Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lercanidipine Viatris 20 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg of lercanidipine hydrochloride, which is equivalent to 18.8 mg of lercanidipine.

Excipient with known effect: each film-coated tablet contains 50.0 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Pink, round, biconvex film-coated tablet, debossed with “LR over 2” on one side of the tablet and with a deep score line 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

Lercanidipine Viatris 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 Lercanidipine Viatris to therapy with a beta-adrenoreceptor 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.

Elderly people
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
The safety and efficacy of Lercanidipine Viatris in children up to 18 years have not been established. No data are available.

Patients with renal and 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 Viatris is contraindicated in patients with severe hepatic impairment or in patients with severe renal impairment (Glomerular Filtration Rate (GFR) < 30 ml/min), including patients undergoing dialysis (see sections 4.3 and 4.4).

Method of administration
For oral use.

Precautions to be taken before handling or administrating the medicinal product:

Treatment should be preferably administered in the morning at least 15 minutes before breakfast.

This product should not be administered with grapefruit juice (see sections 4.3 and 4.5).

4.3 Contraindications

• Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1.

• Left ventricular outflow tract obstruction.

• Untreated congestive cardiac failure.

• Unstable angina pectoris or recent (within 1 month) myocardial infarction.

• Severe hepatic impairment.

• Severe renal impairment (GFR < 30 ml/min), including patients undergoing dialysis

• 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
Lercanidipine should be administered with caution in patients with sick sinus syndrome (without a pacemaker).

Left ventricular dysfunction
Although hemodynamic 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 impairment. Although the usual recommended dose of 10mg daily may be tolerated, an increase to 20 mg daily must be approached with caution. The antihypertensive effect may be enhanced in patients with moderate hepatic impairment and consequently an adjustment of the dosage should be considered.

Lercanidipine contraindicated in patients with severe hepatic impairment or renal impairment (GFR < 30 ml/min) including patients undergoing haemodialysis (see section 4.2 and section 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 recognise as cloudy

peritoneal effluent can be mistaken for infective peritonitis with consequential unnecessary hospitalisation and empiric antibiotic administration.

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

Inducers of CYP3A4
Inducers of CYP3A4 like anticonvulsants (e.g. phenytoin, carbamazepine) and rifampicin may reduce lercanidipine plasma levels and therefore the efficacy of lercanidipine may be less than expected (see section 4.5).

Paediatric population
The safety and efficacy of Lercanidipine Viatris have not been demonstrated in children.

Excipient
This medicinal product contains lactose. 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

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.

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).

Co-prescription of lercanidipine with inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir, erythromycin, troleandomycin, clarithromycin) should be avoided (see section 4.3).

Ciclosporin
Ciclosporin and lercanidipine should not be administered together (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.

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

Grapefruit or grapefruit juice
As for other dihydropyridines, lercanidipine is sensitive to inhibition of metabolism by grapefruit or grapefruit juice, with a consequent rise in its systemic availability and increased hypotensive effect. Lercanidipine should not be taken with grapefruit or grapefruit juice (see section 4.3).

Concomitant use not recommended

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 drugs (see section 4.4).

Precautions including dose adjustment

Substrates of CYP3A4

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, sotalol.

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.

Metoprolol
When lercanidipine 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.

Digoxin
Co-administration of 20 mg lercanidipine in patients chronically treated with β -methyldigoxin showed no evidence of pharmacokinetic interaction. However, a mean increase of 33% in digoxin C_{max} was observed, 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 use with other drugs

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.

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 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
Lercanidipine has been safely administered with diuretics and ACE inhibitors.

Other medications affecting blood pressure
As for all antihypertensive medications, an increased hypotensive effect may be observed when lercanidipine is administered with other medications affecting blood pressure, such as alphablockers for the treatment of urinary symptoms, tricyclic antidepressants, neuroleptics. On the contrary, a reduction of the hypotensive effect may be observed with a concomitant use with corticosteroids.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of lercanidipine in pregnant woman. Studies in animals have not shown teratogenic effects (see section 5.3), but these have been observed with other dihydropyridine compounds. Lercanidipine is not recommended during pregnancy and in women of childbearing-potential not using contraception.

Breast-feeding
It is unknown whether lercanidipine/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Lercanidipine should not be used during breastfeeding.

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 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

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 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 1200 patients receiving lercanidipine and 603 patients receiving placebo) and in active-controlled and uncontrolled long term clinical trials on a total of 3676 hypertensive patients receiving lercanidipine.

The most commonly reported adverse reactions in clinical trials and in the post-marketing experience are: peripheral oedema, headache, flushing, tachycardia and palpitations.

Tabulated list of adverse reactions
In the table below, adverse 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 and 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 (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		Abdominal pain upper;Dyspepsia;Nausea	Vomiting; diarrhoea	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 HPRA Pharmacovigilance, website: www.hpra.ie;.

4.9 Overdose

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

Symptoms
As with other dihydropyridines, lercanidipine overdosage results in excessive peripheral vasodilatation with marked hypotension and reflex tachycardia. However, at very high doses, the peripheral selectivity may be lost, causing bradycardia and a negative inotropic effect. The most common ADRs associated to cases of overdose have been hypotension, dizziness, headache and palpitations.

Treatment
Clinically significant hypotension requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

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. Since the product has a high protein binding, dialysis is not likely to be effective. Patients in whom a moderate to severe intoxication is anticipated should be observed in a high-care setting.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective calcium channel blockerswith 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 1200 patients receiving lercanidipine and 603 patients receiving placebo) and in active-controlled and uncontrolled long term clinical trials on a total of 3676 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-Is, 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 $\pm$ 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 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 Hydrochloride is ingested up to 2 hours after a high fat meal. Accordingly, Lercanidipine Hydrochloride 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 therapeutic 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 dosage elevation.

Other 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 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, 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
Cellulose, microcrystalline
Crospovidone (type A)
Povidone K30
Magnesium stearate

Film coating:
Hypromellose
Titanium dioxide (E171)
Iron oxide yellow (E172)
Macrogol 8000
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Cold form Al/OPA/PVC/Al blister packs containing 7, 14, 28, 35, 50, 56, 98 and 100 tablets.

HDPE bottle with opaque polypropylene cap with desiccant containing 500 and 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23266/057/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd June 2011

Date of last renewal: 30th April 2015

10 DATE OF REVISION OF THE TEXT

May 2025