PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CRAVEDON 6,25 mg tablet

CRAVEDON 12,5 mg tablet

CRAVEDON 25 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CRAVEDON tablets contain contains 6,25 mg; 12,5 mg or 25 mg carvedilol.

Contains sugar:

CRAVEDON 6,25 mg tablets – 40,73 mg lactose monohydrate per tablet

CRAVEDON 12,5 mg tablets – 81,46 mg lactose monohydrate per tablet

CRAVEDON 25 mg tablets – 162,92 mg lactose monohydrate per tablet

For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

CRAVEDON 6,25 mg are white, round shaped, biconvex tablets, with uniform appearance and intact edges.

CRAVEDON 12,5 mg are white, round shaped, biconvex tablets, with uniform appearance and intact edges.

CRAVEDON 25 mg are white, round shaped, biconvex tablets, with uniform appearance and intact edges.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Essential hypertension

Treatment of mild to moderate essential hypertension.

Symptomatic congestive heart failure (CHF)

CRAVEDON is indicated for the treatment of mild, moderate, and severe stable, symptomatic heart failure of ischaemic or cardiomyopathic origin. CRAVEDON may be used as adjunct to standard therapy. CRAVEDON has been used in patients unable to tolerate an ACE-inhibitor and patients who are, or are not, taking digoxin.

Left ventricular dysfunction following uncomplicated acute myocardial infarction

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

Posology

Essential hypertension

Adults

The recommended dose for initiation of therapy is 12,5 mg once a day for the first two days. Thereafter the recommended dosage is 25 mg once a day. Combination with a diuretic may also give the desired response.

Elderly

The recommended dose for initiation of therapy is 12,5 mg once daily, which has provided satisfactory control in some patients. If the response is inadequate, the dose may be titrated at intervals of at least two weeks up to the recommended daily dose of 25 mg once a day or in divided doses.

In hypertensive patients it is not necessary to time the dose in relation to meals.

At doses higher than 25 mg the incidence of side effects increases significantly with only a marginal increase in efficacy.

Treatment of symptomatic congestive heart failure

CRAVEDON should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects.

Dosage must be individualised and closely monitored by a medical practitioner experienced in the management of heart failure, during up-titration. For those patients receiving digoxin, diuretics and ACE-inhibitors, dosing of these medicines should be stabilised prior to initiation of CRAVEDON treatment.

The recommended dose for initiation of therapy is 3,125 mg twice daily for at least 2 weeks. If this dose is tolerated, the dosage may subsequently be increased, at intervals of not less than two weeks, to 6,25 mg twice daily, followed by 12,5 mg twice daily and thereafter 25 mg twice daily. Dosing should be increased to the highest level tolerated by the patient. The maximum recommended dose is 25 mg twice daily in patients weighing less than 85 kg and 50 mg twice daily in patients weighing more than 85 kg.

Before each dose increase, the patient should be evaluated by the medical practitioner for symptoms of worsening heart failure or vasodilation. Transient worsening of heart failure or fluid retention should be treated with increased doses of diuretics, although occasionally it may be necessary to lower the dose of CRAVEDON or temporarily discontinue CRAVEDON treatment.

If CRAVEDON treatment is discontinued for more than two weeks, therapy should be recommenced at 3,125 mg twice daily and up-titrated in line with the above dosing recommendation.

Symptoms of vasodilation such as postural hypotension, headache and dizziness may be managed initially by a reduction in the dose of diuretics. If symptoms persist, the dose of ACE inhibitor (if used) may be reduced, followed by a reduction in the dose of CRAVEDON if necessary. Under these circumstances, the dose of CRAVEDON should not be increased until 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 medical practitioner 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 CRAVEDON: 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. CRAVEDON can then be started between day 3 and day 21 after the myocardial infarction.

First dose of CRAVEDON: 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 CRAVEDON: If the patient has tolerated the first dose (i.e. heart rate > 50 beats/minute, systolic blood pressure > 80 mmHg, measured with the patient seated, 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, measured with the patient seated, 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.

Duration of Treatment

Treatment with CRAVEDON 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.

Special Populations

Renal impairment

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

Hepatic impairment

CRAVEDON is contraindicated in patients with clinical manifestations of liver dysfunction. See (section 4.3).

A pharmacokinetic study in cirrhotic patients has shown that exposure (AUC) to CRAVEDON was increased by 6,8-fold in patients with liver impairment as compared to healthy subjects.

Diabetic Patients

CRAVEDON may increase insulin resistance and mask hypoglycaemic symptoms and decrease the body's response to hypoglycaemia.

Elderly

There is no evidence to support dose adjustment.

Paediatric population

The safety and efficacy of CRAVEDON in children and adolescents (< 18 years) has not been established. See section 5.2, ‘Special populations’.

Method of Administration

The tablets are to be swallowed with sufficient fluid.

4.3 Contraindications

CRAVEDON must not be used in patients with:

- Hypersensitivity to carvedilol or any component of CRAVEDON (see section 6.1)
- Severe heart disease.
- 2nd and 3rd degree atrioventricular (A-V) block.
- Sick sinus syndrome (including sino-atrial block).
- Cardiogenic shock.
- Severe bradycardia (< 50 bpm).
- Asthma.
- Chronic obstructive pulmonary disease (COPD) with a bronchospastic component.
- Clinically manifest liver dysfunction.
- Safety in children has not been established.
- Severe hypotension (systolic blood pressure < 85 mmHg).

4.4 Special warnings and precautions for use

CRAVEDON should not be given to patients with bronchospasm or obstructive airways disease, allergic conditions involving the airways (e.g. allergic rhinitis, glottis oedema), metabolic acidosis, sinus bradycardia, or partial heart block.

It should be given to patients with congestive heart failure only after having achieved adequate clinical control, and then only with great caution. Patients with phaeochromocytoma should first be adequately controlled by alpha blockade before initiating therapy with CRAVEDON. It should be used with caution in patients with renal impairment.

Chronic congestive heart failure

In congestive heart failure patients, worsening cardiac effects or fluid retention may occur during up-titration of CRAVEDON. If such symptoms occur, the dose of diuretics should be increased and the CRAVEDON dose should not be further increased until clinical stability resumes, or it may be necessary to lower the CRAVEDON dose or temporarily discontinue it. Such episodes do not preclude subsequent successful up-titration of CRAVEDON. In patients who have congestive heart failure controlled with digoxin, diuretics and/or an ACE inhibitor, CRAVEDON should be used with caution as both digoxin and CRAVEDON slow A-V conduction. (See section 4.3).

Left ventricular dysfunction following uncomplicated acute myocardial infarction

Before treatment with CRAVEDON 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).

Withdrawal syndrome

CRAVEDON treatment should not be discontinued abruptly, particularly in patients suffering from ischaemic heart disease. The withdrawal of CRAVEDON in these patients should be over the course of one to two weeks.

Bradycardia

CRAVEDON may induce bradycardia. If the pulse rate drops to less than 55 beats/min, the dosage must be reduced.

Diabetes

Care should be taken in the administration of CRAVEDON to patients with diabetes mellitus, as it may be associated with worsening control of blood glucose, or the early signs and symptoms of acute hypoglycaemia may be masked or attenuated. Regular monitoring of

blood glucose is therefore required in diabetics when CRAVEDON is initiated or up-titrated and hypoglycaemic therapy adjusted accordingly.

Thyrotoxicosis

It is to be expected that CRAVEDON may mask the symptoms of thyrotoxicosis.

Renal function in congestive heart failure (CHF)

Patients with renal insufficiency require no dosage adjustment since CRAVEDON is cleared mainly by the liver.

Reversible deterioration of renal function has been observed with CRAVEDON therapy in CHF patients with low blood pressure (systolic < 100 mmHg), ischaemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency. In CHF patients with these risk factors, renal function should be monitored during up-titration of CRAVEDON and the medicine discontinued or dosage reduced if worsening of renal function occurs.

Chronic obstructive pulmonary disease (COPD)

CRAVEDON should not be used in patients with COPD with a bronchospastic component. (See section 4.3). Patients with COPD should be closely monitored during initiation and up-titration of CRAVEDON and CRAVEDON should be discontinued if any evidence of bronchospasm is observed during treatment.

Contact lenses

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

Peripheral vascular disease and Raynaud's phenomenon

CRAVEDON should be used with caution in patients with peripheral vascular disease (e.g. Raynaud's disease or Raynaud's phenomenon) as β-blockers can precipitate or aggravate symptoms of arterial insufficiency.

Anaesthesia and major surgery

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

Hypersensitivity

Care should be taken in administering CRAVEDON to patients with a history of hypersensitivity reactions, and in patients undergoing desensitisation therapy, as β-blockers may increase both the sensitivity towards allergens and the severity of hypersensitivity reactions.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported during treatment with CRAVEDON, (see section 4.8, 'Post-Marketing'). CRAVEDON should be permanently discontinued in patients who experience severe cutaneous adverse reactions possibly attributable to CRAVEDON.

Psoriasis

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

Interactions with other medicinal products

There are a number of important pharmacokinetic and pharmacodynamic interactions with other medicines (e.g. digoxin, ciclosporin, rifampicin, anaesthetic medicines, anti-dysrhythmic medicines). (See section 4.5).

Phaeochromocytoma

In patients with phaeochromocytoma, an alpha-blocking agent should be initiated prior to the use of CRAVEDON.

Prinzmetal's variant angina

CRAVEDON may provoke chest pain in patients with Prinzmetal's variant angina. However, there is no clinical experience with CRAVEDON in these patients, and caution should be exercised in the administration of CRAVEDON to patients suspected of having Prinzmetal's variant angina.

Vagal influences

The patient can be protected against vagal influences by the intravenous administration of 1 - 2 mg atropine. In case of severe postural hypotension CRAVEDON should be discontinued in these patients.

Information about excipients

CRAVEDON contains lactose, therefore patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take CRAVEDON.

4.5 Interactions with other medicinal products and other forms of interactions

Pharmacokinetic interactions

Carvedilol may potentiate the effect of other concomitantly administered medicines that are antihypertensive in action or have hypotension as part of their adverse effect profile.

Effects of CRAVEDON on the pharmacokinetics of other medicines

Carvedilol is a substrate as well as an inhibitor of P-glycoprotein. Therefore, the bioavailability of medicines transported by P-glycoprotein may be increased with concomitant

administration of CRAVEDON. In addition, the bioavailability of carvedilol can be modified by inducers or inhibitors of P-glycoprotein.

Digoxin: An increased exposure of digoxin of up to 20 % has been shown in some studies in healthy subjects and patients with heart failure. Therefore monitoring of digoxin levels is recommended when initiating, adjusting or discontinuing CRAVEDON, (see section 4.4).

Cimetidine: Concomitant therapy with cimetidine may result in increased systemic bioavailability (about 30 %) but causes no change in Cmax of carvedilol.

Phenothiazines: The concurrent use of phenothiazines and beta-blockers may 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, which is a substrate for this isoenzyme. Both CRAVEDON and phenothiazines can cause hypotension, and these effects could be additive.

Ciclosporin: Two studies in renal and cardiac transplant patients receiving oral ciclosporin have shown an increase in ciclosporin plasma concentration following the initiation of carvedilol. It appears that carvedilol increases the exposure to oral ciclosporin by around 10 to 20 %. In an attempt to maintain therapeutic ciclosporin levels, an average of 10 - 20 % reduction of the ciclosporin dose was necessary. The mechanism for the interaction is not known but inhibition of intestinal P-glycoprotein by carvedilol may be involved. Due to wide inter-individual variability of ciclosporin levels, it is recommended that ciclosporin concentrations be monitored closely after initiation of CRAVEDON therapy and that the dose of ciclosporin be adjusted as appropriate. In case of IV administration of ciclosporin, no interaction with CRAVEDON is expected.

Effects of other medicines on the pharmacokinetics of CRAVEDON

Inhibitors as well as inducers of CYP2D6 and CYP2C9 can modify the systemic and/or pre systemic metabolism of carvedilol stereo-selectively, leading to increased or decreased plasma concentrations of R and S-carvedilol. (See section 5.2, ‘Metabolism’). Some

examples observed in patients or in healthy subjects are listed below but the list is not exhaustive.

Rifampicin: In a study in 12 healthy subjects, exposure to carvedilol decreased by around 60 % during concomitant administration with rifampicin and a decreased effect of carvedilol on the systolic blood pressure was observed. The mechanism for the interaction is not known but it may be due to the induction of the intestinal P-glycoprotein by rifampicin. A close monitoring of the β-blockade activity in patients receiving concomitant administration of CRAVEDON and rifampicin is appropriate.

Amiodarone: An in vitro study with human liver microsomes has shown that amiodarone and desethylamiodarone inhibited the oxidation of R and S-carvedilol. The trough concentration of R and S-carvedilol was significantly increased by 2,2·fold in heart failure patients receiving carvedilol and amiodarone concomitantly as compared to patients receiving carvedilol monotherapy. The effect on S-carvedilol was attributed to desethylamiodarone, a metabolite of amiodarone, which is a strong inhibitor of CYP2C9. A monitoring of β-blockade activity in patients treated with the combination CRAVEDON and amiodarone is advised.

Fluoxetine and Paroxetine: In a randomised cross-over study in 10 patients with heart failure, co-administration of fluoxetine, a strong inhibitor of CYP2D6, resulted in stereo-selective inhibition of carvedilol metabolism with a 77 % increase in mean R(+) enantiomer AUC, and a non-statistically significant 35 % increase of the S(-) enantiomer's AUC as compared to the placebo group. However, no differences in adverse events, blood pressure or heart rate were noted between treatment groups. The effect of a single dose paroxetine, a strong CYP2D6 inhibitor, on carvedilol pharmacokinetics was investigated in 12 healthy subjects following single oral administration. Despite significant increase in R and S-carvedilol exposure, no clinical effects were observed in these healthy subjects.

Pharmacodynamic interactions

Insulin or oral hypoglycaemics: The effects of insulin or oral hypoglycaemics may be enhanced. The signs of hypoglycaemia may be masked or attenuated (especially

tachycardia). In patients taking insulin or oral hypoglycaemics, regular monitoring of blood glucose is therefore recommended, (see section 4.4).

Catecholamine-depleting agents: Patients taking both agents with β-blocking properties and a medicine that can deplete catecholamines (e.g. reserpine and monoamine oxidase inhibitors) should be observed closely for signs of hypotension and/or severe bradycardia.

Digoxin: The combined use of β-blockers and digoxin may result in additive prolongation of atrioventricular (AV) conduction time. (See section 4.4).

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

Non-dihydropyridine calcium channel blockers, amiodarone or other anti-dysrhythmics: in combination with CRAVEDON can increase the risk of AV conduction disturbances. Cases of conduction disturbance (some with haemodynamic compromise) have been observed when carvedilol is co-administered with diltiazem. If CRAVEDON is to be administered orally with non-dihydropyridine calcium channel blockers of the verapamil or diltiazem type, amiodarone or other anti-dysrhythmics it is recommended that ECG and blood pressure be monitored.

α- and β- adrenoreceptor-stimulating agents: The effects of CRAVEDON are diminished by β-adrenoreceptor-stimulating agents such as isoprenaline; the hypotensive effects of CRAVEDON may be dangerously reversed and the peripheral vasoconstrictor effects enhanced by α-adrenoreceptor-stimulating agents such as noradrenaline or those with mixed α- and β-adrenoreceptor-stimulating properties such as adrenaline; bradycardia can also occur.

Anti-hypertensives: Carvedilol may potentiate the effect of other concomitantly administered medicines with anti-hypertensive action (e.g. α1-receptor antagonists) or have hypotension as part of their adverse effect profile.

Anaesthetic agents: Careful monitoring of vital signs is recommended during anaesthesia due to the synergistic negative inotropic and hypotensive effects of CRAVEDON and anaesthetic medicines. (See section 4.4). CRAVEDON should be discontinued 48 hours prior to anaesthesia.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): The concurrent use of NSAIDs and CRAVEDON may result in an increase in blood pressure and impairment of blood pressure control.

Beta-agonist bronchodilators: CRAVEDON opposes the bronchodilator effects of β-agonist bronchodilators. Careful monitoring of patients is recommended.

Hydralazine and alcohol may increase the plasma concentration of carvedilol because it is metabolised in the liver.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no adequate clinical experience with CRAVEDON in pregnant women. CRAVEDON 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 has any teratogenic effects.

Breastfeeding

CRAVEDON and/or its metabolites are excreted in breast milk; breast-feeding is therefore not recommended during administration of CRAVEDON.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and to use machines have been performed. Patients taking CRAVEDON should be warned not to drive or operate machinery if they experience dizziness or related symptoms. This applies particularly when starting or changing treatment and in conjunction with alcohol.

4.8 Undesirable effects

Adverse reactions have been ranked under the heading of system-organ class and frequency using frequent and less frequent including isolated cases.

In clinical trials in patients with following indications: chronic heart failure, left ventricular dysfunction following acute myocardial infarction, hypertension and the long term management of coronary heart disease the following adverse drug reactions were reported:

Blood and Lymphatic System Disorders

Frequent: anaemia

Less frequent: thrombocytopenia, leukopenia

Nervous system disorders

Frequent: dizziness, headache, syncope, presyncope

Less frequent: paraesthesia

Psychiatric Disorders

Frequent: depression, depressed mood

Less frequent: sleep disorders

Cardiac disorders

Frequent: cardiac failure, bradycardia, hypervolaemia, fluid overload

Less frequent: atrioventricular block, angina pectoris

Vascular disorders

Frequent: hypotension, orthostatic hypotension, disturbances of peripheral circulation (cold extremities, peripheral vascular disease, exacerbation of intermittent claudication and Raynaud's phenomenon), hypertension

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea, pulmonary oedema, asthma in predisposed patients, wheezing in patients with asthma and COPD

Less frequent: nasal congestion

Gastrointestinal disorders

Frequent: nausea, diarrhoea, vomiting, dyspepsia, abdominal pain

Less frequent: constipation, dry mouth

Hepatobiliary disorders

Less frequent: increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT)

Renal and urinary disorders

Frequent: renal failure and renal function abnormalities in patients with diffuse vascular disease and/or underlying renal insufficiency

Less Frequent: micturition disorders

Reproductive system and breast disorders

Less frequent: erectile dysfunction

Immune System Disorders

Less frequent: hypersensitivity (allergic reactions)

Infections and Infestations

Frequent: pneumonia, bronchitis, upper respiratory tract infection, urinary tract infection

Metabolism and Nutrition Disorders

Frequent: increased weight, hypercholesterolaemia, impaired blood glucose (hyperglycaemia, hypoglycaemia) in patients with pre-existing diabetes

Musculoskeletal and Connective Tissue Disorders

Frequent: Pain in extremities

Eye Disorders

Frequent: visual impairment, decreased lacrimation (dry eye), eye irritation

Skin and Subcutaneous Disorders

Less frequent: Skin reactions (e.g. allergic exanthema, dermatitis, urticarial, pruritus, psoriatic and lichen planus like skin lesions)

General disorders and administration site conditions

Frequent: asthenia (fatigue), oedema, pain

Description of selected adverse reactions

The frequency of adverse reactions is not dose-dependent, with the exception of dizziness, abnormal vision and bradycardia. 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 CRAVEDON dose. (See section 4.4).

Cardiac failure was a very commonly reported adverse event in patients with left ventricular dysfunction following acute myocardial infarction.

Reversible deterioration of renal function has been observed with CRAVEDON 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).

Post-Marketing

The following adverse events have been identified during post-marketing use of carvedilol. Because these events are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency and/or establish a causal relationship to medicine exposure.

Renal and urinary disorders: Cases of urinary incontinence in women, which may resolve upon discontinuation of the medication, have been reported.

Skin and subcutaneous tissue disorders: Alopecia.

Severe cutaneous adverse reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome). (See section 4.4).

Metabolism and nutrition disorders: Due to the β-blocking properties, it is also possible for latent diabetes mellitus to become manifest, manifest diabetes to be aggravated, and blood glucose counter-regulation to be inhibited.

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms: In the event of overdosage, 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.

Treatment: Patients should be monitored for the above mentioned signs and symptoms and managed according to the best judgment of the treating medical practitioners and according to standard practice for patients with β-blocker overdose (e.g. atropine, transvenous pacing, glucagon, phosphodiesterase inhibitor such as amiodarone or milrinone, P-sympathomimetics).

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 a prolonged elimination half-life of CRAVEDON from deeper compartments can be expected. The duration of the supportive therapy depends on the severity of the overdose. The supportive treatment should therefore be continued until the patient's condition has stabilised.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

A 7.1.3 Hypotensives

Pharmacotherapeutic group: Alpha and beta blocking agents.

ATC code: C07AG02

Mechanism of action

Carvedilol is an adrenergic receptor blocker with α1, β1, and β2 adrenergic receptor blockade properties. Carvedilol is racemic, and both R(+) and S(-) enantiomers have the same α-adrenergic receptor blocking properties and antioxidant properties.

Carvedilol's β-adrenergic receptor blocking properties are non-selective for the β1 and β2-adrenoceptors and are associated with the S(-) enantiomer.

Carvedilol suppresses the renin-angiotensin-aldosterone system through β-blockade, which reduces the release of renin.

Carvedilol reduces peripheral vascular resistance via selective blockade of α1-adrenoceptors. Carvedilol attenuates the increase in blood pressure induced by phenylephrine, an α1-adrenoceptor agonist, but not that induced by angiotensin II.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of a 25 mg capsule to healthy subjects, carvedilol is rapidly absorbed with a peak plasma concentration C_{max} of 21 mg/l reached after approximately 1,5 hours (t_{max}). The C_{max} values are linearly related to the dose. Following oral administration, carvedilol undergoes extensive first pass metabolism that results in an absolute availability of about 25 % in healthy male subjects. Carvedilol is a racemate and the S-(-)- enantiomer appears to be metabolised more rapidly than the R-(+)- enantiomer, showing an absolute oral

availability of 15 % compared to 31 % for the R-(+)- enantiomer. The maximal plasma concentration of R-carvedilol is approximately 2 fold higher than that of S-carvedilol.

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

Eating a meal does not influence carvedilol bioavailability. The time to reach maximum serum concentration is delayed by eating a meal.

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 beta1- and beta2-adrenoreceptors.

Distribution

Carvedilol is a highly lipophilic compound, showing a plasma protein binding of around 95 %. The distribution volume ranges between 1,5 and 2 l/kg.

Biotransformation and elimination

In humans, carvedilol is extensively metabolised in the liver via oxidation and conjugation into a variety of metabolites that are eliminated mainly in the bile.

Demethylation and hydroxylation at the phenol ring produce 3 metabolites with β-adrenergic receptor blocking activity.

Based on pre-clinical studies, the 4'-hydroxyphenol metabolite is approximately 13 times more potent than carvedilol for β-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.

Pharmacokinetic studies in humans have shown that the oxidative metabolism of carvedilol is stereo-selective. The results of an in vitro study suggested that different cytochrome P450

isoenzymes may be involved in the oxidation and hydroxylation processes including CYP2D6, CYP3A4, CYP2E1, CYP2C9 as well as CYP1A2.

Studies in healthy volunteers and in patients have shown that the R-enantiomer is predominantly metabolised by CYP2D6. The S-enantiomer is mainly metabolised by CYP2D6 and CYP2C9.

Genetic polymorphism

The results of clinical pharmacokinetic studies in human subjects have shown that CYP2D6 plays a major role in the metabolism of R and of S-carvedilol. As a consequence plasma concentrations of R and S-carvedilol are increased in CYP2D6 slow metabolisers. However, CYP2D6 genetic polymorphism may be of limited clinical significance.

Elimination

Following a single oral administration of 50 mg carvedilol, around 60 % is secreted into the bile and eliminated with the faeces in the form of metabolites within 11 days. Following a single oral dose, only about 16 % is excreted into the urine in form of carvedilol or its metabolites. The urinary excretion of unaltered carvedilol represents less than 2 %. After intravenous infusion of 12,5 mg to healthy volunteers, the plasma clearance of carvedilol reaches around 600 ml/min and the elimination half-life around 2,5 hours. The elimination half-life of a 50 mg capsule observed in the same individuals was 6,5 hours corresponding to the absorption half-life from the capsule. Following oral administration, the total body clearance of the S-carvedilol is approximately two times larger than that of the R-carvedilol.

Special Populations

Renal impairment

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.

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. (See sections 4.3 and 4.2 'Hepatic impairment').

Heart failure

In a study of 24 Japanese 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.

Elderly

Age has no statistically significant effect on the pharmacokinetics of carvedilol in hypertensive patients.

Children

Investigation in paediatrics has shown that the weight adjusted clearance is significantly larger in paediatric as compared to adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, pregelatinised maize starch, lactose monohydrate, copovidone, glycerol dibehenate, colloidal anhydrous silica, magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

4 years

6.4 Special precautions for storage

Store at or below 25 °C in the original package.

Do not remove the blisters from the carton until required for use.

6.5 Nature and contents of container

The tablets are packed in PVC/Aluminium foil blisters strips. The blister strips are packed in cartons containing 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Smart Pharmaceuticals (Pty) Ltd

247 Voortrekker Road

Kraaifontein, Cape Town

7800

8 REGISTRATION NUMBERS

CRAVEDON 6,25 mg tablets: 48/7.1.3/0676

CRAVEDON 12,5 mg tablets: 48/7.1.3/0677

CRAVEDON 25 mg tablets: 48/7.1.3/0678

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 October 2023

10 DATE OF REVISION OF THE TEXT

--