SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[Nationally completed name] 10 mg film-coated tablets
[Nationally completed name] 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg of lercanidipine hydrochloride.

Excipient with known effect
Each film-coated tablet contains 28.5 mg of lactose (as monohydrate).

Each film-coated tablet contains 20 mg of lercanidipine hydrochloride.

Excipient with known effect
Each film-coated tablet contains 57 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

10 mg film-coated tablets:
Yellow film-coated tablet of round biconvex shape (diameter 6.5 mm), scored on one side, marked 'L' on the other side.

20 mg film-coated tablets:
Pink film-coated tablet of round biconvex shape (diameter 8.5 mm), scored on one side, marked 'L' on the other side.

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

[Nationally completed name] is indicated in adults for the treatment of mild to moderate essential hypertension.

4.2 Posology and method of administration

Posology

The recommended dose is 10 mg orally once a day, taken 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 lercanidipine to therapy with a beta-adrenoceptor blocking agent (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 adverse events may increase.

Elderly
Although the pharmacokinetic data and clinical experience suggest that no adjustment of the daily dose is required, special care should be exercised when initiating treatment in the elderly.

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

No data are available.

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.

Lercanidipine is contraindicated for use in patients with severe hepatic impairment or with severe renal impairment (GFR < 30 mL/min), including patients undergoing dialysis (see sections 4.3 and 4.4).

Method of administration
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 breast-feeding (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 hepatic impairment.

- Severe renal impairment (GFR < 30 mL/min), including patients undergoing dialysis.
- Within 1 month of a myocardial infarction.
- Co-administration with:
  - strong inhibitors of CYP3A4 (see section 4.5),
  - ciclosporin (see section 4.5),
  - grapefruit or grapefruit juice (see section 4.5).

4.4 Special warnings and precautions for use

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

Left ventricular dysfunction
Although haemodynamic controlled studies revealed no impairment of ventricular function, care is also required in patients with left ventricular dysfunction.

Ischaemic heart disease
It has been suggested that some short-acting dihydropyridines may be associated with increased cardiovascular risk in patients with ischaemic heart disease. Although lercanidipine 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).

Use in renal or hepatic impairment
Special care should be exercised when treatment is commenced in patients with mild to moderate renal or hepatic impairment. Although the usual 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 dose should be considered.

Lercanidipine is contraindicated for use in patients with severe hepatic impairment or in patients with severe renal impairment (GFR < 30 mL/min), including patients undergoing haemodialysis (see sections 4.2 and 4.3).

Peritoneal dialysis
Lercanidipine has been associated with the development of cloudy peritoneal effluent in patients on peritoneal dialysis. The turbidity is due to an increased triglyceride concentration in the peritoneal effluent. Whilst the mechanism is unknown, the turbidity tends to resolve soon after withdrawal of lercanidipine. This is an important association to be aware of, since cloudy peritoneal effluent may be a sign of peritonitis and result in unnecessary hospitalisation and use of antibiotics.

CYP3A4 inducers
Inducers of CYP3A4 like anticonvulsants (e.g. phenytoin, carbamazepine) and rifampicin may reduce lercanidipine plasma levels and therefore its efficacy 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).

Paediatric population
The safety and efficacy of lercanidipine have not been established in children and adolescents under the age of 18 years.

[Nationally completed name] contains lactose and sodium
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications of concomitant use

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

Co-administration of lercanidipine with inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir, erythromycin, troleandomycin, clarithromycin) 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).

Ciclosporin
Ciclosporin and lercanidipine should not be administered concomitantly (see section 4.3).

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

Grapefruit and grapefruit juice
Lercanidipine should not be taken with grapefruit or 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.

Precautions including dose adjustment

Midazolam

When concomitantly administered at a dose of 20 mg with midazolam orally 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 lercanidipine is administered with other substrates of CYP3A4, e.g., terfenadine, astemizole, class III antiarrhythmic medicinal products such as amiodarone, or quinidine and sotalol.

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.

Metoprolol
When lercanidipine was co-administered with metoprolol, 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 medicinal products of this class. Consequently, lercanidipine may be safely administered with beta-adrenoceptor blocking medicinal products, but dose adjustment may be required.

Not recommended for concomitant use

Inducers of CYP3A4
Co-administration of lercanidipine with CYP3A4 inducers like anticonvulsants (e.g. phenytoin, phenobarbital, 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 (see section 4.4).

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

Concomitant use of other medicinal products

Fluoxetine
An interaction study with fluoxetine (an inhibitor of CYP2D6 and CYP3A4), conducted in volunteers aged 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.

Simvastatin

When a dose of 20 mg of lercanidipine 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 medicinal product.

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

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

Other medicinal products affecting blood pressure
As with all antihypertensive medicinal products, an increased hypotensive effect may occur when lercanidipine is co-administered with other medicinal products that affect blood pressure, such as alpha blockers for the treatment of urinary tract symptoms, tricyclic antidepressants and neuroleptics. Conversely, a reduction in the hypotensive effect may occur with concomitant use of corticosteroids.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of lercanidipine in pregnant women. Animal studies have not shown teratogenic effects (see section 5.3), but these have been observed with other dihydropyridine compounds. Lercanidipine is not recommended during pregnancy or in women of child-bearing potential.

Breast-feeding
It is unknown whether lercanidipine/metabolites are excreted in human milk. A risk in the newborns/infants cannot be excluded. Lercanidipine is contraindicated during breast-feeding (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 channel blockers. In cases where repeated *in vitro* fertilization 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

Lercanidipine 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

Summary of the safety profile

The safety of lercanidipine at a dose of 10-20 mg once daily has been evaluated in double-blind, placebo-controlled clinical trials (with 1,200 patients receiving lercanidipine and 603 patients receiving placebo) and in active-controlled and uncontrolled long-term clinical trials on a total of 3,676 hypertensive patients receiving lercanidipine.
The most commonly reported adverse reactions in clinical trials and in the post-marketing studies are: oedema peripheral, headache, flushing, tachycardia and palpitations.

Tabulated list of adverse reactions
In the table below, adverse drug reactions, reported in clinical trials and in the worldwide post-marketing experience for which a reasonable causal relationship exists are listed 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.

MedDRA System organ class	**Common**	**Uncommon**	**Rare**	**Not known**
Immune system disorders			Hypersensitivity	
Nervous system disorders	Headache	Dizziness	Somnolence, syncope	
Cardiac disorders	Tachycardia, palpitations		Angina pectoris	
Vascular disorders	Flushing	Hypotension		
Gastrointestinal disorders		Dyspepsia nausea, abdominal pain	Diarrhoea, vomiting	Gingival hypertrophy[1], peritoneal cloudy effluent[1]
Hepatobiliary disorders				Serum transaminase increased[1]
Skin and subcutaneous tissue disorders		Rash, pruritus	Urticaria	Angioedema[1]
Musculoskeletal and connective tissue disorders		Myalgia		
Renal and urinary disorders		Polyuria	Pollakiuria	
General disorders and administration site conditions	Oedema peripheral	Asthenia, fatigue	Chest pain	

[1]adverse reactions from spontaneous reporting in the worldwide post-marketing experience

Description of selected adverse reactions

In placebo controlled clinical trials the incidence of peripheral oedema was 0.9 % with lercanidipine 10-20 mg and 0.83 % with placebo. This frequency reached 2 % in the overall study population including long-term clinical trials.

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

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.

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

In the post-marketing experience, some cases of overdose were reported from 30-40 mg up to 800 mg of lercanidipine, including reports of suicide attempt.

Symptoms
As with other dihydropyridines, lercanidipine overdose may cause excessive peripheral vasodilatation with marked hypotension and reflex tachycardia. However, at very high doses, the peripheral selectivity disappears, causing bradycardia as well as a negative inotropic effect. The most common ADRs caused by overdose are hypotension, dizziness, headache and palpitations.

Management
Clinical hypotension requires active cardiovascular stabilisation including frequent monitoring of cardiac and respiratory function, elevation of extremities and monitoring of blood volume and urinary excretion. In view of the prolonged pharmacological effect of lercanidipine, it is essential that the cardiovascular status of the patient is monitored for 24 hours at least. Since lercanidipine is highly protein bound, dialysis is unlikely to be effective. It is expected that patients with moderate to severe intoxication will be admitted for observation.

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 lercanidipine 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
The clinical efficacy and safety of lercanidipine at a dose of 10-20 mg once daily has been evaluated in double-blind, placebo-controlled clinical trials (with 1,200 patients receiving lercanidipine and 603 patients receiving placebo) and in active-controlled and uncontrolled long-term clinical trials on a total of 3,676 hypertensive patients.
Most clinical trials have been conducted in patients with mild to moderate essential hypertension (including elderly and diabetic patients), receiving lercanidipine alone or in combination with ACE inhibitors, diuretics or beta-blockers.

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 ± SD diastolic blood pressure of 114.5 ± 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 lercanidipine. In a double-blind, randomized, controlled study versus placebo in patients with isolated systolic hypertension lercanidipine was efficacious in lowering systolic blood pressure from mean initial values of 172.6 ± 5.6 mmHg to 140.2 ± 8.7 mmHg.

No clinical trial has been performed in the paediatric population.

5.2 Pharmacokinetic properties

Absorption
Lercanidipine is completely absorbed after 10-20 mg oral administration and peak plasma levels, 3.30 ng/ml ± 2.09 s.d. and 7.66 ng/ml ± 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 lercanidipine 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 lercanidipine is ingested up to 2 hours after a high fat meal. Accordingly, lercanidipine 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 impairment, the free fraction of the active substance may be increased.

Biotransformation
Lercanidipine is extensively metabolised by CYP3A4; no parent active substance 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 medicinal products metabolised by CYP3A4 and CYP2D6 by lercanidipine 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 lercanidipine 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 dose elevation.

Additional information on special populations
In elderly patients and in patients with mild to moderate renal impairment 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 impairment or dialysis-dependent patients showed higher levels (about 70%) of the active substance. In patients with moderate to severe hepatic impairment, the systemic bioavailability of lercanidipine is likely to be increased since the medicinal product is normally metabolised extensively in the liver.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for human 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 into breast milk have not been investigated.

Metabolites have not been evaluated separately in toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

10 mg and 20 mg film-coated tablets:
Tablet core:
Magnesium stearate (E 572)
Povidone K-30 (E 1201)
Sodium starch glycolate (Type A)
Lactose monohydrate
Cellulose, microcrystalline (E 460)

10 mg film-coated tablets:
Film-coating:
Macrogol 3350 (E 1521)
Polyvinyl alcohol, partly hydrolysed
Talc (E 553b)
Titanium dioxide (E 171)
Iron oxide, yellow (E 172)

20 mg film-coated tablets:
Film-coating:
Macrogol 3350 (E 1521)
Polyvinyl alcohol, partly hydrolysed
Talc (E 553b)
Titanium dioxide (E 171)
Iron oxide, yellow (E 172)
Iron oxide, red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.
Store in original packaging in order to protect from moisture.

6.5 Nature and contents of container
The film-coated tablets are packed in PVDC/PVC//Aluminium blisters and inserted in a carton.

Pack sizes:
10 mg film-coated tablets:
7, 10, 14, 20, 28, 30, 35, 50, 56, 60, 98, or 100 film-coated tablets

20 mg film-coated tablets:
7, 10, 14, 20, 28, 30, 35, 42, 50, 56, 60, 98, or 100 film-coated 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

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}
Date of latest renewal: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]