SUMMARY OF PRODUCTS CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

<Product name> 10 mg tablets
<Product name> 20 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Manidipine dihydrochloride 10 mg

Excipients: lactose monohydrate 66.40 mg

Manidipine dihydrochloride 20 mg

Excipients: lactose monohydrate 132.80 mg

For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Tablet

The 10 mg tablets are round convex, yellow coloured, with midline score line
The 20 mg tablets are oval convex, yellow coloured, with midline score line

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mild to moderate essential hypertension.

4.2 Posology and method of administration

The recommended starting dose is 10 mg once a day. If, after 2-4 weeks of treatment, the anti-hypertensive effect is insufficient, it is advisable to increase the dosage to the usual maintenance dose of 20 mg once a day.

Use in the elderly
Due to the metabolic slowing in elderly people, the recommended dose is 10 mg once a day. This dosage is sufficient for the majority of elderly patients.
The risk/benefit ratio of any dosage increase must be envisaged cautiously on a case-by-case basis.

Use in patients with impaired renal or liver function
In patients with mild to moderate renal impairment, caution should be taken in increasing the dose from 10 mg to 20 mg per day.
Due to manidipine's extensive metabolism in the liver, dosage in patients with mild liver failure should not exceed 10 mg once a day (see section 4.3 "Contraindications")

The tablets should be taken in the morning after breakfast with a little liquid, and without chewing.

4.3 Contraindications

- Hypersensitivity to the active substance, manidipine, or to other dihydropyridines or to any of the excipients.
- Children.
- 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 liver 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”).

This medicinal product should not be administered to patients with hereditary problems of intolerance to galactose, Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

As occurs with other dihydropyridine calcium channel blockers, it is probable that manidipine metabolism is catalysed by the cytochrome P450 3A4. Caution should be exercised when Manidipine RKG 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 and posology of manidipine should be adjusted if needed.

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.

Tricyclic antidepressant/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. 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 Manidipine RKG 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

The common adverse 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

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 accidents.

Nervous system disorders

- Common: headache, , dizziness and vertigo
- Uncommon: paresthesia
- Rare: somnolence and drowsiness
- Unknown: 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: stomach ache, abdominal pain
- 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

Vascular disorders

- Common: hot flushes
- Uncommon: hypotension
- Rare: hypertension

General disorders and administration site conditions

- Uncommon: asthenia
- Rare: irritability

4.9 Overdose

No case of overdose is known. 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
maize starch
low-substituted hydroxypropylcellulose
hydroxypropylcellulose
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

PVC/PVDC blister sealed with Al/PVDC.

10 and 20 mg: 14, 28, 30, 56, 84, 90, 98, 112 tablets
Not all pack sizes may be marketed

6.6 Special precautions for disposal

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

7. MARKETING AUTHORIZATION HOLDER

To be completed nationally

8. MARKETING AUTHORIZATION NUMBERS

9. DATE OF FIRST AUTHORIZATION

10. DATE OF THE REVISION OF THE TEXT