11 Dec 2025