Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lecalpin 20 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 20 mg lercanidipine hydrochloride, equivalent to 18.8 mg lercanidipine.

Excipient with known effect:
Lecalpin 20 mg film-coated tablet: Lactose monohydrate 60 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Pink colored, round shaped, biconvex, coated tablets debossed with "LT2" on one side and breakline on the other side. The diameter of the tablet is approximately 8.5mm.

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

Lecalpin is indicated for the treatment of mild to moderate essential hypertension.

4.2 Posology and method of administration

Posology
Route of administration: For oral use.

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 lercandipine to therapy with a beta-adrenoreceptor blocking drug, a diuretic (hydrochlorothiazide) or an angiotensin converting enzyme inhibitor.

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.

Elderly
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.

Paediatric population
Lercanidipine is not recommended for use in children and adolescents below the age of 18 years as there is no clinical experience.

Renal or hepatic insufficiency

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

Method of administration

The tablets should be taken with some water at least 15 minutes before a meal.

4.3 Contraindications

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

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 (if a pacemaker is not in situ). Although hemodynamic controlled studies revealed no impairment of ventricular function, care is also required in patients with left ventricular dysfunction. 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.

Angina pectoris
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 dysfunction:
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 not recommended for use in patients with severe hepatic impairment or in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.2).

Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive drugs (see section 4.5).

CYP3A4 inducers
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).

This medicinal product contains lactose monohydrate and therefore should not be administered to patients with Lapp lactase insufficiency, galactosaemia or glucose/galactose malabsorption syndrome.

4.5 Interaction with other medicinal products and other forms of interactions

Metabolic interactions
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.

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

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. Ciclosporin and lercanidipine should not be administered together.

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. Lercanidipine should not be taken with grapefruit juice.

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.

CYP3A4 inducers
Co-administration of lercanidipine 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.

CYP3A4 substrates
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.

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.

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.

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

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

Alcohol
Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive drugs.

Other interactions
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 drugs of this class. Consequently, lercanidipine may be safely administered with beta-adrenoceptor blocking drugs, but dose adjustment may be required.

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 drug.

Lercanidipine has been safely administered with diuretics and ACE inhibitors.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of lercanidipine in pregnant women. Non-clinical data provide no evidence of a teratogenic effect in the rat and the rabbit and reproductive performance in the rat was unimpaired. Since other dihydropyridine compounds have been found teratogenic in animals, lercanidipine should not be administered during pregnancy or to women with child-bearing potential unless effective contraception is used.

Breastfeeding
Because of high lipophilicity of lercanidipine, distribution in milk may be expected. Therefore, it should not be administered to nursing mothers.

4.7 Effects on ability to drive and use machines

Lecalpin has no or negligible 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

The following undesirable effects have been reported in clinical studies and in the post-marketing phase:

Assessment of 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
not known (cannot be estimated from the available data)

System organ class		**Adverse drug reactions**
Immune system disorders	Very rare	Hypersensitivity
Psychiatric disorders	Rare	Somnolence
Nervous system disorders	Uncommon	Headache, dizziness
Cardiac disorders	Uncommon	Tachycardia, palpitations, peripheral oedema
	Rare:	angina pectoris
	Very rare	Chest pain, myocardial infarction, hypotension
	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.	

Vascular disorders	Uncommon	Flushing
Gastrointestinal disorders	Rare	Dyspepsia, diarrhoea, abdominal pain, vomiting
	Very rare	gingival hypertrophy
Skin and subcutaneous tissue disorders	Rare	Rash
Musculoskeletal and connective tissue disorders	Rare	Myalgia
Renal and urinary disorders	Rare	Polyuria
	Very rare	Urinary frequency
General disorders and administration site conditions	Rare	Asthenia, fatigue
Investigations	Very rare	Reversible increases in serum levels of hepatic transaminases

Lercanidipine does not appear to influence adversely 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 national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

In the post-marketing experience, three cases of overdose were reported (150 mg, 280 mg and 800 mg of lercanidipine, respectively, ingested in an attempt to commit suicide).

Dose level	**Signs/Symptoms**	**Management**	**Outcome**
150 mg + undefined amount of alcohol	Sleepiness	Gastric lavage Active charcoal	Recovered
280 mg + 5.6 mg moxonidine	Cardiogenic shock Severe myocardial ischaemia Mild renal failure	High-dose catecholamines Furosemide Digitalis Parenteral plasma expanders	Recovered
800 mg	Emesis Hypotention	Active charcoal Cathartics Dopamine i.v.	Recovered

Overdosage might be expected to cause excessive peripheral vasodilatation with marked hypotension and reflex tachycardia. In case of severe hypotension, bradycardia and unconsciousness, cardiovascular support could be helpful, with intravenous atropine for bradycardia.

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 active substance 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
ATC code: C08CA13

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. 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.

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.

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 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 dosage elevation.

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 dysfunction, the free fraction of the drug may be increased.

Biotransformation
Lercanidipine 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 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.

Elderly, renal and hepatic insufficiency
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 Preclinical safety data

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:
Magnesium stearate
Povidone

Sodium starch glycolate Type A
Lactose monohydrate
Cellulose, microcrystalline

Film-coating:
Macrogol
Polyvinyl alcohol, partly hydrolysed
Talc
Titanium dioxide (E 171)
Iron oxide, yellow (E 172)
Iron oxide, red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister Pack
3 years

6.4 Special precautions for storage

Al/PVC/PVDC blister: Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Blister pack (Aluminium/PVDC) with push-through foil.

Pack sizes:
Blisters (Al/PVC/PVDC):
Lecalpin 20 mg film-coated tablets: 14, 20, 28, 30, 50, 56, 60, 90, 98, 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/186/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th September 2009
Date of last renewal: 2nd July 2014

10 DATE OF REVISION OF THE TEXT

August 2020