SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CARVE-FAR, Carvedilol 25 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg of carvedilol,

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

CARVE-FAR25 mg tablet
White to almost white, flat, round tablets, scored on one side.
The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- First-line treatment of hypertension
It may be used alone or in combination with other antihypertensive agents, in particular thiazidediuretics.

- Long-term treatment of coronary artery disease
Carvedilol is effective in several diseases associated with coronary artery disease syndrome: chronic stable angina, silent myocardial ischemia, unstable angina and left ventricular dysfunction of ischemic cause.

- Treatment of heart failure, classes II to IV, "New York Heart Association" (NYHA)
Carvedilol is indicated for the treatment of heart failure in order to reduce mortality and hospitalizations due to cardiovascular events, improve the well-being of the patient and delay the progression of the disease.

Carvedilol may be used as an adjuvant to the established treatment, as well as in the treatment of patients with intolerance to ACE inhibitors, in patients not treated with digitalis, hydralazine or nitrates.

4.2 Posology and method of administration

The tablets should be swallowed with plenty of water. It is not necessary to associate administration to mealtimes; however, in patients with heart failure, tablets should be taken together with food in order to reduce the absorption rate and the incidence of orthostatic effects.

- Hypertension

A single daily dose is recommended.

Adult Population
The recommended dose for the beginning of treatment is 12.5 mg as a single daily dose for the first two

days; then, the recommended dose is 25 mg once daily. If necessary, the dose may be subsequently increased, at intervals of at least two weeks, to the maximum recommended daily dose of 50 mg given once a day or in divided doses (twice a day).

Elderly Population
The recommended dose for the beginning of treatment is 12.5 mg as a single daily dose, whichhas proved to be sufficient in some patients. If the response is insufficient, the dose may be adjusted, at intervals of at least two weeks, to the maximum recommended daily dose.

- Long-term treatment of coronary artery disease

The recommended dose for the beginning of treatment is 12.5 mg, twice a day, during the first two days. Then, the recommended dose is 25 mg, twice a day. If necessary, the dose may be subsequently increased, at intervals of at least two weeks, to the maximum recommended daily dose of 100 mg given in divided doses (twice a day).

The maximum recommended daily dose in elderly patients is 50 mg given in divided doses (twice aday).

- Treatment of heart failure

The dose should be individually established and the patient carefully monitored by the doctorduring dose adjustment.

If carvedilol is administered to patients already on therapy with digitalis, diuretics or ACE inhibitors, the dose of these drugs should be stabilised before initiating treatment with carvedilol.

The recommended dose for the beginning of treatment is 3.125 mg, twice a day, during two weeks.If this dose is tolerated, it may be increased at intervals of, at least, two weeks to 6.25 mg, twice a day, and thereafter to 12.5 mg twice a day, 25 mg twice a day. The dose should be increased to the maximum level tolerated by the patient.

The maximum recommended dose is 25 mg twice a day in patients weighing less than 85 kg, and 50 mg twice a day in patients weighing more than 85 Kg.

Before each dose increase, the patient must be observed by the doctor to monitor symptoms of worsening heart failure or vasodilation. Transient worsening of heart failure or fluid retention should be treated with higher doses of diuretics, although occasionally it may be necessary to reduce the dose of carvedilol or temporarily discontinue treatment with carvedilol.

If treatment with carvedilol is discontinued for more than two weeks, it should be restarted with 3.125 mg, twice a day, being the dose adjustment performed according to the previousrecommendation.

Symptoms of vasodilation may be initially controlled by reducing the dosage of diuretics. If symptoms persist, it is possible to reduce the dose of ACE inhibitor (if used), and then reduce the dose of carvedilol, if necessary.

Under these circumstances, the dose of carvedilol should not be increased until symptoms of worsening heart failure or vasodilation have been stabilised.

Paediatric population
The safety and efficacy of carvedilol in patients under 18 years has not been established.

4.3 Contraindications

The medicine should not be taken in case of known hypersensitivity to carvedilol or to any of the excipients.

Carvedilol should not be administered to patients with:
- Decompensated heart failure, class IV "New York Heart Association", requiring intravenous inotropic support;
- Chronic obstructive pulmonary disease with a bronchospastic component (see section 4.4);
- Clinically manifest hepatic dysfunction.

As with other beta-blocking agents, carvedilol should not be used in patients with:
- Asthma
- 2nd and 3rd degree A-V block
- Severe bradycardia (<50 bpm)
- Cardiogenic shock
- Sinus node dysfunction (including sino-atrial block)
- Severe hypotension (systolic blood pressure <85 mm Hg).

4.4 Special warnings and precautions for use

Carvedilol should be used with caution in patients with heart failure controlled by digitalis, diureticsand/or ACE inhibitors, since both digitalis and carvedilol prolong the A-V conduction time.

Carvedilol should be administrated with caution to patients with diabetes mellitus, since the early signs and symptoms of acute hypoglycaemia may be masked or reduced. In diabetic patients with heart failure, the use of carvedilol may be associated with greater difficulty in glycaemic control.

In diabetic patients it is therefore necessary to regularly monitor glycaemia when initiating treatment with carvedilol or increasing the dose; the hypoglycaemic treatment should also be adjusted.

Reversible deterioration of renal function was observed during treatment with carvedilol in patients with congestive heart failure, with low blood pressure (systolic blood pressure <100 mmHg), ischaemic heart disease and diffuse vascular disease and/or underlying renal insufficiency.

In patients with heart failure with these risk factors, renal function should be monitored during the adjustment of the dose of carvedilol and the drug should be discontinued or its dose reduced if worsening of renal function occurs.

In patients with congestive heart failure, worsening heart failure or fluid retention may occur during the progressive adjustment of the dose of carvedilol. If such symptoms occur, the dose of diuretics should be increased and the dose of carvedilol should remain unchanged until the clinical situation stabilises. Occasionally, it may be necessary to reduce the dose of carvedilol or temporarily discontinue it. Such episodes do not prevent the subsequent dose adjustment of carvedilol from being successful.

Carvedilol should only be used in patients with chronic obstructive pulmonary disease with a bronchospastic component, not treated through oral route or inhalation, if the expected benefit outweighs the potential risk. In patients with tendency to bronchospastic reactions, respiratory distress resulting from a possible increase in airway resistance may occur.

Patients should be closely monitored during the beginning of treatment and the adjustment of the dose of carvedilol; the dose of carvedilol should be reduced if signs of bronchospasm are observed during the treatment.

Patients wearing contact lenses should take into account the possibility of a reduction in the production of tears.

As with other beta-blocking agents:

- Treatment with carvedilol should not be discontinued abruptly, particularly in patients with ischaemic heart disease. The withdrawal of carvedilol in these patients should be gradual (1-2 weeks).

- Carvedilol should be used with caution in patients with peripheral vascular disease, since beta- blocking agents may precipitate or aggravate symptoms of arterial insufficiency.

- In patients with peripheral circulatory disorders (Raynaud's phenomenon) exacerbation of symptoms may occur.

- Carvedilol, like other beta-blocking agents, may mask the symptoms of hyperthyroidism.

- Caution is advised in patients undergoing general surgery, due to the synergistic negative inotropic and hypotensive effects of carvedilol and anaesthetic drugs.

- Carvedilol may induce bradycardia. If the heart rate decreases to less than 55 beats per minute, the dose of carvedilol should be reduced.

- Carvedilol should be administered with caution to patients with a history of severe hypersensitivity reactions and to patients undergoing desensitisation therapy, as beta-blocking agents may increase sensitivity towards allergens and the seriousness of anaphylactic reactions.

- Patients with a history of psoriasis associated with treatment with beta-blocking agents should only be treated with carvedilol after a careful evaluation of the risk-benefit ratio.

In patients treated with calcium channel antagonists, like verapamil and diltiazem, or other antiarrhythmic drugs, it is necessary to monitor the ECG and blood pressure.

Carvedilol should be used with caution in patients with labile or secondary hypertension until further clinical experience.

In patients with pheochromocytoma, an alpha-blocking agent should be initiated prior to the use of a beta-blocking agent. Although carvedilol has both alpha and beta blocking activities, there is no experience in this situation. Therefore, in patients suspected of having pheochromocytoma, the administration of carvedilol should be done with caution.

The non-selective beta-adrenergic blocking agents may cause chest pain in patients with Prinzmetal's variant angina. There is no clinical experience with carvedilol in these patients, although the alpha-adrenergic activity of carvedilol may prevent these symptoms. Therefore, special care is required when administering carvedilol to patients suspected of having Prinzmetal's variant angina.

4.5 Interaction with other medicinal products and other forms of interaction

As with other beta-blocking agents, carvedilol may potentiate the effect of other drugs with antihypertensive activity (e.g. $alpha_1$-receptor antagonists) or with a profile of adverse effects, including hypotension.

Isolated cases of conduction disturbances (rarely with hemodynamic implications) were observed when carvedilol and diltiazem for oral use were simultaneously administered. Therefore, as with other drugs with beta-blocking activity, a close monitoring of ECG and blood pressure should be performed when co-administering calcium channel antagonists, like verapamil or diltiazem, or classI antiarrhythmic drugs. These drugs should not be intravenously administered during treatment withcarvedilol.

After concomitant administration of carvedilol and digoxin, digoxin concentrations in the valley, in steady state, increased by 16% in hypertensive patients. Increased monitoring of digoxin levels is recommended when initiating, adjusting or discontinuing treatment with carvedilol.

When concomitant treatment with clonidine and carvedilol is to be terminated, carvedilol should be discontinued first, a few days before gradually decreasing the dose of clonidine.

The effects of insulin or oral hypoglycaemic agents may be enhanced. The signs and symptoms of hypoglycaemia may be masked or attenuated (especially tachycardia). Regular monitoring of glycaemia is, therefore, recommended.

Special caution is recommended in patients treated with mixed-function oxidase inducers, e.g. rifampicin, since serum levels of carvedilol may be reduced, or with mixed-function oxidase inhibitors, e.g. cimetidine, since serum levels may be increased.

During anaesthesia, special attention must be given to the synergistic negative inotropic and hypotensive effects of carvedilol and anaesthetic drugs.

4.6 Fertility, pregnancy and breast-feeding

Clinical experience with carvedilol in pregnancy is insufficient. Animal

studies have not shown teratogenic effects with carvedilol.

Beta-blocking agents reduce placental perfusion, which may cause intrauterine foetal death, premature or immature foetuses. In addition, adverse effects, such as hypoglycaemia and bradycardia, may occur in the foetus and neonate.

In the postnatal period, the neonate has an increased risk of pulmonary and cardiac complications.

Carvedilol should not be used during pregnancy, unless the expected benefits outweigh thepotential risks.

As with other beta-blocking agents, studies in lactating rats have shown that carvedilol and/or its metabolites are excreted in breast milk. Breast-feeding is therefore not recommended during administration of carvedilol.

4.7 Effects on ability to drive and use machines

Treatment with carvedilol may cause various individual reactions that affect alertness (e.g. driving ability or use of machines). This applies particularly when starting or changing treatment and in conjugation with alcohol intake.

4.8 Undesirable effects

The most frequently observed side effects in patients in the carvedilol group in clinical trials performed with patients with heart failure and who were not observed with the same incidence in the placebo group, were as follows:

- Blood and lymphatic system disorders
Thrombocytopaenia.

- Metabolism and nutrition disorders
Hyperglycaemia (in patients with diabetes mellitus, see section 4.4), weight increase and hypercholesterolaemia.

- Nervous system disorders

Dizziness.

- Cardiac disorders
Bradycardia, orthostatic hypotension, hypotension and rarely syncope.
Oedema (including generalised, peripheral, dependent and genital oedema, lower limb oedema, hypervolemia and fluid overload).
Rarely A-V block.
Rarely, heart failure during dose adjustment.

- Gastrointestinal disorders
Nausea, diarrhoea and vomiting.

- Others
Visual impairment, rarely acute renal failure and renal function abnormalities in patients with diffusevascular disease and/or impaired renal function (see section 4.4).

The frequency of adverse effects is not dose dependent, with the exception of dizziness, visualimpairment and bradycardia.

The profile of adverse effects associated with the use of carvedilol in the treatment of hypertension and coronary artery disease is consistent with that seen in heart failure; however, the incidence of adverse effects in these patients is lower.

The adverse effects observed in clinical trials in patients with hypertension and coronary artery disease are:

- Blood and lymphatic system disorders
Isolated cases of changes in serum transaminases, thrombocytopaenia and leukopenia.

- Nervous system disorders
Dizziness, headache and fatigue, usually mild and occurring at the beginning of treatment.Rarely mood changes, sleep disorders and paraesthesia.

- Cardiac disorders
Bradycardia, orthostatic hypotension and rarely syncope, especially at the beginning of thetreatment.
Disorders of peripheral circulation (cold extremities).
Rarely, A-V block, angina pectoris, exacerbation of symptoms in patients suffering from intermittent claudication or Raynaud's phenomenon.

- Respiratory, thoracic and mediastinal disorders
Nasal congestion as well as asthma and dyspnoea in predisposed patients.

- Gastrointestinal disorders
Gastrointestinal disorders (nausea, diarrhoea and abdominal pain).

- Skin and subcutaneous tissue disorders
Rarely, allergic skin reactions (e.g. exanthema, urticaria, pruritus).

- Others
Pain in the extremities, decreased tear production, visual impairment, eye irritability.

4.9. Overdose Symptoms

of overdose

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 generalised seizures.

Overdose treatment

In addition to general supportive treatment, the vital parameters must be monitored and corrected,if necessary, under intensive care conditions.

The following supportive treatments may be instituted:
- Atropine: 0.5 to 2 mg i.v. (in case of excessive bradycardia)
- Glucagon: initially 1-10 mg i.v.; then 2-5 mg/h for long-term infusion (to support cardiovascular function)
- Sympathomimetic agents according to body weight and effect: dobutamine, isoprenaline, orciprenaline and adrenaline.

If peripheral vasodilation dominates the overdose profile, norphenefrine or noradrenaline should be administered, with continuous monitoring of the circulation.

In the case of drug-resistant bradycardia, pacemaker therapy should be initiated. In the case of bronchospasm, beta-sympathomimetic agents (as aerosol or, if not effective, intravenous) should be given or i.v. aminophylline. If seizures occur, slow intravenous administration of diazepam and clonazepam is recommended.

In case of severe overdose with symptoms of shock, support treatment must be maintained for a sufficiently long period of time, since prolonged elimination half-life and a redistribution of carvedilol from deeper compartments are possible.

The duration of therapy with an antidote depends on the severity of the overdose; the supportive measures should be maintained until the normalization of the patient's condition.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 3.4.4.2.3 - Cardiovascular system. Antihypertensive agents. Adrenergic activity depressant agents. Beta-blocking agents. Alpha and beta blocking agents, ATCcode: C07AG02

Carvedilol is a non-selective beta-adrenergic blocking agent, vasodilator and with antioxidant properties. Vasodilation is primarily mediated by the selective blockade of $alpha_1$ adrenergicreceptors.

Carvedilol reduces peripheral vascular resistance through vasodilation, and suppresses the renin-angiotensin-aldosterone system through beta-blockage. The activity of plasma renin is reduced, and fluid retention is rare.

Carvedilol has no intrinsic sympathomimetic activity and, like propranolol, has membrane stabilizing properties.

Carvedilol is a racemic mixture of two stereoisomers. In animal models, both enantiomers present $alpha_1$ adrenergic receptor blockage properties. The beta-adrenergic receptor blockage properties are non-selective

for $beta_1$ and $beta_2$ adrenergic receptors and are associated with the levorotatory enantiomer of carvedilol.

Carvedilol is a potent antioxidant and a scavenger of reactive oxygen radicals. The antioxidant properties of carvedilol and its metabolites have been demonstrated in *in vitro* and *in vivo* studiesin animals, and *in vitro* in a number of human cell types.

Clinical studies have shown that the balance of vasodilation and beta-blockage provided bycarvedilol results in the following effects:

- In hypertensive patients, a reduction in blood pressure is not associated with a concomitant increase in total peripheral resistance, as observed with the pure beta-blocking agents. Heart rateis slightly decreased. Renal blood flow and renal function are maintained. Peripheral blood flow is maintained; therefore, the cooling of extremities observed with drugs possessing beta-blocking activity is rare.

- In patients with coronary artery disease, it was demonstrated that carvedilol has anti-ischemic and anti-anginal properties, which remained during prolonged treatments. Acute haemodynamic studies have demonstrated that carvedilol reduces ventricular pre-load and after-load.

- In patients with left ventricular dysfunction or congestive heart failure, carvedilol has demonstrated favourable effects on haemodynamics and improvements in left ventricular dimensions and ejection fraction.

The normal ratio between high density and low density lipoproteins (HDL/LDL) is maintained. Serum electrolytes are not affected.

5.2 Pharmacokinetic properties

General Characteristics

The absolute bioavailability of carvedilol is approximately 25% in humans. The maximum serum concentration is reached 1 hour after an oral dose. There is a linear relationship between the dose and serum concentrations. Ingestion of food does not affect bioavailability or the maximum serum concentration although the time required to reach maximum serum concentration is delayed.

Carvedilol is highly lipophilic; plasma protein binding is approximately 98-99%. The distribution volume is approximately 2 l/kg and increases in patients with liver cirrhosis. The first pass effect after oral administration is approximately 60-75%; enterohepatic circulation of the parent substancehas been shown in animals.

The average elimination half-life of carvedilol ranges from 6 to 10 hours. Plasma clearance is approximately 590 ml/min. Elimination is mainly biliary. The primary route of elimination is faecal. A minor part is eliminated via the kidneys in the form of various metabolites.

In all the animal species studied, as well as in humans, carvedilol is extensively metabolised into a variety of metabolites, which are primarily excreted through the bile.

Carvedilol is extensively metabolised by the liver, being glucuronidation one of the main reactions. Demethylation and hydroxylation at the phenol ring produce 3 active metabolites with beta- adrenergic receptor blocking activity.

According to preclinical studies, the beta-blocking activity of the 4-hydroxyphenol metabolite is approximately 13 times more potent than that of carvedilol. Compared with carvedilol, the three active metabolites have poor vasodilating activity. In humans, their concentrations are about 10 times lower than the parent substance. Moreover, two of the hydroxy-carbazol metabolites of carvedilol are extremely potent antioxidants, showing a power 30-80 times higher than that of carvedilol.

Characteristics in patients

Carvedilol pharmacokinetics is affected by age; plasma concentrations of carvedilol are approximately 50% higher in elderly than in young subjects. In a study conducted with patients with liver cirrhosis, the bioavailability of carvedilol was four times higher and the maximum plasma concentration 5 times higher than in healthy subjects.

In hypertensive patients with mild (creatinine clearance of 20-30 ml/min) to severe (creatinine clearance <20 ml/min) renal failure, there was an increase of approximately 40-55% in plasma concentrations of carvedilol (based on the area under the curve) compared with the values obtained in hypertensive patients with normal renal function. There was, however, a great variability in results and considerable overlap to normal values.

5.3 Preclinical safety data

In carcinogenicity studies performed in rats and mice, at doses up to 75 mg/kg/day to 200 mg/kg/day, respectively, (38 to100 times* the maximum recommended therapeutic dose in humans-MRTD) carvedilol showed no carcinogenic effect.

In studies performed with mammals and non mammals, *in vitro* or *in vivo* showed no evidence of mutagenic effects in carvedilol.

Administration of carvedilol at toxic doses to pregnant rats (□200 mg/Kg = □100 times* MRTD) affected their fertility (infrequent mating, less corpora lutea, less eggs attachment and embryonic responses).

Doses □60 mg/kg (□30 times* MRTD) resulted in delays in the physical growth and development of offspring.

Embryotoxicity was observed (increased mortality after implantation) but there were no abnormalities in the rat and rabbit at doses of 200 mg/kg and 75 mg/kg, respectively (38 to 100 times* MRTD).

* Based on MRTD of 100 mg/day for the "Long-term treatment of coronary artery disease"

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Magnesium stearate
Anhydrous colloidal silica

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30ºC. Store in the original package.

6.5. Nature and contents of container

Packed in PVC/PVDC-Aluminium blisters
Packs with 56 tablets

6.6 Special precautions for disposal and other handling

There are no special requirements.

7. MARKETING AUTHORISATION HOLDER

GP - Genéricos Portugueses, Lda.
Rua Henrique de Paiva Couceiro, n.º 29, Venda Nova2700-
451 Amadora
Portugal (EU)

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