Cardiplot

Manidipine hydrochloride Tablets

1. Name of the Medicinal Product

Cardiplot 10

Cardiplot 20

2. Qualitative and Quantitative Composition

Cardiplot 10 : Each tablet contains 10 mg manidipine hydrochloride

Cardiplot 20 : Each tablet contains 20 mg manidipine hydrochloride

For the full list of excipients, see Section 6.1

3. Pharmaceutical Form

Tablet

Cardiplot 10 : Yellow round tablets with scored between “B” and “L” on one side and scored onto “10” on other side.

Cardiplot 20 : Yellow round tablets with scored between “B” and “L” on one side and scored onto “20” on other side.

4. Clinical Particulars

4.1 Therapeutic indications

- Mild-to-moderate essential hypertension
- Hypertension with renal impairment
- Severe hypertension

4.2 Posology and method of administration

The adult dose is 10 to 20 mg once daily in the morning after breakfast. The recommended starting dose is 10 mg daily. The dose may be increased to 20 mg daily if the antihypertensive effect is inadequate after 2 to 4 weeks. Avoid abrupt withdrawal of calcium channel blocker therapy if possible. Hypertensive crisis has been reported.

Dosage in renal failure

No dosage adjustment is required in patients with mild to moderate renal dysfunction, however caution is advised when increasing the dose from 10 to 20 mg daily.

Dosage in hepatic insufficiency

The data suggest that patients with hepatic insufficiency are at an increased risk of accumulation of manidipine, and that dose reductions should be considered in this population. The dose in patients with mild hepatic dysfunction should not exceed 10 mg daily.

Dosage in geriatric patients

The data suggest that geriatric patients are at an increased risk of accumulation of manidipine, and that dose reductions to 10 mg daily should be considered in this population.

Manidipine may cause hypotension which may result in cerebral infarction. Should start treatment with low dose.

4.3 Contraindications

- Hypersensitivity to the active substance manidipine, or to other dihydropyridines or to any of the excipients listed in section 6.1.
- Paediatric age (no clinical experience).
- Unstable angina or within 4 weeks of a myocardial stroke.
- Untreated congestive heart failure.
- Severe renal failure (creatinine clearance < 10 ml/min).
- Moderate to severe hepatic failure.

4.4 Special warnings and precautions for use

Should be administered with caution in patients with mild hepatic impairment, since the antihypertensive effect may be increased (see section 4.2 “Posology and method of administration”).

A reduction of the dose is required in elderly patients due to the slowing down of the metabolic processes (see section 4.2 “Posology and method of administration”).

Manidipine should be administered with caution in patients with left ventricular failure, in patients who have left ventricular outflow tract obstruction, isolated right heart failure or sick sinus syndrome (with no pacemaker).

Since there are no study results available on patients with stable coronary disease, caution should be taken with these patients due to the possibility of increased coronary risk (see section 4.8 “Undesirable effects”).

Since there are no in vivo interactions study available on the inhibiting or inducing effects of CYP3A4 on the pharmacokinetics of manidipine, Cardiplot should not be administered concomitantly with cytochrome CYP3A4 inhibitors (e.g. antiprotease, cimetidine, ketoconazole, itraconazole, erythromycin, clarithromycin) and cytochrome CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital, and rifampicin) (see section 4.5).

Special caution should be taken in prescribing manidipine concomitantly with other substrates of CYP3A4, such as terfenadine, astemizole, quinidine and class III antiarrhythmics such as amiodarone (see section 4.5).

Excipients

Cardiplot contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The antihypertensive effect of manidipine may be enhanced by the combination with diuretics, beta-blockers and other antihypertensive drugs. In vitro studies have shown that the potential inhibiting effect of manidipine on cytochrome P450 may be considered clinically irrelevant.

As occurs with other dihydropyridine calcium channel blockers, it is probable that manidipine metabolism is catalysed by the cytochrome P450 3A4. Since there are no in vivo interaction study available on the effects of cytochrome CYP3A4 inhibitors or inducers on the pharmacokinetics of manidipine, caution should be exercised when Cardiplot is administered with drugs which inhibit the CYP 3A4 enzyme, such as ketoconazole, itraconazole, or with drugs which induce CYP 3A4, such as phenytoin, carbamazepine, phenobarbital and rifampicin (see section 4.4) and posology of manidipine should be adjusted if needed.

Caution is required in the concomitant prescription of manidipine and other CYP3A4 substrates, such as terfenadine, astemizole, quinidine and class III antiarrhythmics such as amiodarone (see section 4.4).

Moreover, concomitant administration of calcium channel blockers in combination with digoxin may determine increased glucoside levels.

Other antihypertensive drugs

The antihypertensive effect of manidipine can be increased by the concomitant administration of diuretics, betablockers and, in general, any other antihypertensive drugs.

Alcohol

As for all vasodilatory antihypertensives, caution is mandatory if alcohol is consumed concomitantly, as this can enhance their effects.

Grapefruit juice

Grapefruit juice seems to inhibit the metabolism of dihydropyridines, with a resulting increase in its systemic bioavailability and its hypotensive effect. Manidipine must therefore not be administered with grapefruit juice.

Oral hypoglycaemics

No interactions with oral hypoglycaemic agents have been noticed.

Amifostine

Increased risk of the antihypertensive effect.

Tricyclicantidepressant/antipsychotics

Increased antihypertensive effect and increased risk of orthostatic hypotension.

Baclofen

Potentation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adaptation of the antihypertensive if necessary.

Corticosteroids, tetracosactide

Reduction of antihypertensive effect (salt and water retention due to corticosteroids).

Alpha-blockers (prazosin, alfuzosin, doxazosin, tamsulosin, terazosin)

Increased antihypertensive effect and increased risk of orthostatic hypotension.

4.6 Pregnancy and lactation

Pregnancy

No clinical data are available about the use of this medicinal product by pregnant women. Studies with manidipine on laboratory animals do not provide sufficient results on foetal development (see section 5.3 “Preclinical safety data”). Since other medicinal products in the

dihydropyridine family have been shown to be teratogenic in animal species, and since the potential clinical risk is not known, manidipine should not be used during pregnancy.

Lactation

Manidipine and its metabolites are excreted in large quantities in rat milk. As it is not known whether or not manidipine is excreted in human milk, the use of manidipine must be avoided during lactation. If manidipine treatment is necessary, breast-feeding must be discontinued.

Fertility

Reversible biochemical changes in the head of spermatozoa which can impair fecundation have been reported in some patients treated by channel blockers.

4.7 Effect on ability to drive and use machines

Since dizziness may be experienced due to a reduced blood pressure, patients should be advised to take care while driving and operating machinery.

4.8 Undesirable effects

A number of undesirable effects have been observed during treatment with Cardiplot and other dihydropyridines, with the following frequencies:

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1,000 to < 1/100
Rare	≥1/10,000 to < 1/1,000
Very rare	< 1/10,000, including isolated cases
Not known	cannot be estimated from the available data

The common undesirable effects are dose-dependent and usually disappear later on during treatment.

Investigations

- Uncommon: reversible increases in SGPT, SGOT, LDH, gamma-GT, alkaline phosphatase, BUN and serum creatinine
- Rare: bilirubin increased

Cardiac disorders

- Common: palpitations, oedema
- Uncommon: tachycardia
- Rare: chest pain, angina
- Very rare: myocardial stroke and, in isolated cases, patients with pre-existent angina may experience increased frequency, duration and severity of these incidents.

Nervous system disorders

- Common: headache, dizziness and vertigo
- Uncommon: paresthesia
- Rare: somnolence and drowsiness
- Not known: extrapyramidal syndrome has been reported with some calcium inhibitors

Respiratory, thoracic and mediastinal disorders

- Uncommon: dyspnea

Gastrointestinal disorders

- Uncommon: nausea, vomiting, constipation, dry mouth, digestive disorders
- Rare: stomachache, abdominal pain, diarrhoea, anorexia
- Very rare: gingivitis and gingival hyperplasia, which generally disappeared with the withdrawal of the drug and need careful dental care.

Skin and subcutaneous disorders

- Uncommon: rash, eczema
- Rare: erythema, itching
- Not known: erythema multiforme, exfoliative dermatitis

Vascular disorders

- Common: hot flushes
- Uncommon: hypotension

- Rare: hypertension

Hepatobiliary disorders

- Rare: jaundice

Musculoskeletal and connective tissue disorders

- Not known: myalgia

Reproductive system and breast disorder

- Not known: gynaecomastia

General disorders and administration site conditions

- Uncommon: asthenia
- Rare: irritability

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

As occurs with other dihydropyridines, it is expected that an overdose would cause excessive peripheral vasodilatation with severe hypotension and reflex tachycardia.

In this case symptomatic treatment must be started without delay and measures taken to support cardiovascular function. Due to the prolonged duration of the pharmacological effects of manidipine, cardiovascular function must be monitored for at least 24 hours.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective calcium channel blockers, with mainly vascular effects. ATC code: C08CA11

Manidipine is a dihydropyridine calcium channel blocker with anti-hypertensive activity and with pharmacodynamic actions which promote renal function.

The main characteristic of manidipine is its prolonged action, demonstrated in vitro and in vivo, due both to its pharmacokinetic properties and to its high affinity for the receptor binding site. In many experimental hypertension models, manidipine was shown to be more efficient and have a more prolonged action than nicardipine and nifedipine.

In addition, manidipine presented vascular selectivity, particularly in the kidneys, increasing renal blood flow, reducing the vascular resistance of the afferent and efferent glomerular capillary vessels, leading consequently to a reduction of intraglomerular pressure.
This property is complemented by its diuretic action, through the inhibition of water and sodium reabsorbtion in the tubules. In experimental pathology trials, manidipine exercised a protective effect over the development of glomerular damage caused by hypertension at only moderate antihypertensive doses. In vitro studies showed that therapeutic concentrations of manidipine can effectively inhibit cellular proliferative response to vascular mitogens (PDGF, endothelin-1),which may represent the pathophysiological basis for renal and vascular damage in hypertensive patients.

In hypertensive patients, after one single daily dose, a clinically significant reduction in blood pressure was maintained for 24 hours.

This blood pressure reduction caused by the reduction of total peripheral resistance does not lead to a clinically significant increase of cardiac frequency and output during short- or long- term administration.

Manidipine has not been shown to affect glucose metabolism or lipid profile in hypertensive diabetic patients.

5.2 Pharmacokinetic properties

After oral administration, maximum plasma concentration is achieved in 2-3.5 hours.
Manidipine undergoes first-pass metabolism.

Binding to plasma proteins is 99%. The medicinal product is widely distributed to the tissues and is extensively metabolised, mainly by the liver.

It is mainly eliminated through faeces (63%) and, to a lesser extent, through urine (31%).

No accumulation is noted after repeated administration. The drug pharmacokinetic is not modified in patients with renal failure.

Absorption of manidipine increases in the presence of food in the gastrointestinal tract.

5.3 Preclinical safety data

The results of repeated dose toxicity studies have shown only toxic signs linked to the exacerbation of the pharmacological effects.

The toxicological profile of manidipine on reproduction has not been sufficiently evaluated in studies on animals, although the studies which have been carried out do not suggest an increased risk of teratogenic effects. In peri/postnatal reproduction studies in rats, the following adverse effects were observed at high doses: increase in the duration of pregnancy, dystocia, increase in foetal death, neonatal mortality.

Preclinical studies did not show any harmful effect for humans in terms of mutagenicity, carcinogenicity, antigenicity or adverse effects on fertility.

6. Pharmaceutical Particulars

6.1 List of excipients

Lactose monohydrate

Corn starch

Low-substituted hydroxypropylcellulose

Hydroxypropyl cellulose-L

Magnesium stearate

Riboflavin

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister of 10 tablets

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Berlin Pharmaceutical Industry Co., Ltd.
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8. MARKETING AUTHORISATION NUMBER(S)

1A xxxxx/64

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dd/mm/2021

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October 2020