06/07/2007: P&A recommendation as per MCC letter dated 15/06/2007.

1C-002

PROPOSED PACKAGE INSERTS FOR

CIPLAZAR 25 / 50 / 100

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

CIPLAZAR 25 (Tablet)

CIPLAZAR 50 (Tablet)

CIPLAZAR 100 (Tablet)

COMPOSITION:

CIPLAZAR 25 (Tablet):	**CIPLAZAR 25** contains 25 mg losartan potassium equivalent to 25 mg losartan.
CIPLAZAR 50 (Tablet)	**CIPLAZAR 50** contains 50 mg losartan potassium equivalent to 50 mg losartan.
CIPLAZAR 100 (Tablet)	**CIPLAZAR 100** contains 100 mg losartan potassium equivalent to 100 mg losartan.

1C-003

PHARMACOLOGICAL CLASSIFICATION:

A7.1.3 Other hypotensives.

PHARMACOLOGICAL ACTION[1,2]:

MECHANISM OF ACTION:

Losartan is a synthetic, orally active compound which binds selectively to the AT_1 receptor. Both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block the actions of angiotensin II, regardless at the source or route of synthesis. Angiotensin II, a potent vasoconstrictor, is the primary active-hormone of the renin-angiotensin system, and a major determinant of the pathophysiology of hypertension.

Angiotensin II binds to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

Losarlan binds selectively to the AT_1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT_1 receptor, such as the potentiation of bradykinin-mediated effects or the generation of oedema are not associated with losartan.

1C-004

PHARMACOKINETICS:

Absorption:

Following oral administration, losartan undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33 %. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively.

Distribution:

Both losartan and its active metabolite are greater than or equal to 99 % bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

Metabolism:

About 14 % of intravenously- or orally-administered dose of losartan is converted to its active metabolite.

Elimination:

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4 % of the dose is excreted unchanged in the urine, and about 6 % of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan

and its active metabolite are linear with oral losartan doses up to 200 mg.

Following oral administration in normal volunteers, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. Both billary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C-labeled losartan in man, about 35 % of radioactivity is recovered in the urine and 58 % in the faeces. Following an intravenous dose of ^{14}C-labeled losartan in man, about 43 % of radioactivity is recovered in the urine and 50 % in the faeces.

Characteristics in Patients:

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1,7-fold greater than those seen in young patients.Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

PHARMACODYNAMICS:

During losartan administration, removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to a 2-3 fold increase in angiotensin II in plasma. However, antihypertensive

activity and suppression of plasma aldosterone concentration were apparent, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, plasma renin activity and angiotensin II levels declined to untreated levels within 3 days.Losartan is a specific antagonist of the angiotensin II receptor type AT_1, it does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. This provides a pharmacodynamic distinction between losartan and ACE inhibitors.

INDICATIONS[1]:

CIPLAZAR is indicated for the treatment of hypertension.

CONTRA-INDICATIONS[1,3,4]:

CIPLAZAR is contra-indicated in the following conditions:

- Patients who are hypersensitive to losartan or any component of this medicine.
- Pregnancy and lactation

WARNINGS[1,3,4]:

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (less frequently) with acute renal failure and/or death. Similar outcomes have been reported with **CIPLAZAR**. (see "Side Effects and Special Precautions"). Agents that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Similar effects have been reported with **CIPLAZAR**; these changes in renal function may be reversible upon

discontinuation of therapy (see "Side Effects and Special Precautions").

When pregnancy is detected, CIPLAZAR should be discontinued as soon as possible. Not to be used in pregnancy as teratogenicity has been shown in experimental animals.

Women of childbearing age should ensure adequate contraception (see "Pregnancy and lactation").

INTERACTIONS[1,3,4]:

No interactions of clinical significance have been identified. Compounds which have been studied in clinical pharmacokinetic studies include hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital and ketoconazole.

PREGNANCY AND LACTATION[1,3,4]:

The use of **CIPLAZAR** during pregnancy and lactation is not recommended as safety and efficacy have not been established.

Pregnancy:

When pregnancy is detected, CIPLAZAR should be discontinued as soon as possible. Not to be used in pregnancy as teratogenicity has been shown in experimental animals.

Women of childbearing age should ensure adequate contraception.

Paediatric Use:

Safety and effectiveness in children have not been established.

DOSAGE AND DIRECTIONS FOR USE[1,3,4]:

The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. The dose may be increased to 100 mg once daily. For patients with intravascular volume-depletion (e.g., those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see **"SPECIAL PRECAUTIONS"**).

No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis. A lower dose should be considered for patients with a history of hepatic impairment (see **"SPECIAL PRECAUTIONS"**).

CIPLAZAR may be administered with other antihypertensive agents.

CIPLAZAR may be administered with or without food.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS[1,3,4]:

SIDE-EFFECTS:

The following side effects may also occur:

Body as a Whole:

Frequent:	Abdominal pain, asthenia/fatigue, chest pain, oedema/swelling

Cardiovascular System Disorders:

Less Frequent:	Palpitation, tachycardia

Digestive:

Less Frequent: Diarrhoea, dyspepsia, nausea

Musculoskeletal:

Less Frequent: Back pain, muscle cramps

Nervous/Psychiatric:

Less Frequent: Dizziness, headache, insomnia

Respiratory:

Frequent: Cough, nasal congestion, pharyngitis, sinus disorder, upper respiratory infection

Laboratory Test Findings:

In controlled clinical trials, hyperkalemia (serum potassium greater than 5.5 mEq/L) occurred in 1,5 % of patients, but in these trials, discontinuation of losartan therapy due to hyperkalemia was not necessary. Elevations of alanine amino transferase (ALT) have occurred but usually resolved upon discontinuation of therapy.

SPECIAL PRECAUTIONS:

In patients who are intravascularly volume-depleted (e.g., those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of **CIPLAZAR**, or a lower starting dose should be used (see **"DOSAGE AND DIRECTIONS FOR USE"**). Based on pharmacokinetic

data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, halving of the dose should be considered for patients with a history of hepatic impairment (see **"DOSAGE AND DIRECTIONS FOR USE"**).

When impaired renal function is present, changes in renal function as a consequence of inhibiting the renin-angiotensin system including renal failure have been reported in susceptible individuals; in some patients these changes in renal function may be reversible upon discontinuation of therapy.

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (less frequently) with acute renal failure and/or death. Similar outcomes have been reported with **CIPLAZAR.**

Agents that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Similar effects have been reported with **CIPLAZAR**; these changes in renal function may be reversible upon discontinuation of therapy.

Use in the Elderly:

There is no data to suggest age-related difference in efficacy or safety profile of losartan.

1C-011

Effects on Ability to Drive and Use Machines:

There are no data to suggest that **CIPLAZAR** affects the ability to drive and use machines.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT[1]:

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Neither losartan nor the active metabolite can be removed by haemodialysis.

IDENTIFICATION:

CIPLAZAR 25:	White, round film coated tablets plain on both sides.
CIPLAZAR 50:	White oval film coated tablets with central break line on one side and plain on the other
CIPLAZAR 100:	White , oval film coated tablets plain on both sides

PRESENTATION:

CIPLAZAR 25:	A transparent PVC/PE/PVDC and Aluminium foil blister strip of 10 tablets packed in 30's and 60's.
CIPLAZAR 50:	A transparent PVC/PE/PVDC and Aluminium foil blister strip of 10 tablets packed in 30's.
CIPLAZAR 100:	A transparent PVC/PE/PVDC andAluminium foil blister strip of 10 tablets packed in 30's.

06/07/2007: P&A recommendation as per MCC letter dated 15/06/2007.

1C-012

STORAGE INSTRUCTIONS:

Store this medicine in a dry place below 30°C.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

To be allocated

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

CIPLA MEDPRO (PTY) LTD.

Rosen Heights

Pasita Street, Rosen Park,

Bellville

7530

DATE OF PUBLICATION OF THIS PACKAGE INSERT: