PACKAGE INSERT FOR

CARVEDILOL UNICORN 6,25 mg / 12,5 mg / 25 mg

SCHEDULING STATUS:

S3

1. NAME OF MEDICINE

CARVEDILOL UNICORN 6,25 mg

CARVEDILOL UNICORN 12,5 mg

CARVEDILOL UNICORN 25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **CARVEDILOL UNICORN 6,25 mg** tablet contains 6,25 mg carvedilol.

Each **CARVEDILOL UNICORN 12,5 mg** tablet contains 12,50 mg carvedilol.

Each **CARVEDILOL UNICORN 25 mg** tablet contains 25,00 mg carvedilol.

CARVEDILOL UNICORN 6,25 mg tablets contains sugar (lactose monohydrate 72,25 mg and sucrose 5,00 mg.

CARVEDILOL UNICORN 12,5 mg tablets contains sugar (lactose monohydrate 144,50 mg and sucrose 10,00 mg.

CARVEDILOL UNICORN 25 mg tablets contains sugar (lactose monohydrate 85,00 mg and sucrose 60,00 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CARVEDILOL UNICORN 6,25 mg:

A white, oval, slightly biconvex tablet, one side scored with sign S2 on the opposite side.

CARVEDILOL UNICORN 12,5 mg:

A white, oval, slightly biconvex tablet, one side scored with sign S3 on the opposite side.

CARVEDILOL UNICORN 25 mg:

A white, round, slightly biconvex tablets, bevel-edged, one side scored.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CARVEDILOL UNICORN is indicated for the treatment of:

- Essential mild to moderate hypertension.
- Mild to moderate stable symptomatic congestive heart failure either of cardiomyopathic or ischaemic origin. Used as an adjunct to standard therapy. Has been used in patients that are not tolerant to ACE (angiotensin-converting-enzyme) inhibitors. Has been used in patients who may, or may not, be on digitalis therapy.
- Long term treatment following otherwise uncomplicated myocardial infarction, but with left ventricular dysfunction (left ventricular ejection fraction (LVEF) < 40 % or wall motion index < 1,3), in combination with ACE inhibitors and other treatments recommended in the management of patients after myocardial infarction.

4.2 Posology and method of administration

Tablets should be taken after meals and swallowed with sufficient fluid.

Treatment should be started with low doses, and gradually titrated upwards until an optimal effect is achieved.

Treatment with **CARVEDILOL UNICORN** is a long-term therapy. Treatment should not be stopped abruptly but rather gradually reduced at weekly intervals. This is particularly important in the case of patients with concomitant coronary heart disease.

Essential Hypertension:

Adults:

The initial recommended dose is 12,5 mg once daily for the first 2 days. Dosage is then increased to 25 mg daily thereafter.

Combination with a diuretic may assist in attaining the desired clinical response.

Elderly:

Maximum recommended dose for patients weighing:

- less than 85 kg is 25 mg twice a day and
- more than 85 kg is 50 mg twice a day.

The medical practitioner should assess the patient for symptoms of worsening heart failure or vasodilation before the dose increments. The diuretic should be increased to treat the transient worsening heart failure or fluid retention; sometimes lowering the **CARVEDILOL UNICORN** dose or temporary discontinuing **CARVEDILOL UNICORN** may be necessary. When treatment

of **CARVEDILOL UNICORN** has been discontinued for longer than 14 days, the dosage regimen should be initiated from the starting point reflected above. Reduction of the diuretic dose may assist in the management of vasodilation symptoms (such as dizziness, headache and postural hypotension). The ACE-inhibitor dose may be reduced if symptoms continue. If necessary, the **CARVEDILOL UNICORN** dose may be reduced.

CARVEDILOL UNICORN dose should not be increased until the symptoms of worsening heart failure or vasodilation have been stabilised.

Left Ventricular Dysfunction Following Otherwise Uncomplicated Acute Myocardial Infarction:

Dosage must be individualised and closely monitored by a doctor during up-titration.

Treatment may be started as an inpatient or outpatient when the patient is haemodynamically stable and fluid retention has been minimised.

Prior to initiating ***CARVEDILOL UNICORN***: haemodynamically stable patients should have received an ACE inhibitor for at least 48 hours, given at a stable dose during at least the preceding 24 hours. **CARVEDILOL UNICORN** can then be started between day 3 and day 21 after the myocardial infarction.

First dose of ***CARVEDILOL UNICORN***: the initial recommended dose is 6,25 mg. Patients should remain under close medical supervision for at least 3 hours following the initial dose. See section 4.4.

Subsequent doses of ***CARVEDILOL UNICORN***: If the patient has tolerated the first dose (i.e. heart rate > 50 beats/minute, systemic blood pressure > 80 mmHg, and absence of clinical

signs of intolerance), the dose should be increased to 6,25 mg twice daily and maintained for 3 to 10 days.

The dose should be reduced to 3,125 mg twice daily if the patient develops signs of intolerance during this period, in particular bradycardia < 50 beats/minute, systolic blood pressure < 80 mmHg or fluid retention. If this dose is not tolerated, treatment should be stopped.
If it is well tolerated, it should be increased again to 6,25 mg twice daily after 3 to 10 days.
Subsequent up-titration: if the dose of 6,25 mg twice daily is well tolerated, the dose should be increased at intervals of 3 to 10 days to 12,5 mg twice daily and then to 25 mg twice daily. The maintenance dose is the maximum dose tolerated by the patient. The maximum recommended dose is 25 mg twice daily, irrespective of the patient's weight.

Special Dosage Instructions:

Elderly:

Carvedilol plasma levels are approximately 50 % higher in elderly subjects when compared to young subjects; appropriate dosage adjustment should be made.

Renal impairment:

Available pharmacokinetic data in patients with varying degrees of real impairment (including renal failure) suggest no changes in **CARVEDILOL UNICORN** dosing recommendations are warranted in patients with moderate to severe renal insufficiency.

Hepatic impairment:

Carvedilol plasma levels are 5 times higher in patients with liver cirrhosis than in healthy subjects; appropriate dosage adjustment should be made. **CARVEDILOL UNICORN** is contraindicated in patients with clinical manifestations of liver function. See section 4.3.

4.3 Contraindications:

- Hypersensitivity to any of the ingredients.
- Particular caution should be exercised with patients suffering from the following: asthma, bronchitis, chronic respiratory diseases such as chronic obstructive pulmonary disease, second and third degree heart block and bradycardia (less than 50 beats per minute), peripheral vascular diseases, Raynaud's phenomenon, sick sinus syndrome including sino-artrial block, unstable heart failure, decompensated heart failure (New York Heart Association (NYHA) class IV requiring intravenous inotropic support), cardiogenic shock, clinically manifest liver impairment, and severe hypotension (systolic BP < 85 mmHg).
- The normal dose should be reduced in elderly patients, or in patients suffering from renal dysfunction. In the peri-operative period, it is generally unwise to reduce the dosage to which the patient is accustomed, as there may be danger of aggravation of angina pectoris or hypertension. A patient's normal tachycardic response to hypovolaemia or blood loss may be obscured during or after surgery. Particular caution should be taken in this regard.
- *Children*: Safety has not been established.

4.4 Special warnings and precautions for use

- Use with extreme caution in patients with congestive heart failure who have previously achieved adequate clinical control.

- Use with caution in patients with renal impairment.
- Do not use in patients with obstructive airway diseases, bronchospasm, or allergic conditions involving the airways (example, glottis oedema, allergic rhinitis).
- Do not use in patients with metabolic acidosis, partial heart block, or sinus bradycardia.
- A variety of neuropsychiatric disorders, ranging from vague fatigue and nightmares to overt psychosis, have been observed.
- Skeletal muscle weakness has been observed.
- Peripheral gangrene may be precipitated.

Interaction with Clonidine:

Caution should be exercised when transferring a patient from clonidine. The withdrawal of clonidine may result in the release of large amounts of catecholamines that may give rise to a hypertensive crisis. If **CARVEDILOL UNICORN** is administered in these circumstances, the unopposed alpha receptor stimulation may potentiate the effect.

If **CARVEDILOL UNICORN** and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of **CARVEDILOL UNICORN**, as severe rebound hypertension may occur.

Administration to pregnant mothers shortly before giving birth or during labour may result in the newborn infants being born hypotonic, collapsed and hypoglycaemic.

Congestive Heart failure:

When symptoms of worsening cardiac effects or fluid retention occur during dosage increase, the diuretic dose should be increased. **CARVEDILOL UNICORN** dose should not be increased until

the symptoms have been stabilised. It may be necessary to reduce the dose of **CARVEDILOL UNICORN** or temporarily discontinue its use.

As both **CARVEDILOL UNICORN** and digitalis slow AV conduction, **CARVEDILOL UNICORN** should be used with caution in patients who are controlled with digitalis, diuretics and/or ACE-inhibitor treatment.

SPECIAL NOTE: - digitalisation of patients receiving long-term **CARVEDILOL UNICORN** therapy may be necessary if congestive cardiac failure is likely to develop. This combination can be considered despite the potentiation of the negative chronotropic effect of the two medicines. Careful control of dosages, and of the individual patient's response (and notably pulse rate), is essential in this situation.

Left ventricular dysfunction following uncomplicated acute myocardial infarction:

Before treatment with **CARVEDILOL UNICORN** is initiated the patient must be clinically stable and should have received an ACE inhibitor for at least the preceding 48 hours, and the dose of the ACE inhibitor should have been stable for at least the preceding 24 hours. See section 4.2.

Bradycardia:

CARVEDILOL UNICORN may cause bradycardia. If the pulse rate is below 55 beats per minute, **CARVEDILOL UNICORN** dosage should be decreased.

Ischaemic heart disease:

In these patients, treatment with **CARVEDILOL UNICORN** should not be abruptly discontinued. Discontinuation of therapy should be gradual, and patients should be advised to limit the extent of

their physical activity during the period that **CARVEDILOL UNICORN** is being discontinued.

Renal insufficiency:

As **CARVEDILOL UNICORN** is metabolised mainly by the hepatic route, no dosage adjustment is necessary.

However, in patients with congestive heart failure (CHF) having low blood pressure (systolic < 100 mmHg), diffuse vascular disease, ischaemic heart disease and/or an underlying renal insufficiency, reversible deterioration of renal function has been observed.

Given these risk factors in patients with congestive heart failure, monitoring of renal function during dosage adjustment is advised. If worsening of renal function occurs, **CARVEDILOL UNICORN** treatment should be discontinued or the dosage reduced. Adverse reactions are more common in patients with renal decompensation, and in patients who receive the medicine intravenously.

Diabetes mellitus:

CARVEDILOL UNICORN should be used with care in diabetes mellitus patients as the early warning symptoms and signs of acute hypoglycaemia could be enhanced or masked.

In diabetics with CHF, worsening control of blood glucose may be accompanied with **CARVEDILOL UNICORN.** Therefore when **CARVEDILOL UNICORN** therapy is initiated or even during dosage adjustment, regular monitoring of blood glucose is essential and hypoglycaemia treated accordingly.

Pulmonary:

In patients with chronic obstructive pulmonary disease (COPD) with a bronchospastic element, **CARVEDILOL UNICORN** treatment is not recommended.

Where the benefit outweighs the risk in patients not requiring oral or inhaled treatment for their bronchospastic disease, **CARVEDILOL UNICORN** has been initiated.

However, when **CARVEDILOL UNICORN** therapy is initiated or even during dosage adjustment, the patient should be closely monitored. Treatment should be discontinued or even reduced if bronchospasm is observed.

Thyrotoxicosis:

Symptoms may be masked by **CARVEDILOL UNICORN**.

Raynaud's phenomenon:

Symptoms may be exacerbated.

Contact lens wearers:

The possibility of reduced lacrimation should be borne in mind.

Phaeochromocytoma:

Treatment should be initiated with alpha-blocking agents before using any beta-blocking agent. There is currently no documented evidence with **CARVEDILOL UNICORN** use in this condition, despite **CARVEDILOL UNICORN** displaying pharmacological properties of alpha- and beta-blockers.

Peripheral vascular disease:

As beta-blockers can accelerate or exacerbate arterial insufficiency symptoms, **CARVEDILOL UNICORN** should be used with caution.

Prinzmetal's angina:

Medicines having non-selective beta-blocking activity can aggravate chest pains in patients with Prinzmetal's variant angina. Caution should be exercised when initiating **CARVEDILOL UNICORN** treatment in patients suspected of having Prinzmetal's angina as there is no documented evidence of its use in this condition.

Vagal influences

Intravenous administration of 1 - 2 mg atropine can be used for protection against vagal influences.

Anaesthesia and major surgery:

Caution should be exercised in patients undergoing general surgery, because of the synergistic negative inotropic effects of **CARVEDILOL UNICORN** and anaesthetic medicines.

Hypersensitivity

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

Psoriasis:

Patients with a history of psoriasis associated with β-blockers should take **CARVEDILOL UNICORN** only after consideration of the risk-benefit ratio.

Concomitant use of calcium channel blockers:

Careful monitoring of ECG and blood pressure is necessary in patients receiving concomitant therapy of **CARVEDILOL UNICORN** with calcium channel blockers of the verapamil or diltiazem type or other anti-dysrhythmic medicines.

Information on excipients of CARVEDILOL UNICORN:

CARVEDILOL UNICORN contains sucrose and lactose.

- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take **CARVEDILOL UNICORN**.

4.5 Interaction with other medicines and other forms of interaction

Concomitant administration of **CARVEDILOL UNICORN**:

- May result in the potentiation of the effect when used with other antihypertensives or medicines that result in hypotension as a side effect.
- May result in an increase of approximately 16 % in steady state trough digoxin concentrations in hypertensive patients. Digoxin levels should be monitored when **CARVEDILOL UNICORN** therapy is initiated, adjusted or discontinued.
- May result in the increase of systemic bioavailability (approximately 30 %) of **CARVEDILOL**

UNICORN without affecting C_{max} when administered with cimetidine.

- May lead in the reduced systemic availability of **CARVEDILOL UNICORN** when administered with rifampicin.
- With insulin or oral hypoglycaemics may lead to their effects being increased. Regular blood glucose monitoring is recommended as hypoglycaemic signs and symptoms are either hidden or aggravated.
- May lead to an increase in **CARVEDILOL UNICORN** plasma levels when administered with hydralazine and alcohol as they are metabolised by the liver.
- May result in the synergism of effects when administered with diltiazem.
- With medicines that lead to catecholamine depletion; e.g. reserpine, or adrenergic neuron blocking agents like quanethidine or bethanidine may lead to hypotension and/or severe bradycardia. These patients should be closely monitored for these signs and symptoms.
- With beta-adrenoreceptor stimulating agents; e.g. isoprenaline could result in diminished **CARVEDILOL UNICORN** effects.
- With alpha-adrenoreceptor stimulating agents such as noradrenaline or agents with both alpha- and beta-adrenoreceptor stimulating properties such as adrenaline may lead to increased peripheral vasoconstrictor effects and reversal of the hypotensive effects of **CARVEDILOL UNICORN**; bradycardia could occur.
- The concurrent use of phenothiazines and **CARVEDILOL UNICORN** result in a rise in the plasma levels of both medicines, since phenothaizines are inhibitors of cytochrome P450 isoenzyme CYP2D6 and may inhibit the metabolism of **CARVEDILOL UNICORN**, which is a substrate for this isoenzyme. Both **CARVEDILOL UNICORN** and phenothiazines can cause hypotension, and these effects could be additive.

- Modest increases in mean trough ciclosporin concentrations were observed following initiation of **CARVEDILOL UNICORN** treatment. It is recommended that ciclosporin concentrations be monitored closely after initiation of **CARVEDILOL UNICORN** therapy, and that the dose of ciclosporin be adjusted as appropriate.

*Caution should be exercised when **CARVEDILOL UNICORN** is administered with:*

- *Calcium channel blockers:* Synergism occurs if **CARVEDILOL UNICORN** and diltiazem are used concomitantly. When **CARVEDILOL UNICORN** is used simultaneously with calcium antagonist, caution should be exercised, especially in the case of verapamil. This particular combination is contra-indicated in patients with disturbed heart function. It is recommended that ECG and blood pressure be monitored.
- Myocardial depressant agents including anti-arrhythmic like quinidine, disopyramide, lignocaine, procainamide and phenytoin due to the probability of increased AV conduction time and a negative inotropic effect.

Other:

- In patients undergoing anaesthesia, carvedilol use has not been established. It is recommended that carvedilol therapy be discontinued at least 48 hours before anaesthesia. See section 4.4.
- When clonidine and carvedilol therapy are discontinued simultaneously, it is recommended that carvedilol be withdrawn first followed by a gradual decrease of the clonidine dosage a few days after. See section 4.4**.**

4.6 Fertility, pregnancy and lactation

Pregnancy: Safety has not been established and **CARVEDILOL UNICORN** should not be used in pregnant women.

β-blockers reduce placental perfusion, which may result in intrauterine foetal death, and immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia) may occur in the foetus and neonate. There may be an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. There is no evidence from animal studies that **CARVEDILOL UNICORN** has any teratogenic effects.

Lactation: As carvedilol is excreted into breast milk, it should not be administered when breastfeeding.

4.7 Effects on ability to drive and operate machinery

If patients experience dizziness, vision abnormalities, fatigue or related symptoms, they should be advised not to operate any machinery or drive. Caution should be used when driving a motor vehicle, operating machinery or performing potentially dangerous tasks, where loss of concentration may lead to an accident.

4.8 Undesirable effects

With the exception of bradycardia, abnormal vision and dizziness; the adverse event frequency is not dose dependent. These effects are usually mild, short-term and usually occur at the beginning of treatment.

System Organ Class	Frequency	Side Effects

Blood and lymphatic system disorders:	Less frequent:	Thrombocytopenia, hypercholesterolaemia, reduced peripheral circulation, Raynaud's phenomenon or symptom exacerbation of intermittent claudication, leucopenia, changes in serum transaminases
Endocrine disorders:	Frequent:	Hyperglycaemia (patients with pre-existing diabetes mellitus). It is possible for latent diabetes mellitus to become evident and existing diabetes to be exacerbated due to the beta-blocking properties of **CARVEDILOL UNICORN.**
Metabolism and nutrition disorders:	Frequent:	Weight increase.
Nervous system disorders:	Frequent: Less frequent:	Fatigue, headache, dizziness. Sleep disturbances, depressed mood, paraesthesia.
Eye disorders:	Frequent: Less frequent:	Vision abnormalities, reduced lacrimation. Eye irritation, disturbed vision.

Cardiac disorders:	Frequent: Less frequent:	Hypotension, bradycardia, postural hypotension (mainly observed on product initiation or when the dose is increased but the occurrence is reduced when the product is used as recommended). AV block, cardiac failure during dosage increase, syncope, angina pectoris or progression of heart failure. It has been reported that the frequency of side effects are lower in hypertensive patients treated with **CARVEDILOL UNICORN** than in congestive heart failure.
Vascular disorders:	Frequent:	Oedema of the legs, dependent and genital oedema, peripheral or generalised fluid overload, hypervolaemia, pain in the extremities.
Respiratory, thoracic and mediastinal disorders:	Frequent: Less frequent:	Asthma and dyspnoea in predisposed patients. Flu-like symptoms, stuffy nose, wheezing.
Gastrointestinal disorders:	Frequent: Less frequent:	Vomiting, nausea, diarrhoea, abdominal pain. Constipation, dryness of the mouth

Skin and subcutaneous tissue disorders:	Less frequent:	Existing lesions can be aggravated, psoriatic skin lesions, skin reactions, e.g. pruritis, urticaria, lichen planus-like reactions and allergic exanthema.
Renal and urinary disorders:	Less frequent:	Renal abnormalities in patients with diffuse vascular disease and/or impaired function, micturition disturbances, acute renal failure. Cases of incontinence in women, which usually resolves upon discontinuation of the medication, have been reported.
Reproductive system and breast disorders:	Less frequent:	Sexual impotence.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continues monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via “6.04 Adverse Drug Reactions Reporting Form”, found under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

Adverse reactions also must be reported to Unicorn Pharmaceuticals (Pty) Ltd to enquiries@unicornpharma.co.za

4.9 Overdose

Symptoms may include bradycardia, severe hypotension, heart failure, cardiogenic shock and cardiac arrest. Vomiting, bronchospasm, respiratory problems, disturbed consciousness and generalized seizures have also been observed.

Treatment of overdosage:

The patient must be kept under observation preferably under intensive care conditions where necessary. Cases of mild overdose should be observed for at least four hours, as apnoea and cardiovascular collapse may appear suddenly.

The patient should be made to lie down, to improve brain blood supply. The stomach may be emptied by emesis or gastric lavage within four hours of suspected overdose. Repeated activated charcoal is necessary in severe overdose.

Atropine may be used to treat severe bradycardia. If the response is inadequate, glycagon may be given intravenously.

Alternatively, dobutamine or isoprenaline may be required to reverse beta-blockade. Intravenous cardiac pacing may be required for severe bradycardia. Bronchospasm should be treated with IV aminophylline or inhaled, or IV beta–agonist, e.g salbutamol.

Intravenous injection of atropine up to 3 mg should be used to treat the bradycardia immediately.

Sympathomimetics such as dobutamine, isoprenaline, adrenaline or orciprenaline, based on body mass and effect, may be used. When further measures are deemed necessary, it is recommended that noradrenaline be preferred to isoprenaline in order to restore circulation. The recommended initial dose of noradrenaline is intravenous 5 µg to 10 µg and repeated accordingly to the patient's response; alternatively use an IV infusion at 5 µg/minute till a satisfactory clinical response is achieved. Glucogon may be preferred in severe overdosage. The recommended

starting dose is 1 mg – 10 mg intravenously followed by 2 mg - 2,5 mg per hour as a long-term infusion to sustain heart function.

Norfenephrine or noradrenaline may be administered while continuously evaluating the circulatory conditions in cases where intoxication is dominated by peripheral vasodilation.

When bradycardia is resistant to therapy, therapy with a pacemaker should be considered.

Beta-sympathomimetics (IV and/or aerosol) should be used for bronchospasm.

IV injection of clonazepam or diazepam is recommended for seizures.

In cases where there are symptoms of shock during severe intoxication, antidote treatment should be continued for a relatively long period due to the elimination of **CARVEDILOL UNICORN** from its binding sites.

Important Note:

In the event of severe intoxication where there are symptoms of shock, treatment with antidotes must be continued for a sufficiently long period of time since prolonged elimination half-life of **CARVEDILOL UNICORN** from deeper compartments can be expected.

5.1 PHARMACOLOGICAL CLASSIFICATION:

A: 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Mechanism of action:

In the same dosage range, carvedilol exhibits both non-selective beta-blocking properties which

are associated with the laevorotatory S(-) enantiomer and acts as an **antihypertensive** agent having vasodilating properties.

Carvedilol is racemic, and both R(+) and S(-) enantiomers have the same α-adrenergic receptor blocking properties and antioxidant properties.

Carvedilol is a competitive, non-selective antagonist of $beta_1$- and $beta_2$-adrenoreceptors; as demonstrated in both *in vitro* and *in vivo* animal studies.

Its beta-blockade activity leads to a reduction of peripheral vascular resistance via suppression of the renin-angiotensin-aldosterone system and vasodilation. Carvedilol attenuates the increase of blood pressure induced by phenylephrine, an α_1-adrenoceptor agonist, but not that induced by angiotensin II. Selective blockade of alpha 1-adrenoreceptors is responsible mainly for vasodilation.

Carvedilol has no intrinsic sympathomimetic activity.

The pharmacological action of carvedilol in congestive heart failure has not been established. See section 4.1.

5.2 Pharmacokinetic properties:

Absorption:

Carvedilol undergoes extensive first-pass hepatic metabolism resulting in a low and variable absolute bioavailability of 25 %. Maximum serum levels are reached approximately one (1) hour after a single oral dose. Metabolism is primarily hepatic. Linear correlation between dose and serum concentration has been observed.

Distribution:

Carvedilol is extensively (approximately 98 %) bound to plasma protein (primarily alpha-acid glycoproteins and also albumin). The average elimination half-life is 6 to 10 hours. The distribution volume is approximately 2 L/kg.

The rate of absorption (time to reach maximum serum concentration), but not the extent of absorption (bioavailability) is decreased by food.

Metabolism:

In humans, carvedilol is extensively metabolised into a variety of metabolites that are eliminated mainly in the bile. The first-pass effect after oral administration amounts to about 60 - 75 %. Carvedilol is metabolised extensively by the liver and glucuronidation is one of the major reactions. Demethylation and hydroxylation at the phenol ring produce 3 metabolites with beta-adrenergic receptor blocking activity. Based on pre-clinical studies, the 4'-hydroxyphenol metabolite is approximately 13 times more potent than carvedilol for beta-blockade. Compared to carvedilol, the three active metabolites exhibit weak vasodilating activity. In humans, the concentrations of the three active metabolites are about 10 times lower than that of the parent substance.

Elimination:

The average elimination half-life is 6 to 10 hours. Plasma clearance is approximately 500 – 700 ml/min. the primary route of excretion is via the faeces. The metabolites are mainly excreted in the bile, whereas a small part (approximately 15 %) is excreted by the kidneys.

Pharmacokinetics in Special Populations:

Patients with renal impairment:

Dosage adjustment in renally impaired patients is not required

In patients with hypertension and renal insufficiency, the area under the plasma level-time curve, elimination half-life and maximum plasma concentration does not change significantly. Renal excretion of the unchanged medicine decreases in the patients with renal insufficiency; however pharmacokinetic parameters are modest.

Carvedilol is not eliminated during dialysis because it does not cross the dialysis membrane, probably due to its high plasma protein binding.

Patients with hepatic impairment:

In patients with cirrhosis of the liver, the systemic availability of the medicine is increased by up to 80 % because of reduction in the first-pass effect. Therefore, carvedilol is contraindicated in patients which clinically manifest liver dysfunction. See section 4.3.

Geriatric use:

The pharmacokinetics are affected by age; plasma levels of carvedilol are approximately 50 % higher in the elderly compared to young subjects.

Paediatric use:

There is no data available on pharmacokinetics in people younger than 18 years of age.

Diabetic patients:

In hypertensive patients with non-insulin-dependent diabetes no influence of carvedilol on

fasting or post- prandial blood glucose concentration, glycolated haemoglobin A_1 or need for change of the dose of antidiabetic agents was found.

In patients with non-insulin dependent diabetes, carvedilol had no statistically significant influence on the glucose tolerance test. In hypertensive non-diabetic patients with impaired insulin sensitivity (syndrome X) carvedilol improved the insulin sensitivity. The same results were found in hypertensive patients with non-insulin dependent diabetes.

Hypertension:

Carvedilol is an antihypertensive agent with vasodilating and non-selective beta-blocking properties in the same dose range. *In vitro* and *in vivo* animal studies have indicated that carvedilol is a competitive, non-selective antagonist of both $beta_1$- and $beta_2$-adrenoreceptors. Clinical studies have shown that the balance of vasodilation and beta receptor blockade provided by carvedilol results in the following desirable haemodynamic and metabolic effects:

- Myocardial function is maintained. A smaller reduction in the resting heart rate is observed with carvedilol compared to the effect seen with beta receptor blocking medicines which lack additional vasodilating properties. Peripheral blood flow is maintained.
- Cholesterol, triglycerides, high density lipoproteins and low density lipoproteins are not affected. Serum electrolytes are not affected. The activity of plasma renin is reduced, leaving the renal function unaffected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Crospovidone

Lactose monohydrate

magnesium stearate

Povidone

Sucrose.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store at or below 30 °C in a cool, dry place.

Keep the blister in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

CARVEDILOL UNICORN 6,25 mg, 12,5 mg and 25 mg are available in OPA/AL/PVC and Aluminium foil blister packs of 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Corner of Searle and Pontac Street

Cape Town

8001

South Africa

8 REGISTRATION NUMBER(S)

CARVEDILOL UNICORN 6,25 mg: 37/7.1.3/0279

CARVEDILOL UNICORN 12,5 mg: 37/7.1.3/0280

CARVEDILOL UNICORN 25 mg: 37/7.1.3/0281

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

June 2005

10 DATE OF REVISION OF THE TEXT

24 May 2020