Summary of Product Characteristics

1. Name of the medicinal product

VEDICOR 6,25 mg
VEDICOR 12,5 mg
VEDICOR 25 mg
Carvedilol

2. Qualitative and quantitative composition

VEDICOR 6,25 mg tablets
Each tablet contains 6,25 mg of carvedilol.
VEDICOR 12,5 mg tablets
Each tablet contains12,5 mg of carvedilol.
VEDICOR 25 mg tablets
Each tablet contains 25 mg of carvedilol.
For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet.

4. Clinical particulars

4.1 Therapeutic indications

Essential hypertension
Chronic stable angina pectoris
Adjunctive treatment of moderate to severe stable chronic heart failure

4.2 Posology and method of administration

Oral use.
Essential Hypertension
VEDICOR 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:
A twice-daily regimen is recommended.
Adults
The recommended initial dosage is 12.5 mg twice a day for the first two days. Thereafter, the treatment is continued at the dose 25 mg twice a day. If necessary, the dose may be further increased gradually at intervals of two weeks or more rarely to the recommended maximum dose of 100 mg a day divided into two 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:
VEDICOR is given in 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 stabilized for at least 4

weeks prior to treatment. Additionally the patient should have a reduced left ventricular ejection fraction and heart rate 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 this dose is tolerated, the dose may be increased slowly with intervals of not less than two weeks up to 6.25 mg twice a day, then up to 12.5 mg twice a day and finally up to 25 mg twice a day. The dosage should be increased to the highest tolerable level.
The recommended maximum dosage is 25 mg twice a day for patients with a body weight of less than 85 kg, and 50 mg twice a day for patients with a body weight above 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 dose should not be increased. The patient should be monitored by a physician/cardiologist for two hours after starting 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 rhythm). Worsening of heart failure or fluid retention is treated by increasing the dose of diuretic, and the dose of VEDICOR should not be increased until the patient is stabilized. If bradycardia appears or in case of lengthening of AV conduction, the level of digoxin should first be monitored.
Occasionally it may be necessary to reduce the VEDICOR dose or temporarily discontinue treatment altogether. Even in these cases, VEDICOR dose titration can often be successfully continued.
Renal function, thrombocytes and glucose (in case of NIDDM and/or IDDM) should be monitored regularly during dose titration. However, after dose titration the frequency of monitoring can be reduced.
If VEDICOR has been withdrawn for more than two weeks, the therapy should be reinitiated with 3.125 mg twice a day and increased gradually according to the above recommendations.
Renal insufficiency
Dosage must be determined for each patient individually, but according to pharmacokinetic parameters there is no evidence that dose adjustment of VEDICOR in patients with renal impairment is necessary.
Moderate hepatic dysfunction
Dose adjustment may be required.
Paediatric population (< 18 years)
VEDICOR is not recommended for the use in children below 18 years of age due to insufficient data on the efficacy and safety of VEDICOR.
Elderly
Elderly patients may be more susceptible to the effects of VEDICOR and should be monitored more carefully.
As with other beta-blockers and especially in patients with coronary disease, the withdrawal of VEDICOR should be done gradually (see section 4.4).
Methods of administration
The tablets should be taken with the adequate supply of fluid. It is recommended that heart failure patients take their VEDICOR 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 carvedilol or to any of the excipients of VEDICOR listed in section 6.1.
• Heart failure belonging to NYHA Class IV of the heart failure classification with marked fluid retention or overload requiring intravenous inotropic treatment.
• Chronic obstructive pulmonary disease with bronchial obstruction (see section 4.4).
• Clinically significant hepatic dysfunction.
• Bronchial asthma.
• AV block, degree II or III (unless a permanent pacemaker is in place).
• Severe bradycardia (<50 bpm).
• Sick sinus syndrome (incl. sino-atrial block).
• Cardiogenic shock.
• Severe hypotension (systolic blood pressure below 85 mmHg).
• Prinzmetal's angina.
• Untreated phaeochromocytoma.

• Metabolic acidosis.
• Severe peripheral arterial circulatory disturbances.
Concomitant intravenous treatment with verapamil or diltiazem (see section 4.5).

4.4 Special warnings and precautions for use

Warnings to be considered particularly in heart failure patients
In chronic heart failure patients VEDICOR should be administered principally in addition to diuretics, ACE inhibitors, digitalis and/or vasodilators. Initiation of therapy should be under the supervision of a hospital physician. Therapy should only be initiated, if the patient is stabilized on conventional basic therapy for at least 4 weeks. Patients with severe heart failure, salt and volume depletion, elderly or patients with low basic blood pressure should be monitored for approximately 2 hours after the first dose or after dose increase as hypotension may occur. Hypotension due to excessive vasodilatation is initially treated by reducing the dose of the diuretic. If symptoms still persist, the dose of any ACE inhibitor may be reduced. At the start of therapy or during up-titration of VEDICOR worsening of heart failure or fluid retention may occur. In these cases, the dose of diuretic should be increased. However, sometimes it will be necessary to reduce or withdraw VEDICOR medication. The VEDICOR dose should not be increased before symptoms due to the worsening of heart failure or hypotension due to vasodilatation are under control. Reversible deterioration of renal function has been observed during VEDICOR therapy in heart failure patients with low blood pressure (systolic < 100 mm Hg), ischaemic heart disease and generalized atherosclerosis, and/or underlying renal insufficiency. In heart failure patients with these risk factors, renal function should be monitored during dose titration of VEDICOR. If significant worsening of renal function occurs, the VEDICOR dose must be reduced or therapy must be discontinued.
In patients with chronic heart failure treated with digitalis, VEDICOR should be given with caution, as digitalis and VEDICOR both lengthen the AV conduction time (see section 4.5).
Other warnings as regards VEDICOR and beta-blockers in general
Agents with non-selective beta-blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There is no clinical experience with VEDICOR in these patients, although the alpha-blocking activity of VEDICOR may prevent such symptoms. However, caution should be taken in the administration of VEDICOR to patients suspected of having Prinzmetal's variant angina.
Patients with a chronic obstructive pulmonary disease with a tendency towards bronchospasms who are not treated with oral or inhalation medicine should only be given VEDICOR if the expected improvement outweighs the possible risk. Patients should be monitored closely in the initial phase, and titration of VEDICOR and VEDICOR dose should be reduced in case of bronchospasms.
VEDICOR may mask symptoms and signs of acute hypoglycaemia. Impaired blood glucose control may occasionally occur in patients with diabetes mellitus and heart failure in connection with the use of VEDICOR. Therefore, close monitoring of diabetic patients receiving VEDICOR is required by means of regular blood glucose measurements, especially during dose titration, and adjustment of antidiabetic medication as necessary (see section 4.5). Blood glucose levels should also be closely monitored after a longer period of fasting.
VEDICOR may mask features (symptoms and signs) of thyrotoxicosis.
VEDICOR may cause bradycardia. If there is a decrease in pulse rate to less than 55 beats per minute, and symptoms associated with bradycardia occur, the VEDICOR dose should be reduced.
When VEDICOR is used concomitantly with calcium channel blocking agents such as verapamil and diltiazem or with other antiarrhythmics, specifically amiodarone, the patient's blood pressure and ECG have to be monitored. Intravenous co-administration should be avoided (see section 4.5).
Cimetidine should be administered only with caution concomitantly as effects of VEDICOR may be increased (see section 4.5).
Persons wearing contact lenses should be advised of a possible reduction of the secretion of lacrimal fluid.
Care should be taken in administrating VEDICOR to patients with a history of serious hypersensitivity reactions and in those undergoing desensitisation therapy as beta-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions. Cautions should be exercised when prescribing beta-blockers to patients with psoriasis since skin reactions may be aggravated.
VEDICOR should be used with caution in patients with peripheral vascular diseases, as beta-blockers may aggravate symptoms of the disease. The same also applies to those with Raynaud's syndrome, as there may be exacerbation or aggravation of symptoms.

Patients who are known as poor metabolizers of debrisoquine, should be closely monitored during initiation of therapy (see section 5.2).
Since there is limited clinical experience, VEDICOR should not be administered in patients with labile or secondary hypertension, orthostasis, acute inflammatory heart disease, haemodynamic relevant obstruction of heart valves or outflow tract, end-stage peripheral arterial disease, concomitant treatment with α1-receptor antagonist or α2-receptor agonist.
In patients with phaeochromocytoma, an initial treatment with alpha-blockers should be started before using any beta-blocker. Although VEDICOR exercises alpha and beta blockade there is not sufficient experience in this disease, therefore caution should be advised in these patients.
Because of its negative dromotropic action, VEDICOR should be given with caution to patients with first degree heart block.
Beta-blockers reduce the risk of arrhythmias at anasthesia, however the risk of hypotension may be increased as well. Caution should therefore be observed with the use of certain anaesthetic medicines. Newer studies suggest however, a benefit of beta-blockers in preventing perioperative cardiac morbidity and reduction of the incidence of cardiovascular complications.
As with other beta-blockers, VEDICOR should not be discontinued abruptly. This applies in particular to patients with ischaemic heart disease. VEDICOR therapy must be discontinued gradually within two weeks, e.g. by reducing the daily dose to half every three days. If necessary, at the same time replacement therapy should be initiated to prevent exacerbation of angina pectoris.

VEDICOR contains lactose monohydrate . Patients with rare hereditary problems of galactose intolerance, fructose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Antiarrhythmics.
Isolated cases of conduction disturbance (rarely compromised haemodynamics) have been reported, if oral VEDICOR and oral diltiazem verapamil and/or amiodarone are given concomitantly. As with other beta-blockers, ECG and blood pressure should be monitored closely when concomitantly administering calcium-channel-blockers of the verapamil and diltiazem type due to the risk of AV conduction disorder or risk of cardiac failure (synergetic effect). Close monitoring should be done in case of co-administration of VEDICOR, and amiodarone therapy (oral) or class I antiarrhythmics. Bradycardia, cardiac arrest, and ventricular fibrillation have been reported shortly after initiation of beta-blocker treatment in patients receiving amiodarone. There is a risk of cardiac failure in case of class Ia or Ic antiarrhythmics concomitant intravenous therapy.
Concomitant treatment with reserpine, guanethidine, methyldopa, guanfacine and monoamine oxidase inhibitors (exception MAO-B inhibitors) can lead to additional decrease in heart rate. And hypotension Monitoring of vital signs is recommended.

Dihydropyridines.
The administration of dihydropyridines and VEDICOR should be done under close supervision as heart failure and severe hypotension have been reported.
Nitrates.
Increased hypotensive effects.
Cardiac glycosides.
An increase of steady state digoxin levels by approximately 16% and of digitoxin by approximately 13% has been seen in hypertensive patients in connection with the concomitant use of VEDICOR and digoxin. Monitoring of plasma digoxin concentrations is recommended when initiating, discontinuing or adjusting treatment with VEDICOR.
Other antihypertensive medicines.
VEDICOR may potentiate the effects of other concomitantly administered antihypertensives (e.g. α1-receptor antagonists) and medicines with antihypertensive adverse reactions such as barbiturates, phenothiazines, tricyclic antidepressants, vasodilating agents and alcohol.
Cyclosporin.
Modest increases in mean trough cyclosporine concentrations were observed following the initiation of VEDICOR treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30%

of patients, the dose of cyclosporine had to be reduced in order to maintain cyclosporine concentrations with the therapeutic range, while in the remainder no adjustment was needed. On average, the dose of cyclosporine was reduced about 20% in these patients. Due to wide interindividual variability in the dose adjustments required, it is recommended that cyclosporine concentrations be monitored closely after initiation of VEDICOR therapy and that the dose of cyclosporine be adjusted as appropriate.

Antidiabetics including insulin.

The blood sugar-lowering effect of insulin and oral diabetic medicines may be intensified. Symptoms of hypoglycaemia may be masked. In diabetic patients regular monitoring of blood glucose levels is necessary.

Clonidine.

In case of withdrawal of both VEDICOR and clonidine, VEDICOR should be withdrawn several days before the stepwise withdrawal of clonidine.

Inhalational anaesthetics.

Caution is advised in case of anaesthesia due to synergistic, negative inotrope and hypotensive effect of VEDICOR and certain anaesthetics.

NSAIDs, estrogens and corticosteroids.

The antihypertensive effect of VEDICOR is decreased due to water and sodium retention.

Medicines inducing or inhibiting cytochrome P450 enzymes.

Patients receiving medicines that induce (e.g. rifampicin and barbiturates) or inhibit (e.g. cimetidine, ketoconazole, fluoxetine, haloperidol, verapamil, erythromycine) cytochrome P450 enzymes have to be monitored closely during concomitant treatment with VEDICOR as serum VEDICOR concentrations may be reduced by the first agents and increased by the enzyme inhibitors.

Rifampicin reduced plasma concentrations of VEDICOR by about 70%. Cimetidine increased AUC by about 30% but caused no change in Cmax. Care may be required in those patients receiving inducers of mixed function oxidases e.g. rifampicin, as serum levels of VEDICOR may be reduced, or inhibitors of mixed function oxidases e.g. cimetidine, as serum levels may be increased. However, based on the relatively small effect of cimetidine on VEDICOR drug levels, the likelihood of any clinically important interaction is minimal.

Sympathomimetics with alpha-mimetic and beta-mimetic effects.

Risk of hypertension and excessive bradycardia.

Ergotamine.

Vasoconstriction increased.

Neuromuscular blocking agents.

Increased neuromuscular block.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of VEDICOR in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Beta-blockers reduce placental perfusion which may result in intrauterine fetal death and immature and premature deliveries. In addition, adverse reactions (especially hypoglycaemia, hypotension, bradycardia, respiratory depression and hypothermia) may occur in the fetus and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. VEDICOR should not be used during pregnancy unless clearly necessary (that is if the potential benefit for the mother outweighs the potential risk for the fetus/neonate). The treatment should be stopped 2-3 days before expected birth. If this is not possible the new-born has to be monitored for the first 2-3 days of life.

Breastfeeding VEDICOR is lipophilic and according to results from studies with lactating animals, VEDICOR and its metabolites are excreted in breast milk and, therefore, mothers receiving VEDICOR should not breast-feed.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

(a) Summary of the safety profile
The frequency of adverse reactions is not dose-dependent, with the exception of dizziness, abnormal vision and bradycardia.
(b) Tabulated list of adverse reactions
The risk of most adverse reactions associated with VEDICOR is similar across all indications. Exceptions are described in subsection (c).
Frequency categories are as follows:
Very common ≥ 1/10
Common ≥ 1/100 and < 1/10
Uncommon ≥ 1/1,000 and < 1/100
Rare ≥ 1/10,000 and < 1/1,000
Very rare < 1/10,000
Infections and infestations
Common: Bronchitis, pneumonia, upper respiratory tract infection, urinary tract infection
Blood and lymphatic system disorders
Common: Anaemia
Rare: Thrombocytopaenia
Very rare: Leukopenia
Immune system disorders
Very rare: Hypersensitivity (allergic reaction)
Metabolism and nutrition disorders
Common: Weight increase, hypercholesterolaemia, impaired blood glucose control (hyperglycaemia, hypoglycaemia) in patients with pre-existing diabetes
Psychiatric disorders
Common: Depression, depressed mood
Uncommon: Sleep disorders, confusion
Nervous system disorders
Very common: Dizziness, headache
Uncommon: Presyncope, syncope, paraesthesia
Eye disorders
Common: Visual impairment, lacrimation decreased (dry eye), eye irritation
Cardiac disorders
Very common: Cardiac failure
Common: Bradycardia, oedema, hypervolaemia, fluid overload
Uncommon: Atrioventricular block, angina pectoris
Vascular disorders
Very common: Hypotension
Common: Orthostatic hypotension, disturbances of peripheral circulation (cold extremities, peripheral vascular disease, exacerbation of intermittent claudication and Reynaud's phenomenon)
Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea, pulmonary oedema, asthma in predisposed patients
Rare: Nasal congestion
Gastrointestinal disorders
Common: Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain
Rare: dry mouth
Hepatobiliary disorders
Very rare: Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gammaglutamyltransferase (GGT) increased
Skin and subcutaneous tissue disorders
Uncommon: Skin reactions (e.g. allergic exanthema, dermatitis, urticaria, pruritus, psoriatic and lichen planus like skin lesions and increased sweating), alopecia
Very rare: Severe cutaneous adverse reactions (e.g. Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis)
Musculoskeletal and connective tissue disorders
Common: Pain in extremities

Renal and urinary disorders
Common: Renal failure and renal function abnormalities in patients with diffuse vascular disease and/or underlying renal insufficiency, micturition disorders
Very rare: Urinary incontinence in women
Reproductive system and breast disorders
Uncommon: Erectile dysfunction
General disorders and administration site conditions
Very common: Asthenia (fatigue)
Common: Pain
(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 VEDICOR dose (see section 4.4).
Cardiac failure is a commonly reported adverse event in both placebo and VEDICOR-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 VEDICOR therapy in chronic heart failure patients with low blood pressure, ischaemic heart disease and diffuse vascular disease and/or underlying renal insufficiency (see section 4.4).
As a class, beta-adrenergic receptor blockers may cause latent diabetes to become manifest, manifest diabetes to be aggravated, and blood glucose counter-regulation to be inhibited.
VEDICOR may cause urinary incontinence in women which resolves upon 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 listed in Appendix V

4.9 Overdose

Symptoms and signs
In the event of overdose, there may be severe hypotension, bradycardia, heart failure, cardiogenic shock and cardiac arrest. There may also be respiratory problems, bronchospasm, vomiting, disturbed consciousness and generalized seizures.
Treatment
In addition to general supportive treatment, the vital parameters must be monitored and corrected, if necessary, under intensive care conditions.
Atropine can be used for excessive bradycardia, while to support ventricular function intravenous glucagon, or sympathomimetics (dobutamine, isoprenaline) are recommended. If positive inotropic effect is required, phosphodiesterase inhibitors (PDE) should be considered. If peripheral vasodilation dominates the intoxication profile then norfenephrine or noradrenaline should be administered with continuous monitoring of the circulation. In the case of drug-resistant bradycardia, pacemaker therapy should be initiated.
For bronchospasm, β-sympathomimetics (as aerosol or intravenous) should be given, or aminophylline may be administered intravenously by slow injection or infusion. In the event of seizures, slow intravenous injection of diazepam or clonazepam is recommended.
VEDICOR is highly protein-bound. Therefore, it cannot be eliminated by dialysis.
In cases of severe overdose with symptoms of shock, supportive treatment must be continued for a sufficiently long period, i.e. until the patient's condition has stabilised, as a prolongation of elimination half-life and redistribution of VEDICOR from deeper compartments are to be expected.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

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

5.2 Pharmacokinetic properties

Absorption
Carvedilol is rapidly absorbed after oral administration. In healthy subjects, maximum serum concentration is achieved approximately 1 hour after administration. The absolute bioavailability of carvedilol in humans is approximately 25%.
There is a linear relationship between dose and serum concentrations of carvedilol. Food intake did not affect the bioavailability or the maximum serum concentration, although the time needed to reach maximum serum concentration is prolonged.
Distribution
Carvedilol is highly lipophilic. The plasma protein binding is about 98 to 99%. The volume of distribution is approximately 2 l / kg and increases in patients with liver cirrhosis.
Biotransformation In humans and in animal species studied, carvedilol is extensively metabolized to several metabolites which are excreted primarily in bile. The first pass effect after oral administration is about 60-75%. The enterohepatic circulation of the parent substance was demonstrated in animals.
Carvedilol is extensively metabolized in the liver, glucuronidation being one of the main reactions. The demethylation and hydroxylation at the phenol ring produce 3 active metabolites with blocking activity of beta-adrenergic receptors.
According to preclinical studies, the beta-blocking activity of the metabolite 4 - hydroxyphenol is approximately 13 times higher than that of carvedilol. The three active metabolites have a weak vasodilating activity, compared with caarvedilol. In humans, their concentrations are about 10 times lower than the parent substance. Two of the carbazole-hydroxy metabolites are extremely potent antioxidants, showing a potency 30-80 times that of carvedilol.
Elimination
The average half-life of elimination of carvedilol is approximately 6 hours. The plasma clearance is approximately 500-700 ml / min. Elimination is mainly via the bile, and excretion mainly via the faeces. A minor part is eliminated renally in the form of various metabolites.
Pharmacokinetics in Special Populations
Patients with renal impairment
In some of the hypertensive patients with moderate to severe renal impairment (creatinine clearance < 30 ml/min), an increase in plasma carvedilol concentrations of approximately 40-50 % was seen compared to patients with normal renal function. Peak plasma concentrations in patients with renal insufficiency increased also by an average of 10-20 %. However, there was a large variation in the results. Since

carvedilol is primarily excreted via the faeces, significant accumulation in patients with renal impairment is unlikely.
In patients with moderate to severe renal impairment there is no need to modify carvedilol dosage (see section 4.2).
Patients with liver failure
In patients with liver cirrhosis, the systemic availability of carvedilol is increased 80% due to reduced first pass effect. Therefore, carvedilol is contraindicated in patients with clinically manifest hepatic impairment (see section 4.3 Contraindications).

Use in elderly
Age had a statistically significant effect on pharmacokinetic parameters of carvedilol in hypertensive patients. A study in elderly hypertensive patients showed no difference between the adverse event profile of this group and younger patients. Another study involving elderly patients with coronary artery disease showed no difference in reported adverse reactions vs. those that were reported by younger patients.
Use in pediatrics
The available information on pharmacokinetics in subjects younger than 18 years is limited.
Diabetic patients
In hypertensive patients with type 2 diabetes was not observed effect of carvedilol on blood glucose (fasting or postprandial) and glycosylated haemoglobin A1, it was not necessary to change the dose of antidiabetic drugs.
In patients with type 2 diabetes, carvedilol had no statistically significant influence on the glucose tolerance test. In nondiabetic hypertensive patients with altered insulin sensitivity (Syndrome X), carvedilol increased insulin sensitivity. The same results were observed in hypertensive patients with type 2 diabetes.
Heart failure
In a study in 24 patients with heart failure, the clearance of R-and S-carvedilol was significantly lower than previously estimated in healthy volunteers. These results suggested that the pharmacokinetics of R-and S-carvedilol is significantly altered by heart failure.

5.3 Preclinical safety data

Carvedilol demonstrated no mutagenic or carcinogenic potential. High doses of carvedilol impaired fertility and affected pregnancy in rats (increased resorptions). Decreased fetal weight and delayed skeletal development were also seen in rats. Embryotoxicity (increased post-implantation loss) occurred in rats and rabbits.

6. Pharmaceutical particulars
6.1 List of excipients

• lactose monohydrate,

• microcrystalline cellulose,

• copovidone,

• crospovidone

• colloidal silicon dioxide

• magnesium stearate,

• titanium dioxide (E171),

• quinoline yellow (E104)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Box of 30 tablets, round, with brake line on one side, of 6,25 mg carvedilol in blister pack (3 blisters x 10 tablets).

Box of 30 tablets, round, with brake line on one side, of 12,5 mg carvedilol in blister pack (3 blisters x 10 tablets).

Box of 30 tablets, round, of 25 mg carvedilol in blister pack (3 blisters x 10 tablets).

6.6 Special precautions for disposal and other handling

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

7. Marketing authorisation holder

ZADA Pharmaceuticals Ltd.
Donji Bistarac without number
75300 Lukavac
Bosnia and Herzegovina

8. Marketing authorisation number(s)

VEDICOR, tablet, 30 x 6,25 mg: 04-07.3-2-328/15 od 10.03.2015.
VEDICOR, tablet, 30 x 12,5 mg: 04-07.3-2-329/15 od 10.03.2015.
VEDICOR, tablet, 30 x 25 mg: 04-07.3-2-330/15 10.03.2015.

9. Date of first authorisation/renewal of the authorization

VEDICOR, tablet, 30 x 6,25 mg: 04-07.3-2-328/15
VEDICOR, tablet, 30 x 12,5 mg: 04-07.3-2-329/15
VEDICOR, tablet, 30 x 25 mg: 04-07.3-2-330/15

10. Date of revision of the text

03/02/2018