SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Carvedi-Denk 6.25
Carvedi-Denk 25

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: carvedilol

Carvedi-Denk 6.25:
Each tablet contains 6.25 mg carvedilol.

Carvedi-Denk 25:
Each tablet contains 25 mg carvedilol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Round, whitish, half-scored tablets.

The tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is a non-selective beta and alpha1 receptor antagonist.

Carvedi-Denk is used in adults.

Carvedi-Denk 6.25:
- Chronic heart failure:
  In the absence of contraindications, Carvedi-Denk 6.25 mg is indicated in all patients with stable, symptomatic, chronic heart failure of ischaemic or non-ischaemic origin of any intensity, combined with standard therapy (such as ACE inhibitors and diuretics with or without digitalis).

Carvedi-Denk 25:
- Essential hypertension
- Chronic stable angina pectoris
- Chronic heart failure:
  In the absence of contraindications, Carvedi-Denk 25 mg is indicated in all patients with stable, symptomatic, chronic heart failure of ischaemic or non-ischaemic origin of any intensity, combined with standard therapy (such as ACE inhibitors and diuretics with or without digitalis).

Note (on use in chronic heart failure):
Treatment with carvedilol may be commenced only if the patient's condition has been stabilised on conventional, basic heart failure therapy, i.e. the dosage of this existing, standard therapy must have remained stable for at least four weeks prior to starting treatment with carvedilol.

4.2 Posology and method of administration

Posology

Essential hypertension
Treatment should begin with 12.5 mg carvedilol once daily on the first two days. Treatment can then be continued with 25 mg carvedilol once daily. As a rule, 25 mg carvedilol once daily is sufficient.

If the effect is inadequate, the dose can be slowly increased at intervals of no less than two weeks, with the maximum recommended daily dose of carvedilol being 50 mg once daily or 25 mg twice daily.

A daily dose of 50 mg carvedilol must not be exceeded.

Chronic stable angina pectoris
Treatment should begin with 12.5 mg carvedilol twice daily on the first two days. Treatment should then be continued with 25 mg carvedilol twice daily. As a rule, 25 mg carvedilol twice daily in divided doses is sufficient.
If the effect is inadequate, the dose can be slowly increased at intervals of no less than two weeks, with the maximum recommended daily dose being 100 mg in divided doses.

Chronic heart failure
The recommended initial dose is 3.125 mg carvedilol twice daily for two weeks. If this dose is tolerated, it should be increased at intervals of no less than two weeks to 6.25 mg carvedilol twice daily, followed by 12.5 mg twice daily and then 25 mg carvedilol twice daily. The aim thereby should be to achieve the highest dose that can be tolerated by the patient. The minimum effective dose is 6.25 mg carvedilol twice daily. The maximum dose is generally 25 mg carvedilol twice daily in patients with severe chronic heart failure and in patients with mild to moderate chronic heart failure weighing less than 85 kg. Only in patients with mild to moderate chronic heart failure and weighing more than 85 kg can attempts be made, while closely monitoring the patient, to increase the dose to a maximum of 50 mg carvedilol twice daily.

The dose of carvedilol may be increased only if the patient's clinical condition is satisfactory and stable, i.e. if there are no symptoms in the form of exacerbated heart failure or clinically relevant adverse effects – especially those that result from vasodilation (e.g. hypotension, dizziness). Patients must therefore be examined for the above-mentioned symptoms, in particular, before any increase in the dose. In addition, frequent and regular medical examinations (e.g. kidney function, body weight, blood pressure, heart rate and rhythm) must be undertaken, especially when adjusting the dose (dose titration as far as the maintenance dose). An exacerbation of the symptoms of heart failure or the occurrence of adverse effects from carvedilol-mediated vasodilation often are only transient and should be treated by temporarily reducing or, if necessary, discontinuing carvedilol. If the symptoms are mainly caused by fluid retention, however, the dose of the diuretic drug can initially be increased.

The necessary maintenance dose must be determined individually in each patient under close medical supervision. Long-term therapy should then be continued at the respective maximum tolerated dose.
If treatment with carvedilol has been discontinued for more than one week, it should be resumed at a lower dose (twice per day) and again be gradually adjusted individually as described above.
If treatment with carvedilol has been discontinued for more than two weeks, it should be resumed at a dose of 3.125 mg twice per day and again be gradually adjusted individually as described above.

Dosage in patients with chronic heart failure and impaired kidney function

The necessary dose must be determined individually for each patient. The available pharmacokinetic parameters and published clinical studies from patients with renal insufficiency of varying intensity (including renal failure) demonstrate that the dose recommendations for carvedilol in patients with moderate to severe renal insufficiency do not need to be modified (see also section 5.2, Pharmacokinetics in different patient populations).

Dosage in patients with impaired liver function
Carvedilol is contraindicated in patients with clinically manifested liver dysfunction (see sections 4.3 and 5.2, Pharmacokinetics in different patient populations).

Dosage in the elderly
- For essential hypertension
The recommended dose at the start of treatment is 12.5 mg carvedilol, also in elderly patients. An adequate decrease in blood pressure was achieved with this dose in some patients, including during long-term treatment. If the effect is insufficient, the dose can be increased at intervals of no fewer than 14 days to the maximum dosage (a single dose of 25 mg and a maximum daily dose of 50 mg carvedilol).

- For chronic stable angina pectoris
A dose of 25 mg carvedilol twice daily in divided doses should not be exceeded in elderly patients.

Paediatric population
The safety of carvedilol in children and adolescents aged under 18 years has not been established. Carvedilol therefore is not recommended for use in children and adolescents under 18 years of age (see also section 5.2, Pharmacokinetics in different patient populations).

Method of administration
The tablets should be taken whole with sufficient liquid.

It is recommended to take Carvedi-Denk with meals so that carvedilol is absorbed less rapidly (thus possibly preventing orthostatic effects). Treatment with carvedilol usually entails long-term therapy and should - if possible - not be stopped abruptly, but gradually discontinued over a period of one to two weeks.

4.3 Contraindications

- Hypersensitivity to carvedilol or to any of the excipients listed in section 6.1
- Cardiogenic shock
- Unstable/congestive heart failure
- Acute pulmonary embolism
- Prinzmetal's angina
- Severe hypotension (systolic blood pressure < 85 mm Hg)
- Severe bradycardia (< 50 bpm)
- Second-degree or third-degree atrioventricular (AV) block (provided the patient does not have a permanent pacemaker)
- Sick sinus syndrome, including sinoatrial block
- Pulmonary heart disease
- Bronchial asthma or other airway diseases with bronchospastic components (e.g. chronic obstructive pulmonary disease)
- Untreated phaeochromocytoma
- Clinically relevant hepatic impairment
- Metabolic acidosis
- Concurrent treatment with MAO inhibitors (exception: MAO-B inhibitors)
- Concomitant intravenous therapy with verapamil, diltiazem or other antiarrhythmic drugs
- Lactation

4.4 Special warnings and precautions for use

Hypertension

Carvedilol can be used either alone or combined with other antihypertensive drugs, especially thiazide diuretics, in the treatment of essential hypertension. In case of (pre)treatment with diuretics, short-term discontinuation of these drugs is recommended - if possible - before starting carvedilol treatment, where appropriate, so that a potentially excessive drop in the blood pressure can be avoided.

As there is no adequate clinical experience, carvedilol must not be used in unstable or secondary hypertension, complete bundle branch block, tendency towards hypotension on changing position (orthostasis), acute inflammatory heart diseases, haemodynamically relevant changes in the heart valves or outflow tract, end-stage peripheral arterial circulatory disorders, and concurrent treatment with alpha1 receptor antagonists or alpha2 receptor agonists.

If – in justified exceptions – carvedilol and clonidine are to be used concurrently, clonidine must be discontinued gradually only if treatment with carvedilol has been stopped a few days previously.

Chronic (congestive) heart failure

In principle, carvedilol should always be used in addition to standard heart failure therapy – consisting of diuretics, digitalis, ACE inhibitors and/or other vasodilators. Carvedilol treatment must not be commenced unless the patient's condition has been stabilised on conventional basic heart failure therapy, i.e. the dosage of this existing, standard therapy must have remained stable for at least four weeks prior to starting treatment with carvedilol.

In patients with severe heart failure (NYHA ≥ III), salt and/or fluid depletion (e.g. high-dose diuretic treatment), but also in elderly patients (≥ 70 years) or patients with low baseline blood pressure (e.g. systolic < 100 mm Hg), there may be a sharper decrease in blood pressure after administration of the first carvedilol dose but also after an increase of the dose. Consequently, these patients should be medically monitored for about two hours after administration of the first carvedilol dose and after an increase of the dose so that an uncontrolled hypotensive reaction can be avoided.

In patients with (congestive) heart failure, a deterioration in the heart failure or fluid retention can occur during up-titration of the carvedilol dose. If such symptoms occur, the diuretic dose should be increased, but not the carvedilol dose, until the patient is clinically stable.
Occasionally, however, it may also be necessary to reduce the carvedilol dose or, in rare cases, temporarily discontinue treatment. Such incidents do not preclude subsequent successful titration of carvedilol. Due to the negative effect on AV conduction, carvedilol should be used with caution in patients with first-degree AV block.

As both substances delay AV conduction, increased caution is required when co-administering carvedilol and cardiac glycosides (see section 4.5).

Renal function in (congestive) heart failure
A reversible deterioration in renal function was observed on treatment with carvedilol in patients with chronic heart failure and low blood pressure (systolic < 100 mm Hg) who also had ischaemic heart disease or generalised vascular diseases, and/or renal insufficiency. Therefore, renal function must be monitored frequently during titration of carvedilol treatment in patients with these risk factors. If renal function is exacerbated, the carvedilol dose should be reduced or, if appropriate, the therapy discontinued.

Left-ventricular dysfunction after acute myocardial infarction
The patient must be clinically stable before commencing treatment with carvedilol.
In addition, the patient must have received an ACE inhibitor for at least 48 hours beforehand, and the dose of this ACE inhibitor should have remained stable during the last 24 hours.

As only limited clinical data are available on the use of carvedilol in patients with unstable angina pectoris, it should be used with caution in the presence of such symptoms.

Chronic obstructive pulmonary disease
Dyspnoea can develop in patients with a tendency towards bronchial spasms due to a potential increase in airway resistance. Patients with respiratory tract diseases including a bronchospastic component therefore may not be treated with carvedilol (see section 4.3).

Diabetes
Carvedilol should be used with caution in patients with diabetes mellitus as the results of blood glucose monitoring can worsen or early warning signs or symptoms of acute hypoglycaemia may be masked or diminished. Therefore, the blood glucose concentration must be monitored regularly in these patients when commencing treatment and when changing the carvedilol dose, respectively. The antihypertensive treatment may need to be adjusted, accordingly.

Careful medical monitoring of the blood glucose concentration is also necessary on strict fasts (see section 4.5).
Beta-blockers can increase insulin resistance and mask symptoms of hypoglycaemia.
However, numerous studies have demonstrated that vasodilating beta-blockers such as carvedilol have more favourable effects on the glucose and lipid profiles.

Peripheral vascular disease and Raynaud's disease
Carvedilol should be used with caution in patients with peripheral vascular diseases (e.g. Raynaud's disease), as beta-blockers may trigger or aggravate symptoms of impaired arterial circulation.

Hyperthyroidism
Carvedilol can mask the symptoms of hyperthyroidism.

Anaesthesia and major surgery
Due to the additive negative inotropic effects of carvedilol and certain anaesthetics, caution is advised in patients undergoing surgery.

Bradycardia

Carvedilol can cause bradycardia. The dose of carvedilol should generally be reduced if the pulse drops below 55 beats per minute.

Hypersensitivity
Caution should be exercised when administering beta-blocking agents in patients with a history of severe hypersensitivity reactions and in patients undergoing desensitisation therapy, as both sensitivity to allergens and the severity of hypersensitivity reactions can be increased.

Severe skin reactions
Very rarely, there have been reports of severe skin reactions, such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), during treatment with carvedilol (see also section 4.8). Carvedilol should be stopped permanently in patients who experience severe skin reactions that are possibly attributable to carvedilol.

Psoriasis
Patients with a history of psoriasis in association with beta-blocker therapy should take carvedilol only after the benefits and risks have been carefully considered.

Concomitant use of calcium channel blockers
Careful monitoring in the form of ECG and blood pressure measurement is necessary when concurrently administering calcium antagonists, such as verapamil or diltiazem, or other antiarrhythmics.

Phaeochromocytoma
Patients with phaeochromocytoma must not receive treatment with beta-blockers until adequate alpha blockade has been achieved. Although carvedilol has alpha-blocking and beta-blocking pharmacological properties, there is insufficient experience of its use in this condition. Therefore, carvedilol should be used with caution in patients suspected to have phaeochromocytoma.

Prinzmetal's angina
Active substances with non-selective beta-blocking activity may provoke chest pain in patients with Prinzmetal's angina. There is no clinical experience with carvedilol in these patients, although the alpha-blocking activity of carvedilol could prevent such symptoms. Carvedilol is contraindicated in patients diagnosed with Prinzmetal's angina (see section 4.3). Carvedilol should be used with caution in patients suspected to have Prinzmetal's angina.

Contact lenses
Wearers of contact lenses should be aware of the possibility of reduced lacrimation.

Withdrawal syndrome
Carvedilol treatment should not be stopped abruptly, especially in patients with ischaemic heart disease. A gradual reduction of the dose over a period of two weeks is recommended.

Use as a doping agent
The use of Carvedi-Denk can return positive results in antidoping tests. The use of Carvedi-Denk as a doping agent can be harmful to the health.

Paediatric population
Carvedilol is not recommended for use in children and adolescents under 18 years of age due to the insufficient availability of safety data.

Elderly patients
Elderly patients may be more sensitive to the effects of carvedilol and should be monitored more carefully.
As with other beta-blockers, and especially in patients with coronary heart disease, carvedilol should be discontinued gradually.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Influence of carvedilol on the pharmacokinetics of other medicinal products:
Carvedilol is a substrate as well as inhibitor of P-glycoprotein. The bioavailability of medicinal products that are transported by P-glycoprotein could therefore be increased by the concomitant administration of carvedilol. The bioavailability of carvedilol may also be altered by other inducers and inhibitors of P-glycoprotein.

Digoxin: Some studies in healthy subjects and patients with cardiac failure noted an increase of up to 20% in the serum digoxin concentration. The effect was found to be much greater in men than in women. Therefore, closer monitoring of the serum digoxin concentration is recommended when starting treatment, adjusting the dose, and discontinuing carvedilol (see section 4.4). Carvedilol has no influence on intravenously administered digoxin.

Ciclosporin: Two studies in kidney and heart transplant patients given oral ciclosporin found increased plasma ciclosporin concentrations after the start of treatment with carvedilol. Carvedilol appears to increase the bioavailability of orally administered ciclosporin by approximately 10%-20%. To maintain the therapeutic level of ciclosporin, an average reduction of 10%-20% in the ciclosporin dose was required in these patients. The mechanism behind the interaction is not clear, but could be associated with the inhibitory activity of P-glycoprotein in the intestine.
Due to the considerable individual variability of the ciclosporin concentrations, it is recommended that the ciclosporin concentration be monitored carefully after the start of therapy with carvedilol and that the ciclosporin dose be adjusted, if appropriate. No interaction with carvedilol is expected from intravenous administration of ciclosporin.

Influence of other medicinal products on the pharmacokinetics of carvedilol
Both inhibitors and inducers of CYP2D6 and CYP2C9 can effect a stereoselective change in the systemic and/or presystemic metabolism of carvedilol, resulting in an increased or decreased plasma concentration of (R)-carvedilol and (S)-carvedilol (see section 5.2). Some examples of observations made in patients or in healthy subjects are listed below. This list does not claim to be exhaustive, however.

Cimetidine: Cimetidine, hydralazine and alcohol can increase the systemic availability of carvedilol, as they decrease its hepatic metabolism through enzyme inhibition. Careful monitoring of these patients is therefore recommended during concomitant administration.

Rifampicin: In a study of 12 healthy subjects, the availability of carvedilol when administered concurrently with rifampicin was reduced by approx. 60% and carvedilol was seen to have a diminished effect on the systolic blood pressure. The mechanism behind the interaction is not known, but could be attributable to induction of P-glycoprotein in the intestine by rifampicin. Close monitoring of the beta blockade in patients receiving carvedilol and rifampicin concurrently is recommended.

Amiodarone: An *in vitro* study in human liver microsomes revealed that amiodarone and desethylamiodarone inhibit the oxidation of (R)-carvedilol and (S)-carvedilol. There was a significant 2.2-fold increase in the trough level of (S)-carvedilol in patients with cardiac failure who took carvedilol and amiodarone concurrently, as compared to patients receiving carvedilol alone. The influence exerted on (S)-carvedilol was ascribed to desethylamiodarone, a metabolite of amiodarone that is a potent inhibitor of CYP2C9. Monitoring of beta blockade is recommended in patients receiving carvedilol and amiodarone concurrently.

Fluoxetine and paroxetine: Coadministration of carvedilol and fluoxetine, a potent inhibitor of CYP2D6, in a randomised, crossover study involving 10 patients with cardiac failure resulted in the stereoselective inhibition of the metabolism of carvedilol along with a 77% increase in the mean AUC of the (R)-enantiomer and a statistically insignificant increase of 35% in the mean AUC of the (S-

)enantiomer compared to the placebo group. However, in terms of adverse effects, blood pressure and heart rate, no differences were found between the treatment groups. The effect of a single oral dose of paroxetine, a potent CYP2D6 inhibitor, on the pharmacokinetics of carvedilol was studied in 12 healthy subjects. Despite a significant increase in the availability of (R)-carvedilol and (S)-carvedilol, no clinical effects were observed in the subjects.

Pharmacodynamic interactions

Insulin or oral antidiabetics: The effect of insulin and oral hypoglycaemic drugs can be potentiated by beta blockers. The symptoms of hypoglycaemia may be masked or attenuated (especially tachycardia). Regular blood glucose monitoring is therefore necessary in patients who use insulin or oral antidiabetics (see section 4.4).

Catecholamine-depleting agents: Patients taking medicinal products with beta-blocking properties combined with a medicinal product that can deplete catecholamines (e.g. reserpine and MAO inhibitors) should be carefully monitored for signs of hypotension and/or severe bradycardia.

Digoxin: The combined use of beta-blockers and digoxin may result in an additive prolongation of AV conduction.

Calcium channel blockers such as verapamil or diltiazem, amiodarone or other antiarrhythmics: The risk of AV conduction disorders can be increased by the concurrent use of carvedilol and oral calcium antagonists such as verapamil or diltiazem, or other antiarrhythmics such as amiodarone. Isolated cases of conduction disorders (rarely associated with haemodynamic impairment) have been reported in relation to the concurrent administration of carvedilol and diltiazem. If carvedilol must be taken in combination with calcium antagonists such as verapamil or diltiazem, amiodarone or other antiarrhythmics, monitoring of the blood pressure, heart rate and heart rhythm (ECG) is recommended as for other active substances with beta-blocking properties (see also section 4.4).

Clonidine: The combined use of clonidine, reserpine, guanethidine, methyldopa or guanfacine with beta-blockers can additionally reduce the blood pressure and heart rate. If combined use of beta-blockers and clonidine has to be discontinued, the beta-blocker should be stopped first. Clonidine treatment can then be withdrawn several days later by gradually reducing the dose.

Antihypertensives: As with other active substances that have beta-blocking activity, carvedilol can intensify the effect of other antihypertensive drugs (such as alpha1 antagonists) and medicinal products that possibly have hypotensive adverse effects (such as barbiturates, phenothiazine, tricyclic antidepressants, vasodilators and alcohol).

Anaesthetics: Under anaesthesia, the negative inotropic effects and antihypertensive activity of carvedilol and some anaesthetics can be synergistically increased.
For this reason, careful monitoring of vital signs is recommended (see section 4.4).

NSAIDs: The concurrent administration of non-steroidal anti-inflammatory drugs (NSAIDs) and beta-blockers can result in hypertension and diminished blood pressure control.

Beta-adrenergic bronchodilators: Non-cardioselective beta-blockers counteract the bronchodilatory effect of beta-adrenergic bronchodilators. Careful monitoring of these patients is recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy
For carvedilol, no clinical data on exposed pregnancies are available.
Studies in animals have shown reproductive toxicity (see section 5.3).

Beta-blockers reduce placental perfusion. Intrauterine foetal death, miscarriage and premature delivery may result. In addition, adverse effects (especially hypoglycaemia and bradycardia) may occur both in

the foetus and the newborn child. Postnatally, the newborn child is at increased risk of cardiac and pulmonary complications. Carvedilol should therefore be used in pregnancy only if the benefits to the mother justify the potential risk to the unborn or newborn child.
Treatment with beta-blockers should be discontinued 72-48 hours before due date. If this is not possible, the newborn child must be monitored during its first 48-72 hours of life.

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

Fertility
In animal studies, female fertility was impaired after treatment with carvedilol (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies have been conducted into the effect on the ability to drive and use machines.
Individual differences in reactions (e.g. dizziness, fatigue) may alter the ability to drive, use machines or work without a secure hold. This applies in particular at the start of treatment, when increasing the dose and switching medication, as well as in combination with alcohol.

4.8 Undesirable effects

(a) Summary of the safety profile
With the exception of dizziness, visual disturbances, bradycardia and increased cardiac failure, the frequency of the adverse effects is not dose-dependent.

(b) List of undesirable effects
The risk of most adverse effects in association with carvedilol is comparable for all indications. Exceptions are described in subsection (c).

The following frequencies are used for evaluating side effects:
Very common ($\geq$ 1/10)
Common ($\geq$ 1/100 to < 1/10)
Uncommon ($\geq$ 1/1,000 to < 1/100)
Rare ($\geq$ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

Table 1 summarises the undesirable effects that have been reported for carvedilol in pivotal studies of the following indications: chronic heart failure, left-ventricular dysfunction after acute myocardial infarction, hypertension and long-term treatment of chronic angina pectoris.

Table 1 Adverse effects in clinical studies

Organ system	**Adverse effect**	**Frequency**
Infections and infestations	Bronchitis	Common
	Pneumonia	Common
	Upper respiratory tract infections	Common
	Urinary tract infections	Common
Blood and lymphatic system disorders	Anaemia	Common
	Thrombocytopenia	Rare
	Leucopenia	Very rare
Immune system disorders	Hypersensitivity (allergic reactions)	Very rare

Metabolism and nutrition disorders	Weight increase	Common
	Hypercholesterolaemia	Common
	Deterioration in blood glucose regulation (hyperglycaemia, hypoglycaemia) in patients with diabetes mellitus	Common
Psychiatric disorders	Depression, depressed moods	Common
	Sleep disorders	Uncommon
	Nightmares	Uncommon
	Hallucinations	Uncommon
	Confusion	Uncommon
	Psychosis	Very rare
Nervous system disorders	Dizziness	Very common
	Headache	Very common
	Presyncope, syncope	Common
	Paraesthesia	Uncommon
Eye disorders	Visual disturbances	Common
	Lacrimation decreased (dry eye)	Common
	Eye irritation	Common
Cardiac disorders	Cardiac failure	Very common
	Bradycardia	Common
	Hypervolaemia	Common
	Fluid retention	Common
	AV block	Uncommon
	Angina pectoris	Uncommon
Vascular disorders	Hypotension	Very common
	Orthostatic hypotension	Common
	Disturbances of peripheral circulation (cold extremities, peripheral arterial disease, exacerbation of intermittent claudication and of Raynaud's syndrome)	Common
	Hypertension	Common
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Common
	Pulmonary oedema	Common
	Asthma in predisposed patients	Common
	Nasal congestion	Rare
Gastrointestinal disorders	Nausea	Common
	Diarrhoea	Common
	Vomiting	Common
	Dyspepsia	Common
	Abdominal pain	Common
	Constipation	Uncommon
	Dry mouth	Rare
Hepatobiliary disorders	Alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT) and gamma-glutamyltransferase (GGT)	Very rare
Skin and subcutaneous tissue disorders	Skin reactions (e.g. allergic exanthema, dermatitis, urticaria, pruritus, psoriatic and lichen planus-like skin lesions)	Uncommon

	Severe skin reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)	Not known
	Alopecia	Not known
Musculoskeletal and connective tissue disorders	Pain in the extremities	Common
Renal and urinary disorders	Renal failure and abnormal renal function in patients with generalised vascular diseases and/or renal insufficiency	Common
	Micturition disorders	Common
	Urinary incontinence in women	Very rare
Reproductive system and breast disorders	Erectile dysfunction	Uncommon
General disorders and administration site conditions	Asthenia (fatigue)	Very common
	Pain	Common
	Oedema	Common

(c) Description of selected adverse effects

Dizziness, syncope, headache and asthenia are usually mild in nature and are more likely to occur at the beginning of treatment.

In patients with (congestive) heart failure, an exacerbation of heart failure and fluid retention may occur during up-titration of the carvedilol dose (see section 4.4).

Heart failure is a commonly reported adverse effect in patients both on placebo treatment and on carvedilol treatment (14.5% and 15.4%, respectively, in patients with left ventricular dysfunction following acute myocardial infarction).

A reversible deterioration in renal function has been observed (see section 4.4) in patients with chronic heart failure and low blood pressure, ischaemic heart disease and generalised vascular disease and/or renal failure during treatment with carvedilol.

Beta-blockers can lead to the manifestation of latent diabetes mellitus, aggravate manifest diabetes, and impair blood glucose regulation.

In women, carvedilol may cause urinary incontinence that resolves on discontinuation of the medication.

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.

4.9 Overdose

Symptoms of overdose
Overdose can result in severe hypotension, bradycardia, heart failure, cardiogenic shock and cardiac arrest. In addition, respiratory problems, bronchospasm, vomiting, impaired consciousness and generalised seizures can occur.

Treatment of overdose
In addition to general treatment, the vital parameters must be monitored and corrected, under intensive care conditions if necessary, and mechanical ventilation may be necessary in certain circumstances.

Absorption of carvedilol in the gastrointestinal tract may be reduced with the aid of gastric lavage, the use of activated charcoal, and the administration of a laxative.

The patient should be placed in the supine position.

The following antidotes are available:

- *For bradycardia:*
  Intravenous atropine at a dose of 0.5 mg to 2 mg; pacemaker therapy should be undertaken in the case of refractory bradycardia.

- *For hypotension or shock:*
  Plasma substitutes and, if applicable, sympathomimetics.

A dose-dependent decrease in the beta-blocking activity of carvedilol can be achieved with the slow intravenous administration of sympathomimetics, e.g. isoprenaline, dobutamine, orciprenaline or

adrenaline, at doses adjusted to the body weight. If a positive inotropic effect is required, consideration can be given to the administration of a phosphodiesterase inhibitor, e.g. milrinone. If applicable, glucagon (1 mg to 10 mg IV) can be given, followed if necessary by continuous infusion of 2 mg/hour to 5 mg/hour.

If the pattern of intoxication is dominated by peripheral vasodilation, administration of norfenefrine or norepinephrine will be necessary while continuously monitoring the circulation.

In the event of bronchospasm, beta-sympathomimetics (as an aerosol, or intravenously if the effect is inadequate) or aminophylline should be given as a slow intravenous injection or infusion.

In case of seizures, slow intravenous administration of diazepam or clonazepam is recommended.

Important:
In the event of severe intoxication accompanied by symptoms of shock, treatment with antidotes must be continued for a sufficiently long period, as a prolongation of the elimination half-life and redistribution of carvedilol from deeper compartments can be expected. The duration of antidote treatment depends on the severity of the overdose. Countermeasures should therefore be undertaken until the patient's condition has stabilised.

Carvedilol is not eliminated during dialysis, as the active substance is not dialysed, probably due to its high degree of protein binding.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Carvedilol is a non-selective beta-blocking agent with vasodilatory properties, thereby reducing peripheral vascular resistance. Vasodilation results primarily from selective alpha1 receptor blockade. Carvedilol has no intrinsic sympathomimetic activity, and has membrane-stabilising properties.

Carvedilol has antioxidant properties and can inhibit the effect of free oxygen radicals. The antioxidant properties of carvedilol and its metabolites have been demonstrated by *in vitro* and *in vivo* animal studies and by *in vitro* studies in various human cell types, as well as in clinical studies.

The beta-adrenergic receptor blocking activity of carvedilol is non-selective for $beta_1$ and $beta_2$ adrenoceptors and is attributed to the (S)-(-)-enantiomer.

Carvedilol suppresses the renin-angiotensin-aldosterone system through its beta-blocking activity. The release of renin is thus reduced.

The HDL/LDL ratio of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) is not influenced by carvedilol.

Clinical efficacy and safety
The following results have been obtained from clinical studies in carvedilol:

Hypertension:
In hypertensive patients, carvedilol decreases the blood pressure based on a combination of beta blockade and alpha1-modulated vasodilation. The antihypertensive effect is not accompanied by an increase in total peripheral resistance, and the peripheral blood flow remains intact. The heart rate is

moderately decreased. Renal perfusion and renal function usually remain unchanged. Carvedilol maintains the stroke volume and reduces total peripheral resistance.

In hypertensive patients, carvedilol increases the plasma norepinephrine concentration.

Coronary heart disease
In patients with coronary heart disease, carvedilol has anti-ischaemic and antianginal effects, including during long-term treatment. Studies into the acute haemodynamic effect revealed a decrease in the ventricular preload (pulmonary arterial 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 the symptoms and left-ventricular function. The effect of carvedilol is dose-dependent.

In a large international double-blind, placebo-controlled, multicentre mortality study (COPERNICUS), 2289 patients with severe stable chronic heart failure of ischaemic or non-ischaemic origin who had already received optimised standard therapy (e.g. with diuretics, ACE inhibitors, and digitalis and/or vasodilators if appropriate) were randomised to treatment with either carvedilol (1156 patients) or placebo (1133 patients). The patients had left-ventricular systolic dysfunction with a mean ejection fraction of <20%. Total mortality at one year was 35% lower in the carvedilol group at 12.8% than in the placebo group at 19.7% ($p = 0.00013$). The benefit with respect to patient survival was consistent on carvedilol therapy in all the studied subpopulations, such as high-risk patients (EF < 20%, frequent rehospitalisation). The rate of sudden cardiac death was 41% lower in the carvedilol group than in the placebo group (5.3% versus 8.9%).

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

The incidence of severe adverse effects during the study was lower in the carvedilol group than in the placebo group (39.0% versus 45.4%). During the titration phase the incidence of exacerbated heart failure in the carvedilol group also was no higher than in the placebo group.

5.2 Pharmacokinetic properties

Absorption
After oral administration of a 25 mg capsule in healthy subjects, carvedilol is rapidly absorbed after approx. 1½ hours (t_{max}), reaching a maximum plasma concentration (C_{max}) of 21 mg/L. Orally administered carvedilol undergoes extensive first-pass metabolism, resulting in an absolute bioavailability of approx. 25% in healthy male subjects. Carvedilol is a racemate, and the (S)(-)-enantiomer appears to be metabolised more rapidly, with an absolute oral bioavailability of 15%, than the (R)(+)-enantiomer, which has an absolute oral bioavailability of 31%. The maximum plasma concentration of (R)-carvedilol is roughly double that of (S)-carvedilol.

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

Distribution
Carvedilol is highly lipophilic with plasma protein binding of approximately 95%. The volume of distribution is between 1.5 and 2 L/kg. The volume of distribution in patients with liver cirrhosis is higher.

Biotransformation

In humans, carvedilol is converted almost entirely by oxidation and conjugation in the liver to numerous metabolites, which are excreted primarily in the bile. Enterohepatic circulation has been demonstrated in animals.

Three active metabolites with beta-blocking properties result from demethylation and hydroxylation at the phenol ring. Preclinical studies have demonstrated that the beta-blocking activity of the 4´-hydroxyphenol metabolite is approx. 13 times more potent than that of carvedilol. Compared to carvedilol, the three active metabolites have only a weak vasodilatory effect. The concentrations of the three active metabolites are approx. 10 times lower in humans than those of the parent substance. Two of the hydroxycarbazole metabolites of carvedilol are extremely potent antioxidants that have demonstrated an effect which is 30 to 80 times greater than carvedilol.

In slow metabolisers, the action of the vasodilating component can be intensified.

Pharmacokinetic studies in humans have shown that the oxidative metabolism of carvedilol is stereoselective. The results of one *in vitro* study indicated that different cytochrome P450 isoenzymes, including CYP2D6, CYP3A4, CYP2E1, CYP2C9 and CYP1A2, may be involved in the oxidation and hydroxylation processes.

Studies in healthy volunteers and patients have revealed that the (R)-enantiomer is metabolised mainly by CYP2D6, and the (S)-enantiomer mainly by CYP2D6 and CYP2C9.

Genetic polymorphism
The results from pharmacokinetic studies in humans have demonstrated that CYP2D6 plays an important role in the metabolism of (R)-carvedilol and (S)-carvedilol. Consequently, the plasma concentrations of (R)-carvedilol and (S)-carvedilol are increased in slow metabolisers. The results are inconsistent with respect to clinical importance.

Elimination
After a single oral dose of 50 mg carvedilol, approx. 60% of the dose is secreted in the bile and eliminated within 11 days in the faeces in the form of metabolites. After a single oral dose, only approx. 16% is excreted in the urine as carvedilol or its metabolites. Less than 2% of the substance is excreted unchanged in the urine. After intravenous infusion of 12.5 mg carvedilol, the plasma clearance in healthy volunteers amounted to about 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 volunteers was 6.5 hours, which also corresponded to the absorption half-life of the capsule. After oral administration, the clearance of (S)-carvedilol from the entire body is approximately double that of (R)-carvedilol.

Linearity/non-linearity
There is a linear relationship between the dose and the maximum plasma concentration (C_{max}).

Pharmacokinetic/pharmacodynamic relationships

Patients with impaired liver function
A pharmacokinetic study in patients with liver cirrhosis showed that the systemic availability (AUC) of carvedilol in patients with impaired liver function was 6.8 times higher than in healthy subjects. Carvedilol is therefore contraindicated in patients with clinically manifest hepatic impairment (see section 4.3).

Patients with renal insufficiency
The AUC values, elimination half-life and maximum plasma concentration do not change significantly in patients with hypertension and renal insufficiency. The renal elimination of the unchanged active substance is reduced in patients with renal insufficiency; the changes in the pharmacokinetic parameters are minimal, however.
Autoregulation of renal perfusion and glomerular filtration remain unchanged during long-term treatment with carvedilol. No dose adjustment is necessary in patients with moderate to severe renal insufficiency (see section 4.2).

Carvedilol is not eliminated by dialysis as it cannot cross the dialysis membrane, probably due to the high degree of plasma-protein binding.

Patients with heart failure
In one study of 24 Japanese patients with heart failure, the clearance of (R)-carvedilol and (S)-carvedilol was significantly lower than initially presumed from the data obtained from healthy subjects. These results suggest that heart failure significantly modifies the pharmacokinetics of (R)-carvedilol and (S)-carvedilol.

Paediatric population
Studies in children and adolescents have revealed that weight-related clearance is significantly greater than in adults.

Elderly patients
The pharmacokinetics of carvedilol in hypertensive patients was not significantly influenced by age. In one study of elderly hypertensive patients, the adverse effect profile did not differ from that in younger patients. In another study in which elderly patients with coronary heart disease were enrolled, no differences were found with respect to the reported adverse effects compared to those in younger patients. Therefore, no adjustment of the initial dose is necessary in elderly patients (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and development, genotoxicity and carcinogenic potential.

Standard testing produced no evidence of a mutagenic or tumorigenic potential for carvedilol.

The administration of toxic doses of carvedilol (≥ 200 mg/kg, ≥ 100 x MRHD) in adult female rats resulted in decreased fertility (reduced mating frequency, reduced number of corpora lutea and intrauterine implantations).

Embryotoxicity studies in rats and rabbits revealed no teratogenic effects for carvedilol. However, embryotoxic/foetotoxic effects and fertility disorders occurred in the rabbits at subtoxic maternal doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carvedi-Denk 25

Microcrystalline cellulose, magnesium stearate [vegetable], colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Aluminium/aluminium blister

Pack size: 30 tablets

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Denk Pharma GmbH & Co. KG
Prinzregentenstr. 79
D-81675 München
Germany

8. MARKETING AUTHORISATION NUMBERS IN GERMANY

Carvedi-Denk 6.25: 88650.00.00
Carvedi-Denk 25: 88651.00.00

9. DATE OF FIRST AUTHORISATION IN GERMANY

11/10/2013

10. DATE OF REVISION OF THE TEXT

02/2018

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription