PACKAGE INSERT FOR

CARLOC 6,25 / 12,5 / 25 (TABLETS)

SCHEDULING STATUS:

S3

PROPRIETARY NAME (AND DOSAGE FORM):

CARLOC 6,25 (Tablets)

CARLOC 12,5 (Tablets)

CARLOC 25 (Tablets)

COMPOSITION:

CARLOC 6,25: Each tablet contains carvedilol 6,25 mg.

CARLOC 12,5: Each tablet contains carvedilol 12,5 mg.

CARLOC 25: Each tablet contains carvedilol 25,0 mg.

Inactive ingredients are colloidal anhydrous silica, ferric oxide red, ferric oxide yellow, lactose monohydrate, low substituted hydroxyl propyl cellulose, magnesium stearate, maize starch, microcrystalline cellulose and *purified talc.

* Only present in **CARLOC 25**.

Contains sugar (lactose).

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Other hypotensives.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Carvedilol is a vasodilatory, non-selective beta-adrenergic blocking medicine with selective alpha$_1$-adrenergic blocking activity and no intrinsic sympathomimetic activity.

Carvedilol exerts its anti-adrenergic effects by acting as a competitive, non-selective antagonist of both beta$_1$ – and beta$_2$ – adrenoreceptors. Carvedilol is racemic and both R(+) and S(-) enantiomers have the same alpha-adrenergic receptor blocking properties and antioxidant properties. Carvedilol's beta-adrenergic receptor blocking properties are non-selective for the beta$_1$ and beta$_2$-adrenoceptors and are associated with the laevorotatory S(-) enantiomer.

Carvedilol suppresses the renin-angiotensin-aldosterone system through beta blockade and reduces peripheral vascular resistance through vasodilation. Its vasodilating effects are mediated primarily by selective blockade of alpha-$_1$- adrenoreceptors. Blood pressure increases induced by alpha$_1$ adrenoceptor agonists, such as phenylephrine, is attenuated by carvedilol, however not that induced by angiotensin II.

The following desirable haemodynamic and metabolic effects are provided by the balance of vasodilation and beta-receptor blockade following carvedilol administration:

- Maintenance of myocardial function.
- Maintenance of peripheral blood flow.
- The cholesterol, triglycerides, high density lipoprotein and low density lipoprotein levels are not affected. Serum electrolytes are not affected. Reduced plasma renin leaving the renal function unaffected.

Pharmacokinetic properties:

Absorption:

Carvedilol is absorbed from the gastrointestinal tract after oral administration. The absorption rate of carvedilol is slowed by food, but the bioavailability appears not to be affected. Absolute bioavailability is about 25 % due to the considerable first-pass metabolism. Peak plasma concentration occurs approximately 1 hour after administration.

Distribution:

Protein binding, especially to albumin, is more than 98 %. The volume of distribution is approximately 2 ℓ / kg and increase in patients with liver cirrhosis.

Metabolism:

Carvedilol is extensively metabolised in the liver, primarily by aromatic ring oxidation and glucuronidation. Aromatic oxidation produces three active metabolites with weak vasodilating properties.

Elimination:

The elimination half-life is 6 – 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 level of carvedilol is 5 times higher in patients suffering from cirrhosis of the liver, than in healthy subjects. Although the metabolites of carvedilol are excreted mainly in the bile,

the role of the active metabolites excreted by the kidneys (about 15 %) cannot be totally excluded.

INDICATIONS:

- Treatment of mild to moderate essential hypertension.
- Treatment of mild, moderate and severe stable symptomatic heart failure of ischaemic or cardiomyopathic origin in conjunction with standard therapy. **CARLOC** has been used in patients unable to tolerate an ACE inhibitor and also in patients receiving or not receiving digoxin.
- Long-term treatment of left ventricular dysfunction (left ventricular ejection fraction (LVEF) ≤ 40 % or wall motion index ≤ 1,3) following otherwise uncomplicated acute myocardial infarction. **CARLOC** is used in combination with ACE inhibitors and other treatments recommended in the management of patients after myocardial infarction.

CONTRAINDICATIONS:

- Hypersensitivity to carvedilol or any of the excipients of **CARLOC**.
- **CARLOC** should not be prescribed to patients with:
    - Concurrent intravenous treatment with verapamil or diltiazem.
    - Asthma.
    - Allergic conditions involving the airways e.g. allergic rhinitis or glottis oedema.
    - A history of chronic obstructive airway disease with bronchial obstruction.
    - 2nd and 3rd degree atrioventricular block (unless a permanent pacemaker is in place).

- Severe bradycardia (< 50 beats/minute).
- New York Heart Association (NYHA) Class IV decompensated heart failure requiring intravenous inotropic support.
- Cardiogenic shock.
- Sick sinus syndrome (including sino-atrial block).
- Clinically significant hepatic dysfunction.
- Metabolic acidosis.
- Severe hypotension (systolic blood pressure < 85 mmHg).
- Prinzmetal's angina.
- Untreated phaeochromocytoma (see **"WARNINGS and SPECIAL PRECAUTIONS"**).
- Peripheral vascular disease and Raynaud's phenomenon (see **"WARNINGS and SPECIAL PRECAUTIONS"**).

- Safety and efficacy in children have not been established.

<u>WARNINGS and SPECIAL PRECAUTIONS:</u>

Transferring patients from clonidine to **CARLOC** therapy should be done cautiously (see **"INTERACTIONS"**).

CARLOC should be used with caution in patients with compromised renal function. Patients with phaeochromocytoma should never receive **CARLOC** without receiving concomitant alpha-adrenoceptor blocking therapy (see **"CONTRAINDICATIONS"**).

Congestive cardiac failure and marked bradycardia may manifest.

CARLOC 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 digoxin, vasodilators, diuretics and/or ACE inhibitors.

Elderly patients or patients with low basic blood pressure, salt and volume depletion or severe cardiac failure should be monitored for approximately 2 hours after initiation of treatment or after up-titration of the dose as hypotension may occur. Hypotension as a result of excessive vasodilation should be treated by reducing the dose of the diuretic. Should the condition persist, a reduction in the dose of any ACE inhibitor is advised.

Before the dosage of **CARLOC** is increased, the patient should be evaluated for symptoms of worsening heart failure or vasodilation. Transient heart failure and fluid retention may occur at the start of **CARLOC** treatment or at dose increases and should be treated with increased doses of a diuretic. It may be necessary to lower the **CARLOC** dosage or to discontinue **CARLOC** therapy temporarily in some cases.
All symptoms of vasodilation or worsening heart failure must be stabilised before the dose of **CARLOC** is increased in line with the recommended dosage instructions.

Patients with heart failure and hypotension (systolic < 100 mm Hg), ischaemic heart disease and generalised atherosclerosis, or underlying renal deficiency may experience reversible deterioration in renal function with **CARLOC** therapy. Monitoring of renal function is advised during increased doses of **CARLOC**. If significant worsening of renal function is experienced, the dosage of **CARLOC** should be reduced or treatment should be discontinued.

CARLOC should be used with caution in congestive cardiac failure patients treated with digoxin, diuretics and/or an ACE inhibitor as both digoxin and **CARLOC** slow A-V conduction (see **"INTERACTIONS"**).

Bronchoconstriction may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases.

CARLOC should not be prescribed to patients with chronic obstructive pulmonary disease (COPD) with a tendency towards bronchospasms (see **"CONTRAINDICATIONS"**).

In patients with Raynaud's syndrome and peripheral vascular disease **CARLOC** should be avoided since it may exacerbate symptoms of the disease (see **"CONTRAINDICATIONS"**).

Patients who are known to metabolise debrisoquine poorly should be closely monitored during initiation of **CARLOC** therapy.

Since there is limited clinical experience, **CARLOC** should not be administered to patients on concurrent treatment with alpha$_1$-receptor antagonist or alpha$_2$-receptor agonist or with the following disease states:

- Orthostasis
- Acute inflammatory heart disease
- Labile or secondary hypertension
- Haemodynamic relevant obstruction of heart valves or outflow tract
- End-stage peripheral arterial disease

It is of the greatest importance that the anaesthetist be informed that a beta-blocker is being taken by the patient, prior to anaesthesia. **CARLOC** therapy should be

discontinued 48 hours prior to anaesthesia. If this is not possible, medicine 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.

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.

There is no clinical experience in the use of **CARLOC** in patients suffering from Prinzmetal's variant angina. **CARLOC** should not be used in this condition as it may provoke chest pain in patients suspected of suffering from this disease (see **"CONTRAINDICATIONS"**).

Early signs of acute hypoglycaemia may be masked by the administration of **CARLOC**.

Caution is advised when **CARLOC** is prescribed to diabetic patients. A dose reduction of antidiabetic medicine or insulin may be necessary and regular blood glucose monitoring is advised (see **"INTERACTIONS"**).

Concomitant use of **CARLOC** and calcium channel blocking medicines such as verapamil and diltiazem or other antidysrrhythmics, specifically amiodarone, requires careful monitoring of the patient's blood pressure and ECG. Intravenous co-administration should be avoided (see **"CONTRAINDICATIONS"** and **"INTERACTIONS"**).

Concurrent administration with cimetidine should be done with caution as the effects of **CARLOC** may be augmented (see **"INTERACTIONS"**).

The symptoms of hyperthyroidism may be masked by **CARLOC**.

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 **CARLOC**.

CARLOC should not be used during pregnancy and lactation. Administration to pregnant mothers shortly before giving birth, or during labour, may result in the new-born infant being born hypotonic, collapsed and hypoglycaemic (see **"PREGNANCY AND LACTATION"**).

Effects on ability to drive and use machines:

When dizziness or related symptoms are experienced, the patient should be advised not to drive or operate machinery.

Lactose:

CARLOC contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **CARLOC**.

INTERACTIONS:

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 **CARLOC** is administered in these circumstances, the unopposed alpha-receptor stimulation may potentiate this effect.

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

It is dangerous to administer **CARLOC** concomitantly with the following medicines: hypoglycaemic medicines, phenothiazines and various antidysrrhythmic medicines.

Such medicine interactions can have life-threatening consequences.

Special note:

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 medicines causing myocardial depression, such as cyclopropane and trichloroethylene, should be avoided.

CARLOC should be avoided in combination with cardio-depressant calcium channel blockers such as verapamil and diltiazem (see **"CONTRAINDICATIONS"**) or antidysrrhythmics such as amiodarone.

Nitrates such as isosorbide mononitrate and glyceryl trinitrate increases the hypotensive effect of carvedilol.

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

CARLOC may potentiate antidiabetic medicines such as insulin or sulphonylureas.

Myocardial depressant medicines, including antidysrrhythmic medicines, e.g. disopyramide, procainamide, lidocaine and phenytoin, may have a negative inotropic effect on the heart and there may be a potentiation of the A-V conduction time when used concurrently with **CARLOC**.

Enzyme inhibitors, such as quinidine may affect the metabolism and pharmacokinetics of **CARLOC**.

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

Beta-adrenoreceptor stimulating medicines, such as isoprenaline, diminish the effect of carvedilol as in **CARLOC**. Alpha-adrenoreceptor stimulating medicines such as norepinephrine (noradrenaline) and mixed alpha- and beta-adrenoreceptor stimulating medicines, such as epinephrine (adrenaline), may enhance the peripheral vaso-constrictor effects of carvedilol and may reverse the hypotensive effects dangerously.

Rifampicin may decrease the systemic availability of **CARLOC**.

Digoxin levels should be monitored when **CARLOC** dosages are changed.

Concurrent therapy with cimetidine may result in a 30 % increase in the systemic bioavailability of **CARLOC,** but has no effect on the C_{max} (see **"WARNINGS and SPECIAL PRECAUTIONS"**).

Hydralazine and alcohol may increase the plasma concentration of carvedilol by delaying the hepatic metabolism of **CARLOC**.

Modest increases in mean trough ciclosporin concentrations were observed following the initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30 % of patients, the dose of ciclosporin had to be reduced in order to maintain ciclosporin concentrations with the therapeutic range, while in the remainder no adjustment was needed. On average, the dose of ciclosporin was reduced about 20 % in these patients. Due to wide inter-individual variability in the dose adjustment required, it is recommended that ciclosporin concentrations be monitored closely after initiation of carvedilol therapy and that the dose of ciclosporin be adjusted as appropriate.

PREGNANCY AND LACTATION:

Pregnancy:

CARLOC should not be used during pregnancy and lactation.

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

Intrauterine foetal death, immature or premature deliveries may result due to beta-blocker reduced placental perfusion. In addition, adverse effects (especially

hypoglycaemia, hypotension, bradycardia, respiratory depression and hypothermia) 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.

Lactation:

Carvedilol and its metabolites are excreted in breast milk. Therefore, breastfeeding is not advised during **CARLOC** treatment.

DOSAGE AND DIRECTIONS FOR USE:

Essential hypertension:

Adults:

Initial dose: 12,5 mg once daily, for two 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 **CARLOC** should be taken with food to slow the rate of absorption. The bioavailability of **CARLOC** 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 digoxin, diuretics and/or angiotensin-converting enzyme (ACE) inhibitors, should be stabilised prior to **CARLOC** therapy.

Adults:

Initial dose:	3,125 mg twice daily for two weeks.
Increase to:	6,25 mg twice daily for two weeks.
Increase to:	12,5 mg twice daily for two 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 two 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 **CARLOC** dosage or to discontinue carvedilol therapy temporarily in some cases. Should treatment be discontinued for two weeks or more, it is advised that therapy be reinstated at 3,125 mg twice daily for two weeks and the dosage then increased in line with the abovementioned 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 dose of **CARLOC**, if necessary. All symptoms of vasodilation or

worsening heart failure must be stabilised before the dose of **CARLOC** is increased in line with the recommended dose instructions.

Left ventricular dysfunction following otherwise uncomplicated acute myocardial infarction

It is advised that the dosage be individualised and that the patient be closely monitored by an experienced 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 **CARLOC:**

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. **CARLOC** can then be started between day 3 and day 21 after the myocardial infarction.

First dose of **CARLOC**:

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 **"WARNINGS and SPECIAL PRECAUTIONS"**).

Subsequent doses of **CARLOC**:

If the patient has tolerated the first dose (i.e. heart rate > 50 beats/minute, systolic 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, 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:

Renal impairment:

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

Hepatic impairment:

Carvedilol is contraindicated in patients with clinical manifestations of hepatic dysfunction (see **"CONTRAINDICATIONS"**).

SIDE-EFFECTS:

The following side effects can occur:

Infections and infestations:

Frequent:	Bronchitis, pneumonia, upper respiratory tract infection, urinary tract infection.

Blood and lymphatic system disorders:

Frequent: Anaemia, Non-thrombocytopenic purpura, agranulocytosis, transient eosinophilia.

Less frequent: Thrombocytopenia, leukopenia.

Immune system disorders:

Less frequent: Hypersensitivity (allergic reactions).

Metabolism and nutrition disorders:

Frequent: Weight increase, hypercholesterolaemia, impaired blood glucose control (hyperglycaemia, hypoglycaemia) in patients with pre-existing diabetes.

Psychiatric disorders:

Frequent: Malaise, depression, depressed mood.

Less frequent: Sleep disorders, vivid dreams and nightmares, overt psychosis, hallucinations, confusion, and peripheral neuropathy.

Nervous system disorders:

Frequent: Dizziness and headache.

Less frequent: Presyncope, syncope and paraesthesia.

Eye disorders:

Frequent: Decreased tear production, blurred vision, eye irritation.

Less frequent: Ocular pain.

Cardiac disorders:

Frequent: Congestive cardiac failure, bradycardia, generalised oedema, hypervolaemia and fluid overload.

Less frequent: Chest pain, atrioventricular block and angina pectoris.

Heart block may be precipitated in patients with underlying cardiac disorders.

Vascular disorders:

Frequent: Hypotension, orthostatic hypotension, disturbances of peripheral circulation (cold extremities, peripheral vascular disease and even peripheral gangrene may be precipitated, exacerbation of intermittent claudication and Raynaud's phenomenon).

Respiratory disorders:

Frequent: Dyspnoea, pulmonary oedema, bronchoconstriction may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases.

Less frequent: Nasal congestion.

Gastrointestinal disorders:

Frequent: Abdominal cramping, vomiting, dyspepsia, nausea and diarrhoea.

Less frequent: Constipation and dry mouth.

Hepatobiliary disorders:

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

Skin and subcutaneous tissue disorders:

Less frequent: Allergic skin reactions, reversible alopecia.

Musculoskeletal disorders:

Frequent: Skeletal muscle weakness, myopathies, muscle cramps.

Renal and urinary disorders:

Frequent: Renal failure and renal function abnormalities in patients with diffuse vascular disease and/or underlying renal insufficiency, micturition disorders.

Less frequent: Haematuria, urinary incontinence in women.

Reproductive system and breast disorders:

Less frequent: Erectile dysfunction.

General disorders:

Frequent: Asthenia (fatigue), pain.

Less frequent: Fever.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosage may produce bradycardia, and severe hypotension. Bronchospasm 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 dobutamine or isoprenaline. If further measures are required, norepinephrine (noradrenaline) may be preferable in restoring circulation. The recommended starting dose for noradrenaline is 5 – 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 overdosage the following regime may be preferred:
Initially 1 – 10 mg glucagon intravenously, followed by intravenous infusion at a rate of 2 – 2,5 mg/hour.

Bronchospasm should be treated with intravenous aminophylline or inhaled or IV β- agonist such as salbutamol, and cardiac failure with digoxin and diuretics.
Peripheral vasodilation may be treated with norfenefrine or noradrenaline with continuous monitoring of the circulation.

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

Special note:

Since a prolonged elimination half-life of carvedilol 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 **CARLOC**.

IDENTIFICATION:

CARLOC 6,25: Buff coloured, circular, biconvex tablets with cross break-line on one side and plain on the other.

CARLOC 12,5: Cream coloured, circular, biconvex tablets with cross break-line on one side and plain on the other.

CARLOC 25: Light red coloured, circular, biconvex tablets with cross break-line on one side and plain on the other.

PRESENTATION:

CARLOC 6,25: 30 or 60 tablets per pack in blister strips of 10 tablets.

CARLOC 12,5: 30 or 60 tablets per pack in blister strips of 10 tablets.

CARLOC 25: 30 or 60 tablets per pack in blister strips of 10 tablets.

STORAGE INSTRUCTIONS:

Store in well closed containers, at or below 30 °C, protected from light.

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

CARLOC 6,25:	37/7.1.3/0613
CARLOC 12,5:	34/7.1.3/0433
CARLOC 25:	34/7.1.3/0434

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Cipla Medpro (Pty) Ltd,

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CARLOC 6,25:	25 November 2005
CARLOC 12,5 :	25 April 2003
CARLOC 25:	06 February 2002
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