Professional Information

Scheduling status: S3

Proprietary names and dosage forms:

CARVEDILOL 6,25 OETHMAAN

CARVEDILOL 12,5 OETHMAAN

Composition:

Each CARVEDILOL 6,25 OETHMAAN contains: 6,25 mg carvedilol.

Each CARVEDILOL 12,5 OETHMAAN contains: 12,5 mg carvedilol.

Contains sugar.

Pharmacological classification:

A 7.1.3 Other hypotensives

Pharmacological action:

Carvedilol is a competitive non-selective beta 1 and 2 –adrenergic blocking agent with also alpha-adrenergic blocking activity and no intrinsic sympathomimetic activity. Carvedilol reduces peripheral vascular resistance through vasodilation and suppresses the renin-angiotensin-aldosterone system through beta blockade.

Pharmacokinetics:

Carvedilol is absorbed from the gastrointestinal tract and extensively metabolised in the liver, primarily by aromatic ring oxidation and glucuronidation. Absolute bioavailability is about 25 % due to the considerable first-pass metabolism. Peak plasma concentration occurs approximately 1 hour after

administration. Protein binding, especially to albumin, is more than 98 %. The absorption rate of carvedilol is slowed by food, but the bioavailability appears not to be affected.

The elimination half-life is 6 to 10 hours and excretion is mainly in the bile, with a small part (about 15 %) excreted via the kidneys.

The plasma level of carvedilol is an average of about 50 % higher in the elderly, compared with younger patients.

The plasma levels of carvedilol are 5 times higher in patients suffering from cirrhosis of the liver, than in healthy subjects.

Indications:

- Treatment of mild to moderate essential hypertension.
- Treatment of mild or moderate stable symptomatic heart failure of ischaemic or cardiomyopathic origin in conjunction with standard therapy. CARVEDILOL OETHMAAN has been used in patients unable to tolerate an ACE inhibitor and also in patients not receiving digitalis.

Contra-indications:

Hypersensitivity to CARVEDILOL OETHMAAN.

CARVEDILOL OETHMAAN is contra-indicated in patients suffering from bronchospasm or asthma, or patients with a history of obstructive airway disease, bronchitis and chronic respiratory disease.

CARVEDILOL OETHMAAN is contra-indicated in the following conditions: 2nd and 3rd degree atrioventricular block, severe bradycardia (< 50/minute), New York Heart Association (NYHA) Class IV decompensated heart failure requiring intravenous inotropic support, cardiogenic shock, sick sinus syndrome (including sino-atrial block), hepatic function impairment, metabolic acidosis, peripheral vascular disease and Raynaud's phenomenon.

CARVEDILOL OETHMAAN should not be prescribed to patients suffering from allergic conditions involving the airways, e.g. allergic rhinitis or glottis oedema.

CARVEDILOL OETHMAAN should not be used during pregnancy and lactation.

Warnings:

Patients with phaeochromocytoma should never receive CARVEDILOL OETHMAAN without receiving concomitant alpha-adrenoceptor blocking therapy.

CARVEDILOL OETHMAAN should be given to patients with congestive heart failure only after adequate clinical control is achieved, and only then with great caution. Safety and efficacy in children have not been established.

Interactions:

Warning:

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

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

It can be dangerous to administer CARVEDILOL OETHMAAN concomitantly with the following medicines: hypoglycaemic agents, phenothiazines and various antiarrythmic agents.

Such drug-drug interactions can have life-threatening consequences.

<u>Special note:</u>

Digitalisation of patients receiving long-term beta-blocking therapy may be necessary if congestive cardiac failure is likely to develop. This combination may be considered despite the potentiation of

negative chronotropic effect of the two medicines. Careful control of the dosages and of the individual patient's response (and notably pulse rate), is essential in this situation.

Anaesthetic agents causing myocardial depression should be avoided.

CARVEDILOL OETHMAAN should be avoided in combination with cardio-depressant calcium channel blockers such as verapamil and diltiazem.

The hypotensive effects of carvedilol are antagonised by non-steroidal anti-inflammatory agents (NSAIDS).

CARVEDILOL OETHMAAN may potentiate antidiabetic agents such as insulin or sulphonylureas.

Myocardial depressant agents, including antiarrhythmic agents, e.g. disopyramide, procainamide, lignocaine and phenytoin, may have a negative inotropic effect on the heart and there may be a potentiation of the AV conduction time when used concurrently with CARVEDILOL OETHMAAN

Enzyme inhibitors, such as quinidine may affect the metabolism and pharmacokinetics of CARVEDILOL OETHMAAN.

Reserpine and other medicines that can deplete catecholamines, as well as adrenergic neuron blocking agents, such as quanethidine and bethanidine, may cause hypotension and severe bradycardia.

Beta-adrenoreceptor stimulating agents, such as isoprenaline, diminish the effect of carvedilol. Alpha-adrenoreceptor stimulating agents such as noradrenaline and mixed alpha- and beta-adrenoreceptor stimulating agents, such as adrenaline, may enhance the peripheral vasoconstrictor effects of carvedilol and may reverse the hypotensive effects. Rifampicin may decrease the systemic availability of CARVEDILOL OETHMAAN.

Digoxin levels should be monitored when carvedilol dosages are changed. Concurrent therapy with cimetidine may result in a 30 % increase in the systemic bioavailability of CARVEDILOL OETHMAAN, but has no effect on the $C_{max.}$

Hydralazine and alcohol may increase the plasma concentration of carvedilol by delaying the hepatic metabolism of CARVEDILOL OETHMAAN.

Pregnancy and lactation:

CARVEDILOL OETHMAAN should not be used during pregnancy and lactation (see " Contra-indications"). Administration to pregnant mothers shortly before giving birth, or during labour, may result in the newborn infant being born hypotonic, collapsed and hypoglycaemic.

Dosage and directions for use:

Essential hypertension:

Adults:

Initial dose: 6,25 mg twice daily, for 1 to 2 weeks.

Maintenance dose: 12,5 mg twice daily.

Or

Initial dose: 12,5 mg once daily, for 2 days.

Maintenance dose: 25 mg once daily.

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

Elderly:

Usual dose: 12,5 mg once daily.

If necessary the dosage may be increased as tolerated, at intervals of at least 2 weeks, to 25 mg once daily or in divided doses.

Heart failure (in conjunction with standard therapy):

To reduce the incidence of orthostatic effects CARVEDILOL OETHMAAN should be taken with food to slow the rate of absorption. The bioavailability of CARVEDILOL OETHMAAN is not affected by food. It is advised that the dosage be individualised and that the patient be closely monitored by a medical practitioner experienced in the management of heart failure, during up-titration.

Patients receiving digitals, diuretics and/or angiotensin-converting enzyme (ACE) inhibitors, should be stabilised prior to carvedilol therapy.

Adults:

Initial dose: 3,125 mg twice daily for 2 weeks.

Increase to: 6,25 mg twice daily for 2 weeks.

Maintenance dose: 25 mg twice daily for patients weighing < 85 kg (maximum dose).

Increase to: 50 mg twice daily for patients weighing > 85 kg (maximum dose).

An interval of at least 2 weeks should be allowed after each dose increase. Before the dosage is increased, the patient should be evaluated for symptoms of worsening heart failure or vasodilation. Transient heart failure and fluid retention should be treated with increased doses of a diuretic. It may be necessary to lower the CARVEDILOL OETHMAAN dosage or to discontinue carvedilol therapy temporarily in some cases. Should treatment be discontinued for 2 weeks or more, it is advised that therapy be reinstated at 3,125 mg twice daily for 2 weeks and the dosage then increased in line with the above-mentioned dosage instructions.

Symptoms of vasodilation (headache, dizziness, postural hypotension) may initially be managed by a dose reduction of the diuretic.

Should the symptoms persist, the dose of ACE inhibitor may be reduced, followed by a reduction in the in the dose of CARVEDILOL OETHMAAN, if necessary. All symptoms of vasodilation or worsening heart failure must be stabilised before the dose of carvedilol is increased in line with the recommended dose instructions.

Side effects and special precautions:

Side effects:

Blood and lymphatic system disorders:

Frequent:

Thrombocytopenia.

Less frequent:

Non-thrombocytopenic purpura, agranulocytosis and transient oesinophilia.

Endocrine disorders:

Less frequent:

Hypoglycaemia may occur.

Neuropsychiatric disorders:

Frequent:

Vague fatigue and malaise, dizziness.

Less frequent:

Sleeplessness, vivid dreams and nightmares, overt psychosis. Depression, hallucinations, confusion, paraesthesia and peripheral neuropathy have also been reported.

Eye disorders:

Frequent:

Decreased tear production has been reported.

Less frequent:

Blurred vision and ocular pain have been reported.

Cardiovascular disorders:

Frequent:

Marked bradycardia, hypotension may occur. Generalised oedema.

Less frequent:

Exacerbation of peripheral vascular disease or the development of Raynaud's phenomenon (due to unopposed arteriolar alpha-sympathetic activation) may occur. Severe peripheral vascular disease and even peripheral gangrene may be precipitated. Congestive cardiac failure, may occur. Heart block may be precipitated in patients with underlying cardiac disorders. Chest pain, and syncope have also been reported.

Respiratory disorders:

Frequent

Bronchoconstriction may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases. Dyspnoea has also been reported.

Gastrointestinal disorders:

Frequent:

Nausea, vomiting, diarrhoea

Less frequent:

Constipation and abdominal cramping may occur.

Hepatobiliary disorders:

Less Frequent:

Hepatic injury has been reported.

Skin and subcutaneous tissue disorders:

Less frequent:

Allergic skin reactions and reversible alopecia may occur.

Musculoskeletal disorders:

Less frequent:

Skeletal muscle weakness may occur and myopathies, including muscle cramps, have been reported.

Genitourinary disorders:

Less frequent:

Impotence may occur. Renal function may deteriorate in patients suffering from congestive cardiac failure. Haematuria has been reported.

General disorders:

Less frequent:

Fever has been reported

Special precautions:

CARVEDILOL OETHMAAN should be given to patients with congestive heart failure only after adequate clinical control is achieved, and only then with great caution, especially if the heart failure is controlled with digitalis, diuretics and/or ACE inhibitors.

Before the dosage is increased, the patient should be evaluated for symptoms of worsening heart failure or vasodilation. Transient heart failure and fluid retention should be treated with increased doses of a diuretic. It may be necessary to lower the CARVEDILOL OETHMAAN dosage or to discontinue CARVEDILOL OETHMAAN therapy temporarily in some cases.

All symptoms of vasodilation or worsening heart failure must be stabilised before the dose of CARVEDILOL OETHMAAN is increased in line with the recommended dosage instructions.

- It is of the greatest importance that the anaesthetist be informed that a beta-blocker is being taken by the patient, prior to anaesthesia. CARVEDILOL OETHMAAN therapy should be discontinued 48 hours prior to anaesthesia. If this is not possible, an agent such as atropine may be administered to counter increases in vagal tone.

In the perioperative 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 of hypertension.

A patient's normal tachycardiac response to hypovolaemia or blood loss may be obscured during and after surgery. Particular caution should be taken in this regard.

- Safety during long-term administration has not been demonstrated.
- Adverse reactions are more common in patients with renal decompensation, and in patients who receive the medicine intravenously.
- A dose reduction is necessary in elderly patients or in patients suffering from renal dysfunction.
- Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual (over a period of 1 to 2 weeks) and patients should be advised to limit the extent of their physical activity during the period that the medicine is being discontinued.
- Patients with phaeochromocytoma should receive concomitant alpha-adrenoceptor blocking therapy.
- There is no clinical experience in the use of CARVEDILOL OETHMAAN in patients suffering from Prinzmetal's variant angina. Caution is advised as CARVEDILOL OETHMAAN may provoke chest pain in patients suspected of suffering from this disease.
- CARVEDILOL OETHMAAN may cause bradycardia. A dose reduction is advised should the pulse rate drop to < 55 beats/minute.
- Early signs of acute hypoglycaemia may be masked by the administration of CARVEDILOL OETHMAAN. Caution is advised when CARVEDILOL OETHMAAN is prescribed to diabetic patients. A dose reduction of antidiabetic medication or insulin may be necessary.
- The symptoms of hyperthyroidism may be masked by CARVEDILOL OETHMAAN.
- When dizziness or related symptoms are experienced, the patient should be advised not to drive or operate machinery.

- Wearers of contact lenses should be informed that there may be a reduction in lacrimation. Psoriasis may be aggravated. Patients with a history of anaphylaxis to an antigen may be more reactive to repeated challenge with the antigen while taking CARVEDILOL OETHMAAN.

Known symptoms of overdosage and particulars of its treatment:

Overdosage may produce bradycardia and severe hypotension. Brochospasm and cardiac failure may occur in some patients.

Bradycardia and severe hypotension should be treated with intravenous atropine. Incremental doses of up to 3 mg should be given immediately. If necessary, this should be followed by a slow intravenous infusion of isoprenaline. If further measures are required, noradrenaline may be preferable in restoring circulation. The recommended starting dose for noradrenaline is 5 to 10 µg given intravenously, and should be repeated according to the patient's response. Alternatively, it may be given by intravenous infusion at a rate of 5 µg/minute until a response is achieved.

In case of therapy-resistant bradycardia, pacemaker therapy should be performed.

In severe ovedosage the following regimen may be preferred:

Initially 1 to 10 mg glucagon intravenously, followed by intravenous infusion at a rate of 2 to 2,5 mg/hour.

Bronchospasm should be treated with intravenous aminophylline, and cardiac failure with glucagons and/or pacing.

Peripheral vasodilation may be treated with noradrenaline with continuous monitoring of the circulation.

In the event of seizures, diazepam or clonazepam may be given as a slow intravenous injection.

Since a prolonged elimination half-life of CARVEDILOL OETHMAAN can be expected, treatment with antidotes must be continued for a sufficiently long period of time when there are symptoms of shock, following severe intoxication with CARVEDILOL OETHMAAN.

Identification:

CARVEDILOL 6,25 OETHMAAN: White, oval, slightly biconvex tablets, one side scored with sign S2 on the opposite side.

CARVEDILOL 12,5 OETHMAAN: White, oval, slightly biconvex tablets, one side scored with S3 sign on the opposite side.

Presentations:

Packs of 30, 100 or 250 tablets in OPA/PVC/Aluminium foil blister and in white round high density polyethylene container with white round polypropylene child-resistant tamper-evident screw closure.

Storage instructions:

Store in the original pack below 25 °C.

Protect from moisture and light. Blisters should be kept in the carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

Registration numbers:

CARVEDILOL 6,25 OETHMAAN: A39/7.1.3/0555

CARVEDILOL 12,5 OETHMAAN: A39/7.1.3/0556

Name and business address of the holder of the certificate of registration:

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