SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lercadip 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg lercanidipine hydrochloride (equivalent to 9.4 mg lercanidipine).
Excipient(s) with known effect:
One film-coated tablet contains 30 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Yellow, circular, biconvex tablets, scored on one side.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lercadip is indicated in adults for the treatment of mild to moderate essential hypertension.

4.2 Posology and method of administration

Posology

The recommended dosage is 10 mg orally once a day at least 15 minutes before meals; the dose may be increased to 20 mg depending on the individual patient's response.

Dose titration should be gradual, because it may take about 2 weeks before the maximal antihypertensive effect is apparent.

Some individuals, not adequately controlled on a single antihypertensive agent, may benefit from the addition of LERCADIP to therapy with a beta-adrenoceptor blocking drug (atenolol), a diuretic (hydrochlorothiazide) or an angiotensin converting enzyme inhibitor (captopril or enalapril).

Since the dose-response curve is steep with a plateau at doses between 20-30 mg, it is unlikely that efficacy will be improved by higher doses; whereas side effects may increase.

Older patients: although the pharmacokinetic data and clinical experience suggest that no adjustment of the daily dosage is required, special care should be exercised when initiating treatment in the elderly.

Patients with renal or hepatic impairment: special care should be exercised when treatment is commenced in patients with mild to moderate renal or hepatic dysfunction. Although the usually recommended dose schedule may be tolerated by these subgroups, an increase in dose to 20 mg daily must be approached with caution. The antihypertensive effect may be enhanced in patients with hepatic impairment and consequently an adjustment of the dosage should be considered.

LERCADIP is not recommended for use in patients with severe hepatic impairment or in patients with severe renal impairment (GFR < 30 ml/min).

Paediatric population
The safety and efficacy of LERCADIP in children aged up to 18 years have not been established.
No data are available.

Method of administration
For oral use.
Precautions to be taken before handling or administering the medicinal product:
- Treatment should be preferably administered in the morning at least 15 minutes before breakfast.
- This product should not been administered with grapefruit juice (see section 4.3 and 4.5).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy and lactation (see section 4.6).
- Women of child-bearing potential unless effective contraception is used
- Left ventricular outflow tract obstruction.
- Untreated congestive cardiac failure.
- Unstable angina pectoris.
- Severe renal or hepatic impairment.
- Within 1 month of a myocardial infarction.
- Co-administration with:
    - strong inhibitors of CYP3A4 (see section 4.5),
    - cyclosporin (see section 4.5),
    - grapefruit and grapefruit juice (see section 4.5).

4.4 Special warnings and precautions for use

Sick-sinus syndrome
Special care should be exercised when LERCADIP is used in patients with sick sinus syndrome (without a pacemaker).

Left ventricular dysfunction and ischaemic heart disease
Although hemodynamic controlled studies revealed no impairment of ventricular function, care is also required in patients with LV dysfunction. It has been suggested that some short-acting dihydropyridines may be associated with increased cardiovascular risk in patients with ischaemic heart disease. Although LERCADIP is long-acting caution is required in such patients.
Some dihydropyridines may rarely lead to precordial pain or angina pectoris. Very rarely patients with pre-existing angina pectoris may experience increased frequency, duration or severity of these attacks. Isolated cases of myocardial infarction may be observed (see section 4.8).

Patients with renal or hepatic impairment
Special care should be exercised when treatment is commenced in patients with mild to moderate renal or hepatic dysfunction. Although the usually recommended dose schedule may be tolerated by these subgroups, an increase in dose to 20 mg daily must be approached with caution. The antihypertensive effect may be enhanced in patients with hepatic impairment and consequently an adjustment of the dosage should be considered.
LERCADIP is not recommended for use in patients with severe hepatic impairment or in patients with severe renal impairment (GFR < 30 ml/min) (see section 4.2).

Inducers of CYP3A4
Inducers of CYP3A4 like anticonvulsants (e.g. phenytoin, carbamazepine) and rifampicin may reduce lercanidipine's plasma levels and therefore the efficacy of lercanidipine may be less than expected (see section 4.5).
Alcohol
Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive drugs (see section 4.5).

Lactose
One tablet contains 30 mg lactose and therefore should not be administered to patients with Lapp lactase insufficiency, galactosaemia or glucose/galactose malabsorption syndrome.

Paediatric population
The safety and efficacy of Lercadip have not been demonstrated in children and adolescents aged up to 18 years.

4.5 Interaction with other medicinal products and other forms of interaction

Inhibitors of CYP3A4
Lercanidipine is known to be metabolised by the CYP3A4 enzyme and, therefore, inhibitors and inducers of CYP3A4 administered concurrently may interact with the metabolism and elimination of lercanidipine.

Co-prescription of LERCADIP with inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir, erythromycin, troleandomycin) should be avoided (see section 4.3).
An interaction study with a strong CYP3A4 inhibitor, ketoconazole, has shown a considerable increase in plasma levels of lercanidipine (a 15-fold increase of the AUC and an 8-fold increase of the C_{max} for the eutomer S-lercanidipine).

Cyclosporin

Cyclosporin and lercanidipine should not be administered together (see section 4.3). Increased plasma levels of both lercanidipine and cyclosporin have been observed following concomitant administration. A study in young healthy volunteers has shown that when cyclosporin was administered 3 hours after the lercanidipine intake, the plasma levels of lercanidipine did not change, while the AUC of cyclosporin increased by 27%. However, the co-administration of LERCADIP with cyclosporin has caused a 3-fold increase of the plasma levels of lercanidipine and a 21% increase of the cyclosporin AUC.

Grapefruit juice

Lercanidipine should not be taken with grapefruit and grapefruit juice (see section 4.3).

As for other dihydropyridines, lercanidipine is sensitive to inhibition of metabolism by grapefruit juice, with a consequent rise in its systemic availability and increased hypotensive effect.

Midazolam

When concomitantly administered at a dose of 20 mg with midazolam p.o. to elderly volunteers, lercanidipine's absorption was increased (by approximately 40%) and the rate of absorption was decreased (t_{max} was delayed from 1.75 to 3 hours). Midazolam concentrations were not modified.

Substrates of CYP3A4

Caution should be exercised when LERCADIP is co-prescribed with other substrates of CYP3A4, like terfenadine, astemizole, class III antiarrhythmic drugs such as amiodarone, quinidine.

Inducers of CYP3A4

Co-administration of LERCADIP with CYP3A4 inducers like anticonvulsants (e.g. phenytoin, carbamazepine) and rifampicin should be approached with caution since the antihypertensive effect may be reduced and blood pressure should be monitored more frequently than usual.

Metoprolol

When LERCADIP was co-administered with metoprolol, a β-blocker eliminated mainly by the liver, the bioavailability of metoprolol was not changed while that of lercanidipine was reduced by 50%. This effect may be due to the reduction in the hepatic blood flow caused by β-blockers and may therefore occur with other drugs of this class. Consequently, lercanidipine may be safely administered with beta-adrenoceptor blocking drugs, but dose adjustment may be required.

Fluoxetine

An interaction study with fluoxetine (an inhibitor of CYP2D6 and CYP3A4), conducted in volunteers of an age of 65 ± 7 years (mean ± s.d.), has shown no clinically relevant modification of the pharmacokinetics of lercanidipine.

Cimetidine

Concomitant administration of cimetidine 800 mg daily does not cause significant modifications in plasma levels of lercanidipine, but at higher doses caution is required since the bioavailability and the hypotensive effect of lercanidipine may be increased.

Digoxin

Co-administration of 20 mg lercanidipine in patients chronically treated with β-methyldigoxin showed no evidence of pharmacokinetic interaction. Healthy volunteers treated with digoxin following dosing with 20 mg lercanidipine given fasted showed a mean increase of 33% in digoxin C_{max}, while AUC and renal clearance were not significantly modified. Patients on concomitant digoxin treatment should be closely monitored clinically for signs of digoxin toxicity.

Simvastatin
When a dose of 20 mg of LERCADIP was repeatedly co-administered with 40 mg of simvastatin, the AUC of lercanidipine was not significantly modified, while simvastatin's AUC increased by 56% and that of its active metabolite β-hydroxyacid by 28%. It is unlikely that such changes are of clinical relevance. No interaction is expected when lercanidipine is administered in the morning and simvastatin in the evening, as indicated for such drug.

Warfarin
The co-administration of 20 mg lercanidipine to healthy volunteers given fasted did not alter the pharmacokinetics of warfarin.

Diuretics and ACE inhibitors
LERCADIP has been safely administered with diuretics and ACE inhibitors.

Alcohol
Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive drugs (see section 4.4).

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
Data for lercanidipine provide no evidence of a teratogenic effect in the rat and the rabbit and reproductive performance in the rat was unimpaired. Nevertheless, since there is no clinical experience with lercanidipine in pregnancy and lactation, and other dihydropyridine compounds have been found teratogenic in animals, LERCADIP should not be administered during pregnancy or to women with child-bearing potential unless effective contraception is used.

Breast-feeding
It is unknown whether lercanidipine/metabolites are excreted in human milk. A risk in the newborns/infants cannot be excluded. LERCADIP is contraindicated during breastfeeding (see section 4.3) .

Fertility
No clinical data are available with lercanidipine. Reversible biochemical changes in the head of spermatozoa which can impair fecundation have been reported in some patients treated by calcium channel blockers. In cases where repeated in-vitro fertilisation is unsuccessful and where another explanation cannot be found, the possibility of calcium channel blockers as the cause should be considered.

4.7 Effects on ability to drive and use machines

LERCADIP has minor influence on the ability to drive and use machines. However, caution should be exercised because dizziness, asthenia, fatigue and rarely somnolence may occur.

4.8 Undesirable effects

About 1.8% of treated patients experienced adverse reactions.

The table below shows the incidence of adverse drug reactions, at least possibly causally related, grouped by MedDRA System Organ Class classification and ranked by frequency: 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), not known (frequency cannot be estimated from available data). Within each frequency grouping the observed adverse reactions are presented in order of decreasing seriousness.

As shown in the table, the most commonly occurring adverse drug reactions reported in controlled clinical trials are headache, dizziness, peripheral oedema, tachycardia, palpitations, flushing, each occurring in less than 1% of patients.

Spontaneous reports from the post-marketing experience are grouped under the "not known" frequency category.

MedDRA System Organ Class	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not known
Immune System Disorders			hypersensitivity	
Nervous System Disorders	dizziness headache;	somnolence	syncope	
Cardiac Disorders	tachycardia; palpitations	angina pectoris		
Vascular Disorders	flushing			hypotension
Gastrointestinal Disorders		abdominal pain, vomiting, nausea; dyspepsia; diarrhoea		gingival hypertrophy
Skin and Subcutaneous		rash		

Tissue Disorders				
Musculoskeletal and Connective Tissue Disorders		myalgia		
Renal and Urinary Disorders		polyuria		urinary frequency
General Disorders and Administration Site Conditions	oedema peripheral	asthenia; fatigue		chest pain
Investigations				transaminases increased

Some dihydropyridines may lead to precordial pain or angina pectoris. Patients with pre-existing angina pectoris may experience increased frequency, duration or severity of these attacks. Cases of myocardial infarction may be observed.

Lercanidipine does not appear to influence blood sugar or serum lipid levels.

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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose

In the post-marketing experience, some cases of overdose were reported (from 40 up to 800 mg of lercanidipine, including reports of suicide attempt).

Symptoms

As with other dihydropyridines, overdosage might be expected to cause excessive peripheral vasodilatation. Symptoms associated to overdose include marked hypotension, dizziness, fatigue and reflex tachycardia. Cardiac failure, myocardial ischaemia and acute renal failure might occur. In case of severe hypotension cardiovascular support could be helpful.

Treatment

In view of the prolonged pharmacological effect of lercanidipine, it is essential that the cardiovascular status of patients who take an overdose is monitored for 24 hours at least. There is no information on the value of dialysis. Since the drug is highly lipophilic, it is most probable that plasma levels are no guide to the duration of the period of risk and dialysis may not be effective.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective calcium channel blockers with mainly vascular effects –Dihydropyridine derivatives.
ATC code: C08CA13

Mechanism of action

Lercanidipine is a calcium antagonist of the dihydropyridine group and inhibits the transmembrane influx of calcium into cardiac and smooth muscle. The mechanism of its antihypertensive action is due to a direct relaxant effect on vascular smooth muscle thus lowering total peripheral resistance.

Pharmacodynamic effects

Despite its short pharmacokinetic plasma half-life, lercanidipine is endowed with a prolonged antihypertensive activity because of its high membrane partition coefficient, and is devoid of negative inotropic effects due to its high vascular selectivity.
Since the vasodilatation induced by LERCADIP is gradual in onset, acute hypotension with reflex tachycardia has rarely been observed in hypertensive patients.
As for other asymmetric 1,4-dihydropyridines, the antihypertensive activity of lercanidipine is mainly due to its (S)-enantiomer.

Clinical efficacy and safety

In addition to the clinical studies conducted to support the therapeutic indications, a further small uncontrolled but randomised study of patients with severe hypertension (mean $\pm$ SD diastolic blood pressure of 114.5 $\pm$ 3.7 mmHg) showed that blood pressure was normalised in 40% of the 25 patients on 20 mg once daily dose and in 56% of 25 patients on 10 mg twice daily doses of LERCADIP. In a double-blind, randomized, controlled study versus placebo in patients with isolated systolic hypertension LERCADIP was efficacious in lowering systolic blood pressure from mean initial values of 172.6 $\pm$ 5.6 mmHg to 140.2 $\pm$ 8.7 mmHg.

5.2 Pharmacokinetic properties

Absorption

LERCADIP is completely absorbed after 10-20 mg oral administration and peak plasma levels, 3.30 ng/ml $\pm$ 2.09 s.d. and 7.66 ng/ml $\pm$ 5.90 s.d. respectively, occur about 1.5-3 hours after dosing.

The two enantiomers of lercanidipine show a similar plasma level profile: the time to peak plasma concentration is the same, the peak plasma concentration and AUC are, on average, 1.2-fold higher for the (S) enantiomer and the elimination half-lives of the two enantiomers are essentially the same. No "in vivo" interconversion of enantiomers is observed.
Due to the high first pass metabolism, the absolute bioavailability of LERCADIP orally administered to patients under fed conditions is around 10%, although it is reduced to 1/3 when administered to healthy volunteers under fasting conditions. Oral availability of lercanidipine increases 4-fold when LERCADIP is ingested up to 2 hours after a high fat meal. Accordingly, LERCADIP should be taken before meals.

Distribution:
Distribution from plasma to tissues and organs is rapid and extensive.
The degree of serum protein binding of lercanidipine exceeds 98%. Since plasma protein levels are reduced in patients with severe renal or hepatic dysfunction, the free fraction of the drug may be increased.

Biotransformation:
LERCADIP is extensively metabolised by CYP3A4; no parent drug is found in the urine or the faeces. It is predominantly converted to inactive metabolites and about 50% of the dose is excreted in the urine.

"In vitro" experiments with human liver microsomes have demonstrated that lercanidipine shows some degree of inhibition of CYP3A4 and CYP2D6, at concentrations 160- and 40-fold, respectively, higher than those reached at peak in the plasma after the dose of 20 mg.

Moreover, interaction studies in humans have shown that lercanidipine did not modify the plasma levels of midazolam, a typical substrate of CYP3A4, or of metoprolol, a typical substrate of CYP2D6. Therefore, inhibition of biotransformation of drugs metabolised by CYP3A4 and CYP2D6 by LERCADIP is not expected at therapeutic doses.

Elimination:
Elimination occurs essentially by biotransformation**.**
A mean terminal elimination half life of 8-10 hours was calculated and the therapeutical activity lasts for 24 hours because of its high binding to lipid membrane. No accumulation was seen upon repeated administration.

Linearity/non linearity:
Oral administration of LERCADIP leads to plasma levels of lercanidipine not directly proportional to dosage (non-linear kinetics). After 10, 20 or 40 mg, peak plasma concentrations observed were in the ratio 1:3:8 and areas under plasma concentration-time curves in the ratio 1:4:18, suggesting a progressive saturation of first pass metabolism. Accordingly, availability increases with dosage elevation.

Additional information on special populations In elderly patients and in patients with mild to moderate renal dysfunction or mild to moderate hepatic impairment the pharmacokinetic behaviour of lercanidipine was shown to be similar to that observed in the general patient population; patients with severe renal dysfunction or dialysis-dependent patients showed higher levels (about 70%) of the drug. In patients with moderate to severe hepatic impairment, the systemic bioavailability of lercanidipine is likely to be increased since the drug is normally metabolised extensively in the liver.

5.3 Pre-clinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity,carcinogenic potential, toxicity to reproduction.

Safety pharmacological studies in animals have shown no effects on the autonomic nervous system, the central nervous system or on gastrointestinal function at antihypertensive doses.

The relevant effects which have been observed in long-term studies in rats and dogs were related, directly or indirectly, to the known effects of high doses of Ca-antagonists, predominantly reflecting exaggerated pharmacodynamic activity.

Lercanidipine was not genotoxic and showed no evidence of carcinogenic hazard.

Fertility and general reproductive performance in rats were unaffected by treatment with lercanidipine.

There was no evidence of any teratogenic effect in rats and rabbits; however, in rats, lercanidipine at high dose levels induced pre- and post- implantation losses and delay in foetal development.

Lercanidipine hydrochloride, when administered at high dose (12 mg/kg/day) during labour, induced dystocia.

The distribution of lercanidipine and/or its metabolites in pregnant animals and their excretion in breast milk have not been investigated.

Metabolites have not been evaluated separately in toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Povidone K30
Magnesium stearate

Film coating:
Hypromellose
Talc
Titanium dioxide (E171)
Macrogol 6000
Ferric oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Aluminium/opaque PVC blisters.
Packs of 7, 14, 28, 35, 50, 56, 98 and 100 tablets. **Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

RECORDATI Industria Chimica e Farmaceutica S.p.A.
Via M. Civitali, 1 – 20148 Milan - Italy

8. MARKETING AUTHORISATION NUMBER

PL 04595/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th October 2005
Date of latest renewal:

10 DATE OF REVISION OF THE TEXT

14/09/2015